BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
Carson City, Nevada 89701
(775) 684-3676 · Fax (775) 687-3893

RICHARD WHITLEY, MS
Director

MARTA JENSEN
Acting Administrator

NOTICE OF PUBLIC MEETING – PHARMACY AND THERAPEUTICS COMMITTEE

AGENDA

Date of Posting:	**xxxxx**
Date of Meeting:	**Thursday, December 3, 2015 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Pharmacy and Therapeutics Committee.**
Place of Meeting:	**JW Marriott – Las Vegas** **Marbella Room** **221 N. Rampart Blvd** **Las Vegas, NV 89145** **Phone: (702) 869-7777** **Please check with hotel staff to verify room location** **A visual and audio feed will also be broadcast via the internet and phone for those who are unable to attend in person. See below for details.**
Webinar Pre-Registration:	https://catamaranrx.webex.com/catamaranrx/onstage/g.php?MTID=e6caebf863da965b41ca7ba5f5a4c5731 ****Must Pre-Register**** **Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting**
Webinar Event:	https://catamaranrx.webex.com/catamaranrx/onstage/g.php?MTID=e6caebf863da965b41ca7ba5f5a4c5731
Event Number:	**740 124 858**

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Teleconference: **1 (855) 210-1642**

Access Code: **3844816**

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Tanya Benitez at: 775-684-3722 or email Tanya.Benitez@dhcfp.nv.gov in advance, but no later than two working days prior to the meeting, so that arrangements may be conveniently made.

Items may be taken out of order.
Items may be combined for consideration by the public body.
Items may be pulled or removed from the agenda at any time.

Public comment is limited to 5 minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

AGENDA

1. **Call to Order and Roll Call**

2. **Public Comment**

   No action may be taken on a matter raised under this item of the agenda until the matter itself has been specifically included on the agenda as an item upon which action can be taken.

3. **Administrative**

   A. **For Possible Action:** Review and Approve Meeting Minutes from September 23, 2015.

   B. Status Update by DHCFP
      1.Public Comment

4. **Annual Review – Drug Classes Without Proposed Changes From September 23, 2015 Meeting**
   A. Public Comment

B. Presentation of Recommendations for Preferred Drug List (PDL) inclusion by OptumRx and the Division of Health Care Financing and Policy without Changes.

C. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

1. Tramadol And Related Drugs
2. Non-Sedating H1 Blockers
3. Inhaled Aminoglycosides
4. Antivirals - Alpha Interferons
5. Anti-Hepatitis Agents – Polymerase Inhibitors/Combination Products
6. Anti-Hepatitis Agents – Protease Inhibitors
7. Anti-Hepatitis Agents – Ribavrins
8. Anti-Herpetic Agents
9. Influenza Agents
10. Second-Generation Cephalosporins
11. Third-Generation Cephalosporins
12. Macrolides
13. Quinolones - 2nd Generation
14. Quinolones - 3rd Generation
15. Self-Injectable Epinephrine
16. Multiple Sclerosis Agents - Specific Symptomatic Treatment
17. Angiotensin Ii Receptor Antagonists
18. Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)
19. Calcium-Channel Blockers
20. Direct Renin Inhibitors
21. Vasodilators – Inhaled
22. Bile Acid Sequestrants
23. Cholesterol Absorption Inhibitors
24. Fibric Acid Derivatives
25. Hmg-Coa Reductase Inhibitors (Statins)
26. Niacin Agents
27. Antipsoriatic Agents - Topical Vitamin D Analogs
28. Topical Analgesics
29. Acne Agents: Topical, Benzoyl Peroxide, Antibiotics And Combination Products
30. Impetigo Agents: Topical
31. Topical Antivirals
32. Topical Scabicides
33. Immunomodulators: Topical
34. Topical Retinoids

35. Serotonin-Receptor Antagonists/Combo
36. H2 Blockers
37. Proton Pump Inhibitors (PPIs)
38. Gastrointestinal Antiinflammatory Agents
39. Gastrointestinal Enzymes
40. 5-Alpha Reductase Inhibitors
41. Alpha-Blockers
42. Bladder Antispasmodics
43. Anticoagulants – Injectable
44. Colony Stimulating Factors
45. Platelet Inhibitors
46. Alpha-Glucosidase Inhibitors/Amylin Analogs/Misc.
47. Biguanides
48. Dipeptidyl Peptidase-4 Inhibitors
49. Meglitinides
50. Sulfonylureas
51. Thiazolidinediones
52. Growth Hormone Modifiers
53. Progestins For Cachexia
54. Antigout Agents
55. Bisphosphonates
56. Nasal Calcitonins
57. Restless Leg Syndrome Agents
58. Skeletal Muscle Relaxants
59. Alzheimer's Agents
60. Barbiturates
61. Benzodiazepines
62. Hydantoins
63. Non-Ergot Dopamine Agonists
64. Carbonic Anhydrase Inhibitors/Beta-Blockers
65. Ophthalmic Prostaglandins
66. Ophthalmic Antihistamines
67. Ophthalmic Macrolides
68. Ophthalmic Quinolones
69. Ophthalmic Corticosteroids
70. Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDS)
71. Otic Quinolones
72. Antidepressants – Other
73. Selective Serotonin Reuptake Inhibitors (SSRIS)
74. Atypical Antipsychotics

75. Nasal Antihistamines
76. Leukotriene Receptor Antagonists
77. Nasal Corticosteroids
78. Phosphodiesterase Type 4 Inhibitors
79. Respiratory Antimuscarinics
80. Long-Acting Respiratory Beta-Agonist
81. Short-Acting Respiratory Beta-Agonist
82. Respiratory Corticosteroid/Long-Acting Beta-Agonist Combinations
83. Antidotes - Opiate Antagonists

5. Established Drug Classes

A. Antidepressants - Other
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. Nasal Antihistamines
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. Nasal Calcitonins
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action

a. Approve Clinical/Therapeutic Equivalency of Agents in Class
b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. Platelet Inhibitors

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. Bladder Antispasmodics

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

F. Angiotensin II Receptor Antagonists

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

G. Immunomodulators: Topical
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
    a. Approve Clinical/Therapeutic Equivalency of Agents in Class
    b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

H. Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
    a. Approve Clinical/Therapeutic Equivalency of Agents in Class
    b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

I. Disease-Modifying Antirheumatic Agents
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
    a. Approve Clinical/Therapeutic Equivalency of Agents in Class
    b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy

5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

6. Established Drug Classes Being Reviewed Due to the Release of New Drugs

A. Alzheimer's Agents
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. Oral Atypical Antipsychotics
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. Ophthalmic Antihistamines
1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
   a. Approve Clinical/Therapeutic Equivalency of Agents in Class
   b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. Short-Acting Respiratory Beta-Agonist

1. Public Comment
2. Drug Class Review Presentation – OptumRx
3. **For Possible Action**: Committee Discussion and Action
    a. Approve Clinical/Therapeutic Equivalency of Agents in Class
    b. Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by OptumRx and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

7. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions

8. Closing Discussion

A. Public comments on any subject.

B. Date and location of the next meeting.

1. Discussion of the time of the next meeting.

C. Adjournment.

This notice and agenda have been posted at http://dhcfp.nv.gov and http://notice.nv.gov

Notice of this meeting will be available on or after the date of this notice at the DHCFP Web site www.dhcfp.nv.gov, Carson City Central office and Las Vegas DHCFP. The agenda posting of this meeting can be viewed at the following locations: Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a copy of the meeting materials will be mailed to you. Requests and/or written comments may be sent to Robyn Heddy at the Division of Health Care Financing and Policy, 1100 E. William Street, Suite 101, Carson City, NV 89701, at least 3 days before the public hearing.

All persons that have requested in writing to receive the Public Hearings agenda have been duly notified by mail or e-mail.

Division of Health Care Financing and Policy

Nevada Medicaid Preferred Drug List

Effective Sept. 1, 2015

			Preferred Products	PA Criteria	Non-Preferred Products
Analgesics					
	Analgesic/Miscellaneous				
		Neuropathic Pain Agents			
			CYMBALTA® GABAPENTIN LYRICA®	* PA Required	GRALISE® LIDODERM® * HORIZANT®
		Tramadol and Related Drugs			
			TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
	Opiate Agonists				
			MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) QL FENTANYL PATCH QL	**PA Required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUTRANS® DOLOPHINE® DURAGESIC® PATCHES QL EMBEDA® EXALGO® HYSINGLA ER® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL NUCYNTA® ER OPANA ER® OXYCODONE SR QL OXYCONTIN® QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Antihistamines					
	H1 blockers				
		Non-Sedating H1 Blockers			
			CETIRIZINE D OTC CETIRIZINE OTC LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non-preferred drug will be authorized.	ALLEGRA® CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®

Nevada Medicaid Preferred Drug List

Effective Sept. 1, 2015

	Preferred Products	PA Criteria	Non-Preferred Products
Antiinfective Agents			
Aminoglycosides			
Inhaled Aminoglycosides			
	BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals			
Alpha Interferons			
	PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents			
Polymerase Inhibitors/Combination Products			
	HARVONI® SOVALDI® VIEKIRA PAK®	**PA Required** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	
Protease Inhibitors			
	INCIVEK® VICTRELIS® OLYSIO®	**PA Required** https://www.medicaid.nv.gov/Downloads/provider/FA-75.pdf	
Ribavrins			
	RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents			
	ACYCLOVIR FAMVIR® VALCYCLOVIR		
Influenza Agents			
	AMANTADINE TAMIFLU® RIMANTADINE RELENZA®		

	Preferred Products	PA Criteria	Non-Preferred Products
Cephalosporins			
Second-Generation Cephalosporins			
	CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins			
	CEFDINIR CAPS and SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides			
	AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		BIAXIN® DIFICID® ZITHROMAX® ZMAX®
Quinolones			
Quinolones - 2nd Generation			
	CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation			
	AVELOX® AVELOX ABC PACK® LEVOFLOXACIN		LEVAQUIN®
Autonomic Agents			
Sympathomimetics			
Self-Injectable Epinephrine			
	AUVI-Q® * EPINEPHRINE® EPIPEN® EPIPEN JR.®	* PA Required	ADRENACLICK® QL
Biologic Response Modifiers			
Immunomodulators			
Disease-Modifying Antirheumatic Agents			
	ENBREL® HUMIRA®	Prior authorization is required for all drugs in this	ACTEMRA® CIMZIA®

			Preferred Products	PA Criteria	Non-Preferred Products
				class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	KINERET® REMICADE® SIMPONI® ORENCIA® STELARA®
	Multiple Sclerosis Agents				
		Injectable			
			AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	
		Oral			
			AUBAGIO® GILENYA® TECFIDERA®		
		Specific Symptomatic Treatment			
			AMPYRA® QL	PA required	
Cardiovascular Agents					
	Antihypertensive Agents				
		Angiotensin II Receptor Antagonists			
			DIOVAN® DIOVAN HCTZ® LOSARTAN LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® EDARBI® EDARBYCLOR® EPROSARTAN IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
		Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
			BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® TRANDOLAPRIL UNIVASC®

			Preferred Products	PA Criteria	Non-Preferred Products
		Beta-Blockers			
			ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL METOPROLOL (Regular Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL	*Restricted to ICD-9 codes 490-496	
		Calcium-Channel Blockers			
			AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
		Direct Renin Inhibitors			
			TEKAMLO® TEKTURNA® TEKTURNA HCT® VALTURNA®		AMTURNIDE®

			Preferred Products	PA Criteria	Non-Preferred Products
		Vasodilators			
		Inhaled			
			VENTAVIS® TYVASO®		
		Oral			
			ADCIRCA® LETAIRIS® SILDENAFIL TRACLEER®		ADEMPAS® OPSUMIT® ORENITRAM® REVATIO ®
	Antilipemics				
		Bile Acid Sequestrants			
			COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
		Cholesterol Absorption Inhibitors			
			ZETIA®		
		Fibric Acid Derivatives			
			FENOFIBRATE FENOFIBRIC GEMFIBROZIL LIPOFEN®		ANTARA® FENOGLIDE® FIBRICOR® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
		HMG-CoA Reductase Inhibitors (Statins)			
			ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR®
		Niacin Agents			
			NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®

	Preferred Products	PA Criteria	Non-Preferred Products
Dermatological Agents			
Antipsoriatic Agents			
Topical Vitamin D Analogs			
	CALCIPOTRIENE		CALCITENE® DOVONEX® CREAM SORILUX® TACLONEX® VECTICAL®
Topical Analgesics			
	LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS VOLTAREN® GEL		EMLA® FLECTOR® LIDODERM® QL LIDAMANTLE® PENNSAID®
Topical Antiinfectives			
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products			
	AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SULFACETAMIDE	PA required if over 21 years old	ACANYA DUAC CS® ERYTHROMYCIN CLINDAMYCIN/BENZOYL PEROXIDE GEL SODIUM SULFACETAMIDE/SULFUR
Impetigo Agents: Topical			
	MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antifungals (onychomycosis)			
	CICLOPIROX SOLN TERBINAFINE TABS	**PA Required**	
Topical Antivirals			
	ABREVA® DENAVIR® ZOVIRAX®, OINTMENT		
Topical Scabicides			
	NATROBA® * NIX® PERMETHRIN RID® SKLICE®	* PA Required	EURAX® LINDANE MALATHION OVIDE® ULESFIA®
Topical Antiinflammatory Agents			
Immunomodulators: Topical			
	ELIDEL® QL	Prior authorization is	

			Preferred Products	PA Criteria	Non-Preferred Products
			PROTOPIC® QL	required for all drugs in this class	
	Topical Antineoplastics				
		Topical Retinoids			
			RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents					
	Phosphate Binding Agents				
			CALCIUM ACETATE ELIPHOS® FOSRENOL® RENAGEL® RENVELA®		PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents					
	Antiemetics				
		Serotonin-receptor antagonists/Combo			
			GRANISETRON QL ONDANSETRON QL	PA Required for all	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
	Antiulcer Agents				
		H2 blockers			
			FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
		Proton Pump Inhibitors (PPIs)			
			NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®

			Preferred Products	PA Criteria	Non-Preferred Products
Gastrointestinal Antiinflammatory Agents					
			ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		APRISO® ASACOL HD® COLAZAL® GIAZO® LIALDA ®
Gastrointestinal Enzymes					
			CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents					
Benign Prostatic Hyperplasia (BPH) Agents					
	5-Alpha Reductase Inhibitors				
			AVODART® FINASTERIDE		JALYN® PROSCAR®
	Alpha-Blockers				
			DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® UROXATRAL®
Bladder Antispasmodics					
			OXYBUTYNIN TABS/SYRUP/ER SANCTURA XR® TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents					
Anticoagulants					
	Oral				
			COUMADIN® ELIQUIS® *	* No PA required if approved Dx code transmitted on claim	

			Preferred Products	PA Criteria	Non-Preferred Products
			JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *		
		Injectable			
			ARIXTRA® ENOXAPARIN FRAGMIN®		FONDAPARINUX INNOHEP® LOVENOX®
	Colony Stimulating Factors				
			ARANESP® QL PROCRIT® QL	PA Required Quantity Limit	EPOGEN® QL OMONTYS® QL
	Platelet Inhibitors				
			AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE TICLOPIDINE	* PA Required	EFFIENT® * QL PLAVIX® ZONTIVITY®
Hormones and Hormone Modifiers					
	Androgens				
			ANDROGEL® ANDRODERM®	**PA Required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	AXIRON® FORTESTA® STRIANT® TESTIM® TESTOSTERONE GEL VOGELXO®
	Antidiabetic Agents				
		Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.			
			ACARBOSE (Precose®) GLYSET® PRECOSE® SYMLIN® (PA required)		CYCLOSET®
		Biguanides			
			FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		

			Preferred Products	PA Criteria	Non-Preferred Products
		Dipeptidyl Peptidase-4 Inhibitors			
			JANUMET® JANUMET XR® JANUVIA® JENTADUETO® JUVISYNC® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		KAZANO® NESINA® OSENI®
		Incretin Mimetics			
			BYDUREON® * BYETTA® * VICTOZA® *	* PA Required	TANZEUM® TRULICITY®
		Insulins (Vials and Pens)			
			APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG®		
		Meglitinides			
			NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
		Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors			
			FARXIGA® INVOKANA®		INVOKAMET® JARDIANCE® XIGDUO XR®
		Sulfonylureas			
			AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®)		

			Preferred Products	PA Criteria	Non-Preferred Products
			GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE® METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
		Thiazolidinediones			
			ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
	Pituitary Hormones				
		Growth hormone modifiers			
			GENOTROPIN® NORDITROPIN®	**PA Required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
	Progestins for Cachexia				
			MEGESTROL ACETATE, SUSP		MEGACE ES®
Musculoskeletal Agents					
	Antigout Agents				
			ALLOPURINOL		
	Bone Resorption Inhibitors				
		Bisphosphonates			
			ALENDRONATE TABS FOSAMAX PLUS D®		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE IBANDRONATE SKELID®

			Preferred Products	PA Criteria	Non-Preferred Products
		Nasal Calcitonins			
			MIACALCIN®		
	RESTLESS LEG SYNDROME AGENTS				
			PRAMIPEXOLE REQUIP XL ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP
	Skeletal Muscle Relaxants				
			BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents					
	Alzheimers Agents				
			DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN NAMENDA® TABS NAMENDA® XR TABS RIVASTIGMINE CAPS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER RAZADYNE® RAZADYNE® ER
	Anticonvulsants				
			BANZEL® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPITOL® ETHOSUXIMIDE FELBATOL® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR®	PA Required for members under 18 years old	APTIOM® FYCOMPA® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR®

			Preferred Products	PA Criteria	Non-Preferred Products
			LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE (IR AND ER) TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		
		Barbiturates			
			LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA Required for members under 18 years old	
		Benzodiazepines			
			CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM DIAZEPAM rectal soln KLONOPIN® TRANXENE T-TAB® VALIUM®	PA Required for members under 18 years old	ONFI®
		Hydantoins			
			CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE®	PA Required for members under 18 years old	

			Preferred Products	PA Criteria	Non-Preferred Products
			PHENYTEK® PHENYTOIN PRODUCTS		
	Anti-Migraine Agents				
		Serotonin-Receptor Agonists			
			RELPAX® SUMATRIPTAN NASAL SPRAY SUMATRIPTAN INJECTION SUMATRIPTAN TABLET ZOMIG® ZMT	PA Required for exceeding Quantity Limit	AMERGE® AXERT® FROVA® IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN SUMAVEL® TREXIMET® ZOMIG®
	Antiparkinsonian Agents				
		Non-ergot Dopamine Agonists			
			PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
	Fibromyalgia agents				
			CYMBALTA® LYRICA® SAVELLA®	*No PA required for drugs in this class if ICD-9 code=729.1.*	
Ophthalmic Agents					
	Antiglaucoma Agents				
		Carbonic Anhydrase Inhibitors/Beta-Blockers			
			ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LEVOBUNOLOL METIPRANOLOL SIMBRINZA® TIMOLOL DROPS/ GEL SOLN		ALPHAGAN® BETAGAN® BETOPTIC ® COSOPT® COSOPT PF® OCUPRESS® OPTIPRANOLOL® TIMOPTIC® TIMOPTIC XE® TRUSOPT®
		Ophthalmic Prostaglandins			
			LATANOPROST TRAVATAN®		LUMIGAN® XALATAN®

			Preferred Products	PA Criteria	Non-Preferred Products
			TRAVATAN Z® ZIOPTAN®		
	Ophthalmic Antihistamines				
			ALAWAY® BEPREVE® PATADAY® ZADITOR OTC®		ELESTAT® EMADINE® LASTACRAFT® OPTIVAR® PATANOL®
	Ophthalmic Antiinfectives				
		Ophthalmic Macrolides			
			ERYTHROMYCIN OINTMENT		
		Ophthalmic Quinolones			
			BESIVANCE® CIPROFLOXACIN MOXEZA® OFLOXACIN® VIGAMOX®		CILOXAN® ZYMAXID®
	Ophthalmic Antiinflammatory Agents				
		Ophthalmic Corticosteroids			
			ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
		Ophthalmic Nonsteroidal Antiinflammatory Drugs (NSAIDs)			
			ACULAR® ACULAR LS® ACULAR PF® DICLOFENAC FLURBIPROFEN NEVANAC®		ACUVAIL® BROMDAY® BROMFENAC® ILEVRO® PROLENSA®
Otic Agents					
	Otic Antiinfectives				
		Otic Quinolones			
			CIPRODEX® OFLOXACIN		
Psychotropic Agents					
	ADHD Agents				
			AMPHETAMINE SALT COMBO XR	**PA Required for entire class**	ADDERALL® ADDERALL XR®

			Preferred Products	PA Criteria	Non-Preferred Products
			AMPHETAMINE SALT COMBO DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA DEXTROAMPHETAMINE TAB DEXTROSTAT® FOCALIN XR® INTUNIV® METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® VYVANSE®	**Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf * (No PA required for ICD-9 codes 347.00, 347.01, 347.10, 347.11, 780.53 and 780.57)	CONCERTA® DAYTRANA® DESOXYN® DEXEDRINE® FOCALIN® KAPVAY® MODAFINIL NUVIGIL® METADATE ER® PROVIGIL®* PROCENTRA® RITALIN®
Antidepressants					
	Other				
			BUPROPION BUPROPION SR BUPROPION XL CYMBALTA®(PA not required for ICD-9 code 729.1 or MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA Required for members under 18 years old	APLENZIN® BRINTELLIX® DULOXETINE DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® VIIBRYD® WELLBUTRIN®
	Selective Serotonin Reuptake Inhibitors (SSRIs)				
			CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA Required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics					

			Preferred Products	PA Criteria	Non-Preferred Products
		Atypical Antipsychotics			
			ABILIFY® CLOZAPINE FANAPT® LATUDA® OLANZAPINE QUETIAPINE RISPERIDONE SAPHRIS® SEROQUEL XR® ZIPRASIDONE	**PA Required for Ages under 18 years old** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-70.pdf	CLOZARIL® FAZACLO® GEODON® INVEGA® RISPERDAL® SEROQUEL® ZYPREXA®
	Anxiolytics, Sedatives, and Hypnotics				
			ESTAZOLAM FLURAZEPAM ROZEREM® * TEMAZEPAM TRIAZOLAM ZOLPIDEM	*(PA not required for ICD-9 code 307.42) PA Required for members under 18 years old	AMBIEN® AMBIEN CR® DORAL® EDLUAR® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZALEPLON ZOLPIDEM CR ZOLPIMIST®
Respiratory Agents					
	Nasal Antihistamines				
			ASTEPRO® DYMISTA® PATANASE®		AZELASTINE
	Respiratory Antiinflammatory Agents				
		Leukotriene Receptor Antagonists			
			MONTELUKAST ZAFIRLUKAST		ACCOLATE® SINGULAIR®
		Respiratory Corticosteroids			
			ASMANEX® BUDESONIDE NEBS* FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR®	*No PA required if < 4 years old	AEROSPAN HFA® ALVESCO® ARNUITY ELLIPTA®
		Nasal Corticosteroids			
			FLUTICASONE NASONEX®		BECONASE AQ® FLONASE®

			Preferred Products	PA Criteria	Non-Preferred Products
					FLUNISOLIDE NASACORT AQ® OMNARIS® QNASL® RHINOCORT AQUA® TRIAMCINOLONE ACETONIDE VERAMYST® ZETONNA®
		Phosphodiesterase Type 4 Inhibitors			
			DALIRESP® QL	PA Required	
	Respiratory Antimuscarinics				
			ANORO ELLIPTA® COMBIVENT RESPIMAT® IPRATROPIUM/ALBUTEROL NEBS QL IPRATROPIUM NEBS SPIRIVA®	Only one agent per 30 days is allowed	INCRUSE ELLIPTA® SPIRIVA RESPIMAT® TUDORZA®
	Respiratory Beta-Agonists				
		Long-Acting Respiratory Beta-Agonist			
			ARCAPTA NEOHALER® FORADIL® SEREVENT DISKUS® QL		BROVANA® PERFOROMIST® SOLUTION FOR INHALATION STRIVERDI RESPIMAT®
		Short-Acting Respiratory Beta-Agonist			
			ALBUTEROL NEB/SOLN PROVENTIL® HFA PROAIR® HFA XOPENEX® HFA* QL XOPENEX® Solution* QL	* PA required	MAXAIR AUTOHALER® VENTOLIN HFA® LEVALBUTEROL
	Respiratory Corticosteroid/Long-Acting Beta-Agonist Combinations				
			ADVAIR DISKUS® ADVAIR HFA® DULERA® SYMBICORT®		BREO ELLIPTA®
Toxicology Agents					
	Antidotes NEW				
		Opiate Antagonists NEW			
			EVZIO ® NEW NALOXONE NEW	* Injectable can be used intranasally with nasal atomizer	
	Substance Abuse Agents				
		Mixed Opiate Agonists/Antagonists			
			BUNAVAIL® SUBOXONE®	PA Required for class	BUPRENORPHINE/NALOXONE ZUBSOLV®

2. Standard Preferred Drug List Exception Criteria
Drugs that have a “non-preferred” status are a covered benefit for recipients if they meet the coverage criteria.
a. Coverage and Limitations
1. Allergy to all preferred medications within the same class;
2. Contraindication to or drug-to-drug interaction with all preferred medications within the same class;
3. History of unacceptable/toxic side effects to all preferred medications within the same class;
4. Therapeutic failure of two preferred medications within the same class.
5. If there are not two preferred medications within the same class therapeutic failure only needs to occur on the one preferred medication;
6. An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or a FDA-approved indication;
7. Antidepressant Medication – Continuity of Care.
Recipients discharged from acute mental health facilities on a nonpreferred antidepressant will be allowed to continue on that drug for up to 90 days following discharge. After 90 days, the recipient must meet one of the above five (5) PDL Exception Criteria; or
8. For atypical or typical antipsychotic, anticonvulsant and antidiabetic medications the recipient demonstrated therapeutic failure on one preferred agent.
b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms/aspx.

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective through June 30, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

(d) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty; and

(d) The criteria for prescribing an atypical or typical antipsychotic medication, anticonvulsant medication or antidiabetic medication that is not on the list of preferred drugs to a patient who experiences a therapeutic failure while taking a prescription drug that is on the list of preferred prescription drugs.

4. Except as otherwise provided in this subsection, the list of preferred prescription drugs established pursuant to subsection 1 must include, without limitation, every therapeutic prescription drug that is classified as an anticonvulsant medication or antidiabetic medication that was covered by the Medicaid program on June 30, 2010. If a therapeutic prescription drug that is included on the list of preferred prescription drugs pursuant to this subsection is prescribed for a clinical indication other than the indication for which it was approved as of June 30, 2010, the Committee shall review the new clinical indication for that drug pursuant to the provisions of subsection 5.

5. The regulations adopted pursuant to this section must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

6. The Medicaid program must make available without prior authorization atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness, anticonvulsant medications and antidiabetic medications for a patient who is receiving services pursuant to Medicaid if the patient:

(a) Was prescribed the prescription drug on or before June 30, 2010, and takes the prescription drug continuously, as prescribed, on and after that date;

(b) Maintains continuous eligibility for Medicaid; and

(c) Complies with all other requirements of this section and any regulations adopted pursuant thereto.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985)

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective July 1, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness of a patient who is receiving services pursuant to Medicaid;

(b) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

(g) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs; and

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty.

4. The regulations must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985, effective July 1, 2015)

Definition of "Therapeutic Alternative"

A "Therapeutic Alternative" is defined by the AMA as: "Drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses."

BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
Carson City, Nevada 89701
www.dhcfp.nv.gov

RICHARD WHITLEY
Director

LAURIE SQUARTSOFF
Administrator

Nevada Medicaid
Pharmacy and Therapeutics
Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee held a public meeting on **September 24, 2015**, beginning at **1:00 p.m.** at the following location:

JW Marriott – Las Vegas
Marbella Room
221 N Rampart Blvd
Las Vegas, NV 89145
702-869-7777

Board Members Present:
Mark Decerbo, Pharm.D.; Shamim Nagy, MD; Weldon Havins, MD; Joseph Adashek, MD; Adam Zold, Pharm.D. Evelyn Chu, Pharm.D.

Board Members Absent:
David Fluitt, RPh; Bill Evans, MD; Mike Hautekeet, RPh

Others Present:
DHCFP:
Coleen Lawrence, Chief, Program Services; Mary Griffith, RN, Pharmacy Services Specialist; Shannon Richards, Deputy Attorney General;

HPES:
Beth Slamowitz, Pharm.D.

OptumRx:
Carl Jeffery, Pharm.D., Kevin Whittington, RPh, Robert Earnest, Pharm.D, JD

Others:
Cynthia Patterson, BioDelivery; Jennifer Lauper, BMS; Lee Stout, Chiesi; Nick Casale, Indivior; Mark Edwards, Mylan; Elizabeth Ariano, Indivior; Melissa Walsh, Novartis; Rupa Shah, Purdue; Sergio

Gonzalez, Takeda; Amy Everitt, Sunovion; Robert Jaramillo, Sunovion; Phil Walsh, Sunovian; Jon Bloomfiled, Jazz; James McAdams, Orexo; Mike Strong, Novo Noardisk; Bret Ferguson, Pfizer; Rob Bigham, Shire; Frank Ragone, Genzyme; Mark Schwartz, GSK; Lauren Nelson, Genzyme; Tyson Park; Teva; Deron Grothe, Teva; Kara Sperandeo, Astra Zenaca; Efrain Alton, Merck; Tom O'Connor, Novartis; Markus Laughlin, BI; Lovell Robinson, Abbvie; M. Kelly Bafield, NNI; Julie McDavitt, BI; Samantha Muir, Otsuka; Krystal Joy, Otsuka; Sarica Cohen, Mylan; Todd Schuidec, BIPI; Don Nopper, United Therapeutics; Kirk Lane, United Therapeutics; Corinne Copeland, Eisai; Soheyla Azizi, Eisai; Charissa Anne, J&J; Marykay Queener, J&J; James Kutasky, Gilead; Roy Palmer, Pfizer; David Post, Actelion; Sal Lofaso, Horizon; Gina Sota, Alkermes; Yumi Yamamoto, Alkermes; Ben Skoog, Biogen; Dana Conell, NNF; Sandy Sierawsky, Pfizer; Theresa Benkert, Eisai; Shane Hall, Purdue; Susan Lawrence, Amgen; James Tate, IHC; Chi Kohlhoff, Kadman; Kim Jacoby, Lundbeck

I. CALL TO ORDER AND ROLL CALL

Meeting called to order at 1:04 PM

Coleen Lawrence – DHCFP
Mary Griffith – DHCFP
Beth Slamowitz – HPES
Mark Decerbo
Adam Zold
Evelyn Chu
Joseph Adashek
Weldon Havins
Shamim Nagy, Chairperson
Shannon Richards – DAG
Kevin Whittington – OptumRx
Carl Jeffery – OptumRx

II. PUBLIC COMMENT

Shamim Nagy, Chairperson: Public comment?

None.

III. **FOR POSSIBLE ACTION**: Review and Approval of the March 26, 2015 Meeting Minutes

Shamim Nagy, Chairperson: We need a motion to approve the minutes from the last meeting.
Joseph Adashek: I move to approve.
Weldon Havins: Second.
Voting: Aye's across the board – motion carries.

IV. STATUS UPDATE BY DHCFP

Coleen Lawrence: We have a couple updates from our last legislative session. With SB459, Naloxone is going to continuously be a preferred agent, it moved automatically October 1, 2015. It did not require any action by the Committee members due to statutory requirements. Also, we have a new interim administrator, Ms. Marta Jensen. She was previously with the Division as Compliance Chief. Effective October 1, 2015, ICD-10 is here. We count on field reps to assist us. The pharmacies will be impacted with lots of coding that allow claims to bypass PA when the correct ICD code is submitted. With Nevada Medicaid and Nevada Checkup, we will not be running parallel systems, we will not be accepting ICD-9 and ICD-10. Please work with your field reps to help educate prescribers. Also coming November 1, 2015, we are moving to NADAC, an actual acquisition cost. With the NADAC, the dispensing fee will be increasing to one fee across the board to $10 and some change. CMS required the dispensing fee survey.

We have some ground rules to run an effective and efficient meeting. The NRS requires that Nevada Medicaid reviews the preferred drug list every year. There are some other states don't review their PDL on a regular basis. We don't wait until the year review to review the classes. A class may not be reviewed if there are not any changes in that class. We break this down to two sections, the drugs that we are going to review today, the Second. section is one motion that we say there are not any changes to these drug classes. We recommend to the Committee to approve classes in one motion. The first section is broken down further to new drugs to be reviewed, and then classes that are requested to be reviewed by Committee members or the community. Please keep your speaking to 5 minutes per entity. We are very transparent in our recommendations, they will be listed on the screen before public comment is opened. Testimony should be limited to new information only. The P&T Committee role is to decide preferred and non-preferred only, the clinical criteria is decided by the DUR board. Please do not discuss cost. This Committee is prohibited of listening or deliberating products related to cost.

Shamim Nagy, Chairperson: Any comments from the public?

None.

V. ANNUAL REVIEW - NEW DRUG CLASSES

A. ANTI-EMETIC – MISCELLANEOUS

Shamim Nagy, Chairperson: Public Comment?

None.

Carl Jeffery: There are two new products in this antiemetic, miscellaneous class. The more popular one is Diclegis. This is indicated for treatment of nausea in pregnancy. The other product is Emend, which does not fall into any other class. It is indicated for chemotherapy induced nausea. Optum recommends these two products be considered clinically and therapeutically equivalent.

Joseph Adashek: Move.
Weldon Havins: Second.
Vote: Ayes across the board.

Carl Jeffery: OptumRx recommends these two agents be considered preferred.

Joseph Adashek: Move.
Adam Zold: Second.
Votes: Ayes across the board.

B. PSYCHOSTIMULANTS - NARCOLEPSY AGENTS

Shamim Nagy, Chairperson: Public comment?

None.

Carl Jeffery: This is a new class, they are currently in the ADD/ADHD class. We don't feel this is quite appropriate. It makes sense to break them out to their own class. The DUR Board did just update the clinical criteria, including the Xyrem which is really only used for cataplexy and narcolepsy. The others have similar indications. The clinical guidelines recommend modafinil as first line, but the guidelines have not been updated since Nuvigil was released. Optum recommends these products be considered clinically and therapeutically equivalent.

Mark Decerbo: Thank you for breaking the class out, we have seen some products being shoehorned into classes that may not fit.

Adam Zold: I move these be considered clinically and therapeutically equivalent.
Mark Decerbo: Second.
Votes: Ayes across the board.

Carl Jeffery: Optum recommends brand Provigil preferred, the others non-preferred

Adam Zold: Motion.
Chu: Second.
Votes: Ayes across the board, the motion carries.

C. LONG-ACTING ABUSE DETERRENT OPIOIDS

Carl Jeffery: A quick overview of the class before the public comment for the long-acting abuse deterrent opioids. We brought this up at the request of the Committee at the last meeting. This is an option of the Committee to add this as a new class. We can consider pulling out these products into their own class, it is fully up to the Committee.

Weldon Havins: By the way, the bill that was proposed did not pass, the legislature did not pass it. I don't know if that will make a difference if you feel this should be a separate category.

Shamim Nagy, Chairperson: Public Comment?

Rupa Shaw, clinical pharmacist and clinical liaison with Purdue: Provided an overview of abuse deterrent opioids. The FDA is in support of the development of opioids with abuse deterrent properties. The FDA released guidance with suggested studies, how they will be evaluated and what labeling claims will be included. Section 9.2 is where the data will be listed. In Section 9.2 in the PI, each product lists how it will deter abuse. Some opiate products may have some abuse deterrent properties, but not all have been recognized by the FDA. Three products are available on the market now. OxyContin and Hysingla have been approved for labeling with abuse deterrent properties. Purdue is pursuing epidemiological studies. Please consider products recognized by the FDA.

Roy Palma, Pfizer: The previous speaker did a great job covering the FDA's stance. Studies are robust to get the labeling claims. Embeda has done abuse studies for the FDA labeling. We encourage making this a separate class. These products will have a significant impact in the treatment of pain management.

Carl Jeffery: There are three letters handed out from physicians in the area talking about abuse deterrent opioids. The FDA has changed how they evaluate the abuse deterrent opioids. There are just Embeda, OxyContin and Hysingla that have the FDA abuse deterrent labeling. There are some others in the works, they claim they have abuse deterrent properties, but have not been given the ok from the FDA. Most have a physical barrier, the Embeda is little different in that it is combined with naloxone. We have some options, we can combine with the current class of opioids, or make it its own class or not do anything. Within this class, we consider these clinically and therapeutically equivalent.

Mark Decerbo: This makes sense to separate these out. I have no problem separating out the abuse deterrent agents. My concern is what are our criteria in how we determine what agents are in this class, with two of the agents working toward the labeling, but not having it yet. I don't want to box us in going forward. The oxymorphone and hydromorphone not having the label yet, is there a reason we should include or exclude these two from the new class?

Adam Zold: I agree it should be a separate class and it should be limited to products approved by the FDA.

Evelyn Chu: I agree as well, but they all have abuse potential. Do we wait until the FDA approves all of them? Do we know when they will approve these?

Carl Jeffery: We don't know the exact timeline of when these will be approved. For example, Zohydro told me they have the properties, but they don't have the label ok from the FDA. We struggle with this class just for this reason as Dr. Zold said, should we limit to FDA approved products?

Coleen Lawrence: When we are looking at therapeutic alternative, we are not looking at if they are FDA approved, based on our definition of FDA approved indication to be in the therapeutic class.

Evelyn Chu: So what does this mean for a patient population, when they come in with prescriptions?

Carl Jeffery: All of these are nonpreferred right now, so they will have to try one of our two preferred agents, long-acting morphine or fentanyl patches before getting one of the abuse deterrent agents. Adding this class as we have proposed, they would have access to Embeda first line without having to step through fentanyl or morphine first.

Evelyn Chu: Then I agree it should be its own class.

Shamim Nagy, Chairperson: Then it sounds like it should be its own class. We are in agreement.

Coleen Lawrence: So then we will put them in their own bucket.

Weldon Havins: Could some of these be in two different classes? In both long-acting opioids and abuse deterrent?

Carl Jeffery: They could be if between meetings until they can be reviewed.

Mark Decerbo: I hate having to rely on the FDA as the final arbiter, but if there is another product that was sub-par that did not receive the FDA label, but they stated it because was abuse deterrent, I would hate to be bound to include that product in this class. I think there is some value in the FDA labeling. It is hard to see doing this without the FDA labeling.

Carl Jeffery: So I hear that we would just list the FDA label products, Embeda, OxyContin and Hysingla would be considered clinically and therapeutically equivalent.

Mark Decerbo: Yes, I would support that.

Carl Jeffery: Then to complete the thought, Exalgo and Opana would go back to the regular long-acting opioid class.

Mark Decerbo: Unless we can think of another mechanism or until they receive FDA labeling.

Coleen Lawrence: So you would utilize the FDA label indication?

Mark Decerbo: Yes,

Carl Jeffery: So the motion would be consider Embed, Hysingla and OxyContin clinically and therapeutically equivalent.

Mark Decerbo: Correct.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Embeda would be preferred and OxyContin and Hysingla non-preferred.

Coleen Lawrence: Dr. Jeffery, sorry, you cannot make the motion, it must come from a Committee member.

Mark Decerbo: I move that we strike the oxymorphone and hydromorphone products from the right side as non-preferred.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Coleen Lawrence: So we need a therapeutic equivalent motion, and that is based on the Committee that the long acting opioids is based on FDA indication.

Mark Decerbo: I move that the Embeda, Hysingla and OxyContin be considered clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

D. ANTILIPEMICS – OMEGA-3 FATTY ACIDS

Shamim Nagy, Chairperson: Next class, antilipedemic. Public comment?
None.

Carl Jeffery: We have a new class we are proposing, the omega 3 fatty acids. They have been around for a long time. They lower the triglycerides. There are two brand products and one generic. Optum considers these clinically and therapeutically equivalent.

Weldon Havins: do we need a motion to make this new category?

Shamim Nagy, Chairperson: No, I need a motion for clinical and therapeutic equivalency.

Adam Zold: Motion.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends Lovaza and Vascepa be considered preferred and the generic Omega-3 acid and Omtryg be considered non-preferred.

Shamim Nagy, Chairperson: Any comments?

Adam Zold: Motion to accept recommendation.

Mark Decerbo: Second.

Voting: Aye's across the board – motion carries.

E. RESPIRATORY LONG-ACTING BETA AGONISTS/LONG-ACTING ANTIMUSCARINIC COMBINATIONS

Shamim Nagy, Chairperson: Respiratory Long-acting antimuscarinics/long-acting beta agonists combination. Any public comment?

JM, Pharm.D. with BI: We make Stiolto, a combination of Spiriva and Striverdi. I promise not to go into the safety and efficacy of the drug, but I wanted to show the Committee the delivery device (hands out sample inhalers). The delivery system is Respimat, it is a hand-held pocket device that used mechanical energy, there is a spring in here, to deliver a slow moving aerosol cloud of medication. The effort needed is minimal, the medication is delivered independent of inspiratory capacity. There is a simple pneumonic, TOP, turn, open, press. Turn the base, open the lid, press the button. Are there any questions?

Shamim Nagy, Chairperson: Any question or comments?

None.

Carl Jeffery: This is a proposed new class, the long-acting antimuscarinic and long-acting beta agonist combinations. Anoro has been out for a little, and it was shoehorned into another class. Both are indicated for maintenance of COPD. Stiolta was approved on these studies, about 5,000 patients, showing good results. We have an alternative of having people use two agents that would accomplish the same result, and the screen shows the other products available. Optum recommends these be considered clinically and therapeutically equivalent.

Weldon Havins: Moved these be considered clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: With this being a new class, Optum recommends both products be considered preferred.

Weldon Havins: Moves to accept recommendation.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

VI. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES

A. NEUROPATHIC PAIN AGENTS

Shamim Nagy, Chairperson: Neuropathic agents, any public comment?

None.

Carl Jeffery: We currently have two classes with some overlap, the Neuropathic agents and the Fibromyalgia agents. The only one that sticks out a little is Savella, it is only indicated for fibromyalgia whereas the others go back and forth. We want to combine these two classes. The reason this is coming up is the generic Cymbalta has been out for some time and the other agents have been out for a long time. Optum recommends these be considered clinically and therapeutically equivalent with the footnote that Savella is for fibromyalgia only.

Shamim Nagy, Chairperson: Comments?

None, we need a motion.

Adam Zold: Moves these products be considered clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: By combining these, we keep everything as before except switch the brand Cymbalta to non-preferred and duloxetine to preferred.

Mark Decerbo: This is somewhat off the topic, but is it up to the DUR Board to update the ICD-9 codes?

Coleen Lawrence: The state is working on this to get it taken care of.

Evelyn Chu: Motion to accept the recommendation.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

B. FIBROMYALGIA AGENTS

C. OPIATE AGONISTS

Shamim Nagy, Chairperson: Next topic is Long-acting opioid agonists. Public comment?

None.

Carl Jeffery: This class was included because we were altering the abuse deterrent opioids. To these slides we will add Opana ER and Exalgo to the list. Optum recommends these be considered clinically and therapeutically equivalent with the addition of Opana ER and Exalgo.

Mark Decerbo: Move that these be considered clinically and therapeutically equivalent with the addition of the Opana and Exalgo.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: This slide will need some updating with the addition of Opana ER and Exalgo to non-preferred, keeping morphine sulfate extended release and fentanyl patch as preferred.

Weldon Havins: Move to accept the recommendation.

Joseph Adashek: Second.

Voting: Aye's across the board – motion carries..

Coleen Lawrence: We should have asked before, but are there any practicing providers that would like to speak so they can get back to their practice?

JT: Dr. James Tate, I practice here in town. This is the issue that all prescribers face. Most of these will not fill, the reason is, and insurance companies won't pay for it, including Medicaid. I don't know if you want people to become addicted, because these are abuse deterrent. In two years, we are going to have to pay for it, because drug companies and big pharma is moving away from immediate release. Because of the blood brain barrier. If you take an IR opioid, it crosses the blood brain barrier. If you have one that doesn't cross the blood brain barrier or does so slowly, it loses its street value. Remember when it was called "Hillbilly Heroin"? It's not called that anymore because it is an abuse deterrent medication. Because you can't chop it up, snort it or inject it, so it loses its street value. But nobody wants to pay for it. But a month's supply is $500. What is your rationale for not paying for it, do you want people to become addicted. You need to think about why we are doing it, or why are we not. All I want to do is prescribe medications for my patients without putting them in jeopardy. So I ask you to consider what medications you put on the list. Frankly, it is not my job as a practicing physician to figure out who is doing what. So fix it, thank you.

D. MULTIPLE SCLEROSIS AGENTS - INJECTABLE

Ben Stoag, Pharm.D. with Biogen. I want to talk about Plegridy. Biogen has four drugs for MS, I'm not sure where Tecfidera is since it will be reviewed next, so I can present both now. Avonex, is an IM once weekly injection, Pegridy is a SQ every 14 day injection, Tysabri is Q 4 week IV infusion and Tecfidera is an oral medication. MS is a disease where the body's own immune system is attacking itself. The disease depends on the number of plagues. Most patients will need some assistance in walking within 10 to 20 years. The goal is to slow the progression of the disease. There are three main points in clinical trials. Annualized relapse rate, reduction of disability and reduction of MRI lesions. Plegridy, approved at the end of 2014, SQ pegylated interferon. Developed to reduce the

number of injections, this is 26 injections per year, vs. others with much more. Plegridy shows 36% reduction in annualized relapse rate. It has a 30% reduction and 12 week affirmed disability at one year. And then it is significant for MRI endpoints. The safety profile is similar to other interferon's. Plegridy offers once every 14 day injection, side effects are similar and it has demonstrated efficacy. For Tecfidera, 155,000 patients have been on Tecfidera. Tecfidera has been shown safe and effective as outlined (Study information outlined with safety information).

Shamim Nagy, Chairperson: Thank you. No more comments.

Carl Jeffery: A couple new drugs added. The biosimilars are coming out, Glatopa is the generic version of Copaxone. We heard about Plegridy. We have the class broken down to relapsing remitting multiple sclerosis. Lemtrada has a two phase study. This one has been trying to come out for several years. It has a unique delivery system, given once per year. It sounds convenient and the efficacy is good, but the adverse effects are alittle scary. The injection site reaction is almost everyone. And then two deaths reported during the study. I'm not sure this one should be first-line. We heard about Plegridy, good efficacy and safety profile and dosed conveniently. For the class, we would like to consider these clinically and therapeutically equivalent.

Evelyn Chu: Motion the class be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Vote: Ayes across the board, motion carries.

Carl Jeffery: Optum recommends we keep the preferred side the same with Avonex, Betaseron, Copaxone, Extavia, Rebif and Tysabri be preferred, leaving Glatopa, Lemtrada and Plegridy as non-preferred.

Mark Decerbo: I move we accept the preferred and non-preferred agents as presented.

Joseph Adashek: Second.

Votes: Ayes across the board, motion carries.

E. MULTIPLE SCLEROSIS AGENTS - ORAL

Shamim Nagy, Chairperson: Oral Agents for MS, any public comment?

None.

Carl Jeffery: This is another carry over from the injectable agents. The fingolimod has some recent cases of cardiac related death. Teriflunomide has two black box warnings regarding hepatotoxicity and the risk of teratogenicity. Dimethyl fumarate, limited post-marketing data shows it likely has the mildest side effects. Optum recommends these three products be considered clinically and therapeutically equivalent.

Mark Decerbo: I move these three agents be considered clinically and therapeutically equivalent.

Adam Zold: Second.

Votes: Ayes. Motion carries.

Carl Jeffery: Optum recommends moving Gilenya to non-preferred and keeping Aubagio and Tecfidera preferred.

Mark Decerbo: What was behind the moving of Gilenya to non-preferred, and what are the ramifications for patients currently stabilized on this medication?

Carl Jeffery: We have the option to grandfather recipients already on this medication when removing agents. The utilization was relatively low. We can grandfather those recipients that are currently on it. The reason behind it is for the interest of the State.

Mark Decerbo: I would support the move as long as people can be grandfathered in, especially with Gilenya that can cause some symptoms with the flares and other issues with withdrawal. I move to accept as presented with the caveat the people currently on Gilenya be grandfathered.

Weldon Havins: Second.

Votes: Ayes . Motion carries.

F. VASODILATORS – ORAL

Shamim Nagy, Chairperson: Vasodilators – Oral. Public comment?

David Post, PharmD. with Activia Pharmaceuticals. I would like to talk about the Opsumit. PAH is a rapidly progressing cardio-pulminary disease that ultimately leads to death. Opsumit is indicated for PAH to delay disease progression, demonstrating a 45% risk reduction vs. placebo. Opsumit reduces risk of hospitalization. The effects of Opsumit was demonstrated in a study (outlines details of study). In summary, the FDA approval is based on the largest placebo controlled trial, it reduces hospitalizations and improves outcomes. For this reason I would like you to consider adding Opsumit to the preferred drug list.

Kirk Lane, MSL United Therapeutics. Provided an overview of PAH disease and an overview of available therapies. Combinations from different classes are often used today. Adcirca, once a day approved for group one for PAH. Adcirca, like other oral PAH agents, may be considered first-line therapy, or as an add-on therapy with other therapies. Adcirca clinical study and adverse events presented. In summary, Adcirca provides once day therapy of PDE-5 for PAH. I ask you consider adding Adcirca to the PDL.

Carl Jeffery: There are basically four different medications in this class. We break out the inhaled forms, and they are not included in this review. Adcirca, which is the same molecule as Cialis, and we want to make sure we have one, and the sildenafil covers. The guidelines talk about recommendations, start with a PDE-5 or endothelin inhibitor and then work your way down. Optum recommends the oral agents in this class be considered clinically and therapeutically equivalent.

Adam Zold: I move these be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends to move Adcirca to non-preferred to move people to sildenafil, and then add Orenitram to add another option.

Evelyn Chu: I move to accept the list as presented.

Joseph Adashek: Second.

Voting: Aye's across the board – motion carries.

G. PHOSPHATE BINDING AGENTS

Shamim Nagy, Chairperson: Phosphate binding agents, public comment?

None.

Carl Jeffery: There is a new agent in this class, Auryxia. It is a little different because it is ferric Citrate. They all have similar indications to reduce phosphate in renal disease. Ferric citrate has been shown safe and effective in two clinical trials, placebo controlled. What I thought was interesting, because it is a ferric compound, it didn't decrease the iron levels in the body as much and required less erythropoietin. I'm not sure if this is significant. All the other ones are the same. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I motion they are clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends the new agent Auryxia be considered non-preferred and the rest of the class remain the same.

Adam Zold: I move we accept the recommendation.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

H. INCRETIN MIMETICS

Shamim Nagy, Chairperson: diabetic agents, public comment?

None.

Carl Jeffery: We brought this up because we thought there were going to be some changes, but that didn't pan out. We also need to get these new agents to the DUR board. These medications have been reviewed before, but we are not recommending any changes at this time. Optum recommends these be considered clinically and therapeutically equivalent.

Evelyn Chu: I move these be considered clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends keeping everything the same, Bydureon, Byetta and Victoza as preferred and Tanzeum and Trulicity as non-preferred.

Joseph Adashek: move to accept recommendations

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

I. SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

Joseph Adashek: In the future, could you list the generic name underneath these. In the studies they publish the generic names, that would be great.

Carl Jeffery: Sure, no problem.

Shamim Nagy, Chairperson: SGLT-2 class. Public comment?

CD with BI, We make Jardiance, Glyxambi and Synjardy. Jardiance is an SGLT-2 that you have heard about before. Synjardy is a combination with Jardiance and metformin. The one I want to talk about today is Glyxambi. It is a first-in-class medication that inhibits both the SGLT-2 with the combination of a DPP-4, which is linagliptin or Tradjenta. It is not recommended for type 1 diabetes or those with ketoacidosis. [Study information presented]. I ask the Committee to consider adding Glyxambi as preferred. And since we are the makers of Jardiance and the Synjardy, the SGLT2 class has been in the press a lot lately, I am here for any other questions.

Carl Jeffery: We just heard about some of these new combination products. I won't go over them again. This slide shows the breakdown of what each agent is. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I move these are clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum's recommendation is to move Invokamet to preferred and Xigduo XR to preferred and the two new products Glyxambi and Synjardy non-preferred.

Evelyn Chu: I make a motion that we accept the recommendation.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

J. ANTI-MIGRAINE AGENTS - SEROTONIN-RECEPTOR AGONISTS

Shamim Nagy, Chairperson: Antimigraine agents, public comment?

Carl Jeffery: What brought this up is that we have a new drug, Zecuity transdermal. A novel treatment option and delivery mechanism. It moves the sumatriptan transdermally. It has been shown to decrease the symptoms, it doesn't seem to have anything better than the other agents. It sounds like a fancy new toy, but the other products on the list we have all covered before. Optum recommends these be considered clinically and therapeutically equivalent.

Shamim Nagy, Chairperson: Is the pump included in the package?

Carl Jeffery: It's not a pump, it has a battery that…

Rob Earnest: It is on the molecular charge to move the medication. It is only available through specialty pharmacy. It really it is being used for patients who experience nausea and difficulty taking the tablet formulation. It is not being considered first-line therapy.

Mark Decerbo: I move the listed agents be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends moving the Zomig ZMT non-preferred and Rizatriptan ODT generic preferred and the new Zecuity non-preferred.

Adam Zold: I move we accept the class as presented.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

K. ADHD AGENTS

Shamim Nagy, Chairperson: ADHD agents, public comment?

None.

Carl Jeffery: No new agents in this class, we are just shuffling things around. Displayed is a breakdown of the agents in the class. Xyrem is on this list, but we included that I the narcolepsy agents. Optum recommends these to be considered clinically and therapeutically equivalent.

Adam Zold: I move these be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: A couple products to shuffle around. A few meetings ago, Adderall XR was moved to non-preferred., we want to move that back so the brand Adderall XR is preferred and the generic amphetamine XR be non-preferred. The Procentra is the brand-name for the dextroamphetamine solution, we want to make the brand preferred and the generic non-preferred.

Adam Zold: I move we accept the recommendations.

Mark Decerbo: Second.

Voting: Aye's across the board – motion carries.

L. RESPIRATORY CORTICOSTEROIDS

Shamim Nagy, Chairperson: Respiratory Corticosteroids, public comment?

None.

Carl Jeffery: Last time we had this class, Aerospan HFA had just been reintroduced and now the Pulmicort Respules have a generic. This slide shows a quick breakdown of the class, they all have the same indication. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I move these be considered clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum proposed the Aerospan HFA be considered preferred and the brand Pulmicort Respules be non-preferred, this still leaves the generic version budesonide nebs as preferred.

Adam Zold: Move to accept the recommendations.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

M. SUBSTANCE ABUSE AGENTS - MIXED OPIATE AGONISTS/ANTAGONISTS

Shamim Nagy, Chairperson: Substance abuse agents – mixed opiate agonists/antagonists. Public comment?

None.

Carl Jeffery: Another class we just discussed not too long ago. I think it was a tough decision from last time. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I move these be considered clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends adding Zubsolv to the preferred list.

Evelyn Chu: Motion to accept the proposed preferred list.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

VII. ANNUAL REVIEW - ESTABLISHED DRUG CLASSES BEING REVIEWED DUE TO THE RELEASE OF NEW DRUGS.

A. ANTICOAGULANTS - ORAL

Shamim Nagy, Chairperson: Anticoagulants – Oral. Public comment?

None.

Carl Jeffery: Savaysa is a new product in this class. It is similar to the other agents in this class. It has fewer indications as the others. There are some decent studies, showing non-inferior to warfarin, no difference an annualized bleeding. Outcomes were similar to warfarin. Something a little unique, it actually has a black-box warning if your creatnine clearance is too high. It shouldn't be used if you

are over 95. Just a little unique. It increases risk of ischemic stroke. Optum recommends these be considered clinically and therapeutically equivalent.

Evelyn Chu: I make a motion that these agents be considered clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Since we have other products on the market already with additional indications, Optum recommends Savaysa be considered non-preferred.

Mark Decerbo: I move to accept the recommendation of the preferred list as presented.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

B. INSULINS (VIALS AND PENS)

Shamim Nagy, Chairperson: Insulins, public comment?

None.

Carl Jeffery: there are three new agents to this class. We haven't seen anything new here for a while. Afrezza is the new inhaled insulin and then a couple new strengths of existing insulins. This slide shows the break out of the fast acting vs. long acting. These are the same agents we have seen for years, just a little different strength. Afrezza to be shown to be non-inferior to insulin for A1c lowering, but it will be a pretty unique population it is intended for. It did not cause as much hypoglycemia and weight gain for Type 1. When they looked at it for Type 2 diabetics, it wasn't much better than placebo. For the purpose of the class review, Optum recommends these products be considered clinically and therapeutically equivalent.

Joseph Adashek: I move we accept the recommendations.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends the new agents, Afrezza, Humalog U200 and Toujeo Solo 300 be considered non-preferred and the remaining as preferred.

Adam Zold: I move we accept the recommendations as presented.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

C. ANXIOLYTICS, SEDATIVES, AND HYPNOTICS

Shamim Nagy, Chairperson: Anxiolytics, sedatives and hypnotics, public comment?

None.

Carl Jeffery: There are a few new agents in the class, Belsomra, eszopiclone, which is the generic for Lunesta and another new agent, Hetlioz. These were recently discussed by the DUR Board. Hetlioz is pretty specific to who it is intended to treat. It was studied in people completely blind, to keep their circadian rhythm. It is indicated for the non-24 hour sleep/wake cycle. The DUR Board put some criteria on this medication. Belsomra, it had good hopes for being a good drug, but it is working the same as some of the others that are already on the market. I'm not aware of any benefit of this one over the others. Optum makes the recommendation these be considered clinically and therapeutically equivalent.

Shamim Nagy, Chairperson: Do we have a motion?

Mark Decerbo: Move to accept the medications as shown as clinically and therapeutically equivalent.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends the new agents, Belsomra, eszopiclone and Hetlioz be considered as non-preferred and the rest of the class remain the same.

Evelyn Chu: I make the motion we accept the list as presented.

Joseph Adashek: Second.

Voting: Aye's across the board – motion carries.

D. BETA-BLOCKERS

Shamim Nagy, Chairperson: Beta blockers. Public comment?

Carl Jeffery: We have a new agent in this class, Sotylize, a liquid form of sotalol. When I first saw this I thought it would be for pediatric use, but looking at the package insert, it is not studied in kids, it hasn't been shown safe and effective in children. I'm not sure who the target is for this medication. I don't want to see this mis-used in the nursing homes for the ease of the nursing staff. It is the same as the sotalol that has been available for a long time. Optum recommends these be considered clinically and therapeutically equivalent.

Adam Zold: I move these agents be considered clinically and therapeutically equivalent.

Mark Decerbo: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Without the indication for children, Optum recommends the Sotylize be considered non-preferred. The rest of the class remains the same.

Adam Zold: I move we accept the recommendation.

Joseph Adashek: Second.

Voting: Aye's across the board – motion carries.

E. TOPICAL ANTIFUNGALS (ONYCHOMYCOSIS)

Shamim Nagy, Chairperson: Topical Antifungal Agents, public comment? None.

Carl Jeffery: This is another class that was just discussed by the DUR Board. They updated the criteria to make it a step through for oral agents before moving to a topical agent. It has to do with the efficacy of the oral agents vs. the topical agents. We want to clarify the class name as well since we have topical agents and oral agents, but the class is to treat topical fungal infections. Onychomycosis is really what this class is intended for. We have the class broken out. I didn't include griseofulvin because it has some other indications, so it is not just for Onychomycosis. The studies show terbinafine and itraconazole as far superior to topical agents, and unless they have some contraindication, they should use these agents first. Some of the topical agents, removing the nail bed and using these topically, there is still a high recurrence rate. Jublia and Kerydin have a very low cure rates, about 17%. Optum recommends this class be considered clinically and therapeutically equivalent.

Adam Zold: I move we consider these clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: We haven't looked at this for a while, we have some new drugs, Jublia, Kerydin, Penlac and Itraconazole, which we realize can be used for other indications, would be considered non-preferred.

Adam Zold: When it says "PA required", does that include the entire class?

Carl Jeffery: Yes, the whole class requires PA. The DUR Board established that criteria.

Mark Decerbo: Move to accept the recommended preferred and non-preferred agents and include the aforementioned name change to the class to include topical fungal infection agents.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

F. ANTICONVULSANTS

Shamim Nagy, Chairperson: Anticonvulsants, public comment?

Roberta Hobneil, Sanovian – I want to share some updates for Aptiom. Covered indications. Only requires once daily dosing and requires only one week of titration. No blackbox warning as with some others. Over three months, reduced seizure frequency 30-40% compared to other classes. Even with many therapies available, there are still treatment challenges. Sunovian would like the Committee to provide access to Aptiom to provide more options to the community.

Carl Jeffery: We included this class because we thought there was going to be a new agent on the market, but it didn't come out in time to review it. We don't have any changes at this time. Optum recommends this class be considered clinically and therapeutically equivalent.

Adam Zold: I motion they clinically and therapeutically equivalent.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: There are not changes proposed so Optum recommends the class remain the same.

Joseph Adashek: I move we accept the recommendations.

Adam Zold: Second.

Voting: Aye's across the board – motion carries.

G. ANDROGENS

Shamim Nagy, Chairperson: Androgens, public comment?

None.

Carl Jeffery: Natesto is a new drug in this class, a nasal administration. Studies reviewed. It was effective, but given multiple times a day. Optum recommends this class be considered clinically and therapeutically equivalent.

Adam Zold: I move they be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends Natesto be considered non preferred.

Adam Zold: I move we accept the recommendation.

Evelyn Chu: Second.

Voting: Aye's across the board – motion carries.

H. DISEASE-MODIFYING ANTIRHEUMATIC AGENTS

Shamim Nagy, Chairperson: Antirheumatic agents, public comment?

Mellissa Walsh, Novartis, MSL for Cosentyx: First, this is under "Disease-Modifying Antirheumatic agents", but we do only have one indication for moderate to severe plaque psoriasis. Covered indications and trials. We request it be added as preferred, but it only has the one indication.

Chris Connor, BMS, Orencia: Covered the indications for Orencia. Data not covered well in the class review. One and two year trials of head-to-head vs. adalimumab in RA who failed methotrexate. The efficacy measures showed no significant measures, but what was missing, the investigators also looked at adverse events, injection site reactions were fewer in abatacept. While this may not be a significant effect, but they looked at discontinuations. Patients on abatacept had fewer discontinuations. In conclusion, consider tolerability along with efficacy and consider adding Orencia to the PDL.

Carl Jeffery: We were just discussing this class, it does get a little muddy. We have several agents in the review that do not fit into the class. We can bring this class back with a proposed class name that makes more sense. Talking about Cosentyx, it was shown to be safe and effective for patients with plaque psoriasis. For the purpose of the review today, Optum recommends the drugs in this class be considered clinically and therapeutically equivalent.

Evelyn Chu: I make a motion these agents be considered clinically and therapeutically equivalent.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

Carl Jeffery: Optum recommends making the new agent Cosentyx non-preferred. We will bring this up again at the next meeting.

Adam Zold: Motion to accept the recommendation and also to bring it up at the next meeting.

Weldon Havins: Second.

Voting: Aye's across the board – motion carries.

VIII. ANNUAL REVIEW – DRUG CLASSES WITHOUT PROPOSED CHANGES

Shamim Nagy, Chairperson: Drug classes without proposed changes

Carl Jeffery: We have several pages of the remaining classes that we do not propose any changes to. Optum recommends these drug classes remain without changes.

Coleen Lawrence: During the meeting, we received a comment in our offices regarding one of the classes for Hep C. The comment was not pertinent to P&T, so we will redirect to the DUR board, but did want to acknowledge the comment.

Shannon Richards: It isn't an action item, there is nothing to vote on.

A. TRAMADOL AND RELATED DRUGS
B. NON-SEDATING H1 BLOCKERS
C. INHALED AMINOGLYCOSIDES
D. ANTIVIRALS - ALPHA INTERFERONS
E. ANTI-HEPATITIS AGENTS – POLYMERASE INHIBITORS/COMBINATION PRODUCTS
F. ANTI-HEPATITIS AGENTS – PROTEASE INHIBITORS
G. ANTI-HEPATITIS AGENTS – RIBAVRINS
H. ANTI-HERPETIC AGENTS
I. INFLUENZA AGENTS
J. SECOND.-GENERATION CEPHALOSPORINS
K. THIRD-GENERATION CEPHALOSPORINS
L. MACROLIDES
M. QUINOLONES - 2ND GENERATION
N. QUINOLONES - 3RD GENERATION
O. SELF-INJECTABLE EPINEPHRINE
P. MULTIPLE SCLEROSIS AGENTS - SPECIFIC SYMPTOMATIC TREATMENT
Q. ANGIOTENSIN II RECEPTOR ANTAGONISTS
R. ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)
S. CALCIUM-CHANNEL BLOCKERS
T. DIRECT RENIN INHIBITORS
U. VASODILATORS – INHALED
V. BILE ACID SEQUESTRANTS
W. CHOLESTEROL ABSORPTION INHIBITORS
X. FIBRIC ACID DERIVATIVES
Y. HMG-COA REDUCTASE INHIBITORS (STATINS)
Z. NIACIN AGENTS
AA. ANTIPSORIATIC AGENTS - TOPICAL VITAMIN D ANALOGS
BB. TOPICAL ANALGESICS

CC. ACNE AGENTS: TOPICAL, BENZOYL PEROXIDE, ANTIBIOTICS AND COMBINATION PRODUCTS
DD. IMPETIGO AGENTS: TOPICAL
EE. TOPICAL ANTIVIRALS
FF. TOPICAL SCABICIDES
GG. IMMUNOMODULATORS: TOPICAL
HH. TOPICAL RETINOIDS
II. SEROTONIN-RECEPTOR ANTAGONISTS/COMBO
JJ. H2 BLOCKERS
KK. PROTON PUMP INHIBITORS (PPIS)
LL. GASTROINTESTINAL ANTIINFLAMMATORY AGENTS
MM. GASTROINTESTINAL ENZYMES
NN. 5-ALPHA REDUCTASE INHIBITORS
OO. ALPHA-BLOCKERS
PP. BLADDER ANTISPASMODICS
QQ. ANTICOAGULANTS – INJECTABLE
RR. COLONY STIMULATING FACTORS
SS. PLATELET INHIBITORS
TT. ALPHA-GLUCOSIDASE INHIBITORS/AMYLIN ANALOGS/MISC.
UU. BIGUANIDES
VV. DIPEPTIDYL PEPTIDASE-4 INHIBITORS
WW. MEGLITINIDES
XX. SULFONYLUREAS
YY. THIAZOLIDINEDIONES
ZZ. GROWTH HORMONE MODIFIERS
AAA. PROGESTINS FOR CACHEXIA
BBB. ANTIGOUT AGENTS
CCC. BISPHOSPHONATES
DDD. NASAL CALCITONINS
EEE. RESTLESS LEG SYNDROME AGENTS
FFF. SKELETAL MUSCLE RELAXANTS
GGG. ALZHEIMERS AGENTS
HHH. BARBITURATES
III. BENZODIAZEPINES
JJJ. HYDANTOINS
KKK. NON-ERGOT DOPAMINE AGONISTS
LLL. CARBONIC ANHYDRASE INHIBITORS/BETA-BLOCKERS
MMM. OPHTHALMIC PROSTAGLANDINS
NNN. OPHTHALMIC ANTIHISTAMINES
OOO. OPHTHALMIC MACROLIDES
PPP. OPHTHALMIC QUINOLONES
QQQ. OPHTHALMIC CORTICOSTEROIDS

RRR. OPHTHALMIC NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)
SSS. OTIC QUINOLONES
TTT. ANTIDEPRESSANTS – OTHER
UUU. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)
VVV. ATYPICAL ANTIPSYCHOTICS
WWW. NASAL ANTIHISTAMINES
XXX. LEUKOTRIENE RECEPTOR ANTAGONISTS
YYY. NASAL CORTICOSTEROIDS
ZZZ. PHOSPHODIESTERASE TYPE 4 INHIBITORS
AAAA. RESPIRATORY ANTIMUSCARINICS
BBBB. LONG-ACTING RESPIRATORY BETA-AGONIST
CCCC. SHORT-ACTING RESPIRATORY BETA-AGONIST
DDDD. RESPIRATORY CORTICOSTERIOD/LONG-ACTING BETA-AGONIST COMBINATIONS
EEEE. ANTIDOTES - OPIATE ANTAGONISTS

IX. REPORT BY CATAMARAN ON NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS

Shamim Nagy, Chairperson: New drugs to market.

Carl Jeffery: There are a lot of drugs in the pipeline in different phases. Many of them are biologics. A few to point out, a new morphine with abuse deterrent properties, an oral testosterone, another biosimilar to Remicade, and a monthly aripiprazole injection. Some patent expirations that will impact the PDL are Ivega, Travatan Z, Nasonex, Renagel, Androderm, Prempro, Epogen, and Neupogen.

IX. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME

A. December 3, 2015

Shamim Nagy, Chairperson: Next meeting, when and where?

Carl Jeffery: December 3, 2015 works well for everyone, 1:00 PM. Location to be determined. I like it at the JW Marriott if they will accommodate us.

X. PUBLIC COMMENT

Weldon Havins: Coleen, there was a bill to change the P&T, did that pass and how does it impact us?

Coleen Lawrence: Yes, that did pass, and it changed the composition requirements for the Committee. It was mathematically difficult to meet the requirements. It reduced the requirements and it is now more flexible. It doesn't impact the current members, but it does give us flexibility with the addition of new members. The quorum is still based on the total number of members that are on the board. We are still looking for new members.

Shamim Nagy, Chairperson: Public comment?

None.

Meeting is adjourned.

XI. ADJOURNMENT

Meeting adjourned at 3:15 PM

Therapeutic Class Overview
Serotonin and Norepinephrine Reuptake Inhibitors

Therapeutic Class

- **Overview/Summary:** The antidepressants are approved to treat a variety of mental disorders, including anxiety disorders, depressive disorders, eating disorders (bulimia nervosa) and premenstrual dysphoric disorder.[1-2] Anxiety disorders include agoraphobia, anxiety disorder due to another medical condition, generalized anxiety disorder, other specified anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder or social phobia, specific phobia, substance/medication induced anxiety disorder and unspecified anxiety disorder.[3-4] Some of the antidepressants are also approved to treat nonpsychiatric conditions, such as chronic musculoskeletal pain, diabetic peripheral neuropathy, fibromyalgia, insomnia, moderate to severe vasomotor symptoms associated with menopause, nocturnal enuresis and tobacco abuse.[1-2]

  The antidepressants are categorized into six different American Hospital Formulary Service (AHFS) subclasses, including monoamine oxidase inhibitors (MAOIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs) and miscellaneous agents. The agents which make up these subclasses differ with respect to their FDA-approved indications, mechanism of action, pharmacokinetics, adverse events and drug interactions.

  The SNRIs include desvenlafaxine, duloxetine, levomilnacipran, milnacipran and venlafaxine. These agents are believed to exert their effects through potentiating the serotonergic and noradrenergic activity in the central nervous system.[1-2,5-13] As a result, the SNRIs are used in the management of a variety of psychiatric disorders and all SNRIs are Food and Drug Administration (FDA)-approved for the treatment of major depressive disorder.[1-2,5-13] The venlafaxine extended-release capsules are also indicated for the treatment of generalized anxiety disorder and panic disorder. Both extended-release formulations are also indicated for social anxiety disorder. In addition to major depressive disorder and generalized anxiety disorder, duloxetine is approved for the management of various pain syndromes including chronic musculoskeletal pain, fibromyalgia and neuropathic pain associated with diabetic peripheral neuropathy.[1-2,11-13] Desvenlafaxine is the primary active metabolite of venlafaxine and is approved for once-daily dosing. Unlike venlafaxine, desvenlafaxine does not undergo metabolism through cytochrome P450 2D6, and is therefore safe to use with inhibitors of this isoenzyme.[1-2,5-7] The adverse event profiles appear to be similar between the two agents.

  Levomilnacipran is a new SNRI approved by the FDA for the treatment of major depressive disorder. Of note, levomilnacipran has shown to be twice as selective for norepinephrine as serotonin. In addition, levomilnacipran has demonstrated 10-fold higher selectivity for norepinephrine vs serotonin reuptake inhibition when compared to duloxetine, venlafaxine and desvenlafaxine.[14-16] It is important to understand that despite the higher selectivity for norepinephrine reuptake inhibition, levomilnacipran has comparable binding potency at the norepinephrine reuptake pump to duloxetine, and a lower binding potency at the serotonin reuptake pump than duloxetine.[17]

  Levomilnacipran is the more active enantiomer of milnacipran (Savella®), a medication FDA-approved for the treatment of fibromyalgia, a functionally impairing disease state. Levomilnacipran is approximately twice as potent for reuptake inhibition of norepinephrine compared to milnacipran, its racemic mixture.[3,10]

  Currently, venlafaxine is available generically in both immediate- and extended-release formulations, while desvenlafaxine and duloxetine are only available as branded products.[5,6]

Table 1. Current Medications Available in the Therapeutic Class[1-2,5-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Desvenlafaxine succinate (desvenlafaxine ER, Pristiq®, Khedezla®)	Treatment of major depressive disorder	Extended-release tablet: 50 mg 100 mg	-
Duloxetine (Cymbalta®)	Management of chronic musculoskeletal pain*; management of fibromyalgia; management of neuropathic pain associated with diabetic peripheral neuropathy; treatment of generalized anxiety disorder; treatment of major depressive disorder	Delayed-release capsule: 20 mg 30 mg 60 mg	-
Levomilnacipran (Fetzima®)	Treatment of major depressive disorder	Extended-release capsules: 20 mg 40 mg 80 mg 120 mg	-
Levomilnacipran (Fetzima®)	Management of fibromyalgia	Tablet: 12.5 mg 25 mg 50 mg 100 mg	-
Venlafaxine (Effexor®, Effexor XR®, venlafaxine ER)	Treatment of generalized anxiety disorder (extended-release capsule); treatment of major depressive disorder (extended-release capsule, extended-release tablet, tablet); treatment of panic disorder, with or without agoraphobia (extended-release capsule); treatment of social anxiety disorder (extended-release capsule)	Extended-release capsule (Effexor XR®): 37.5 mg 75 mg 150 mg Extended-release tablet: 37.5 mg 75 mg 150 mg 225 mg Tablet: 25 mg 37.5 mg 50 mg 75 mg 100 mg	a

ER, XR=extended-release
*This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the serotonin and norepinephrine reuptake - inhibitors are outlined in Table 4.[14-111]
- Desvenlafaxine, duloxetine and venlafaxine have been shown to be efficacious for the management of major depressive disorder, as measured by improvements in Hamilton Rating Scale for Depression-17 and Montgomery-Åsberg Depression Rating Scale scores, when compared to

placebo.[14-33,38] Duloxetine and venlafaxine have also been shown to be comparable to other antidepressants for the treatment of major depressive disorder.[41-72] A limited number of head-to-head trials comparing duloxetine and venlafaxine have yet to demonstrate that one of these agents is more efficacious than the other for the treatment of major depressive disorder.[42-43] Trials comparing desvenlafaxine to an active comparator have not been conducted.

- Results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[73-77] In addition, results from several clinical trials demonstrate the efficacy of duloxetine in reducing pain severity in adults with fibromyalgia when compared to placebo.[78-80]
- Duloxetine is consistently more effective compared to placebo in alleviating pain, improving functional outcomes and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey and Euro Quality of Life assessment scores. Commonly reported adverse events in patients receiving duloxetine include nausea, somnolence anorexia and dysuria.[97-103]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - National and international treatment guidelines for the treatment of depression state that selecting an agent should be driven by anticipated side effects, tolerability, patient preference, and quantity and quality of available clinical data, and that the effectiveness of antidepressants is usually comparable within and between medication classes.[112-115]
  - Guidelines also state that medications that can be considered first-line therapy for most patients include selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, or bupropion, while monoamine oxidase inhibitors (MAOIs) should be reserved for patients who are unresponsive to other available medications. These guidelines do not recommend one SSRI, SNRI or MAOI over another.[112-115]
  - Antidepressants are recommended as first-line treatment for GAD, with the following agents considered treatment options: SSRIs, SNRIs, and nonsedating tricyclic antidepressants (TCAs).[116-118]
  - For the treatment of neuropathic pain, the SNRIs are recommended as initial therapy along with TCAs and anticonvulsants.[124-128]
- Other Key Facts:
  - Duloxetine (Cymbalta®) is the only agent within the class that carries indications for treating fibromyalgia, chronic musculoskeletal pain and painful diabetic neuropathy.
  - All of the SNRI products have a Black Box Warning regarding the potential for antidepressants to increase suicidal thoughts in children and young adults.[1-12]

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Therapeutic Class Overview
Intranasal Histamine H_1-receptor Antagonists (Antihistamines)

- **Therapeutic Class Overview/Summary:** The intranasal histamine-1 receptor antagonist (H_1-antihistamines) products that are approved for the management of rhinitis include azelastine (Astelin®, Astepro®), olopatadine (Patanase®) and azelastine hydrochloride/fluticasone propionate (Dymista®).[1-4] Allergic rhinitis, often referred to as rhinosinusitis, is a condition characterized by episodes of sneezing, rhinorrhea, nasal congestion, itchy and watery eyes, nose and palate. Other common symptoms may include cough, postnasal drip, and fatigue.[5] Allergic rhinitis is also referred to in terms of the cyclical or persistent nature of symptoms. Seasonal allergic rhinitis is that which occurs at a particular time of the year; whereas, perennial allergic rhinitis describes symptoms that are present year round. Mast cell activation, histamine release, prostaglandin and leukotrienes propagation, along with other cytokine mediators (e.g., platelet activating factor, tumor necrosis factor, transforming growth factor beta, eosinophils, etc.) are known to play a direct role in the disease pathology and symptomatology.[6] Allergic rhinitis may be classified by its intermittent or persistent pattern and by severity (mild or moderate to severe). Intermittent patterns involve the presence of symptoms for less than four days per week or for less than four weeks; whereas persistent patterns entail the presence of symptoms more than four days per week and for more than four weeks. Conditions associated with allergic rhinitis include: allergic conjunctivitis, sinusitis, asthma, atopic dermatitis, oral allergy syndrome, eustachian tube dysfunction, sleep disturbances, nasal obstruction leading to anosmia, and migraine headaches.[5,7]

  The azelastine hydrochloride products include an aqueous solution with benzalkonium chloride and edetate disodium (Astelin®) and an isotonic aqueous solution with sorbitol and sucralose (Astepro®). The difference in formulation was made to minimize the potential for the adverse event of bitter taste that is associated with Astelin®. Azelastine hydrochloride/fluticasone propionate (Dymista®) is the only product available that combines an H_1-antihistamine and a steroid and is indicated when patients require treatment with both azelastine and fluticasone propionate for symptomatic relief.[1-4] Both azelastine hydrochloride (Astelin®) and olopatadine hydrochloride (Patanase®) are available generically.

Table 1. Current Medications Available in the Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Azelastine hydrochloride (Astelin®*, Astepro®)	Relief of the symptoms of seasonal allergic rhinitis†, relief of the symptoms of perennial allergic rhinitis (Astepro®) and relief of the symptoms of vasomotor rhinitis (Astelin®)	Nasal spray: Astelin® 137 µg/spray (0.1%) Astepro® 137 µg/spray (0.1%) 205.5 µg/spray (0.15%)	a
Olopatadine hydrochloride (Patanase®*)	Relief of the symptoms of seasonal allergic rhinitis‡	Nasal spray: 665 µg/spray (240 sprays)	a
Combination Products			
Azelastine hydrochloride/ fluticasone propionate (Dymista®)	Relief of the symptoms of seasonal allergic rhinitis§	Nasal spray: 137 µg /50 µg/ spray (120 sprays)	-

*Generic is available in at least one dosage form or strength.
†Astelin is approved for use in patients ≥5 years of age, Astepro is approved for use in patients ≥6 years of age.
‡ Patanase is approved for use in patients ≥6 years of age.
§ Dymista is approved for use in patients ≥12 years of age who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

Evidence-based Medicine

- Azelastine hydrochloride nasal spray has been found to be safe and effective over 14 days of treatment in placebo-controlled trials.[8-10] In a study by Shah et al comparing azelastine hydrochloride 0.1% and 0.15% formulations, there was a significantly greater improvement in total nasal symptom score (TNSS) for patients treated with azelastine 0.15% compared to patients receiving azelastine 0.1% (*P*=0.047).[11]
- Olopatadine hydrochloride has been proven safe and effective in placebo-controlled trials using various doses of olopatadine hydrochloride.[12-17] Head-to-head studies have not demonstrated any statistically significant differences in efficacy between olopatadine hydrochloride and azelastine hydrochloride.[18-20] In a study by Shah et al, there was no statistically significant difference between the treatments with regard to TNSS score or quality of life over 16 days of treatment.
- The results of a study by Ratner and colleagues demonstrated that the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray was significantly more effective compared to the individual agents alone in improving various symptom scores. The TNSS score improved by 27.1% with fluticasone, 24.8% with azelastine and 37.9% with the combination (*P*<0.05 for the combination vs either agent alone).[21] Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores and quality of life compared to each agent administered as monotherapy.[22-24]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Intranasal corticosteroids should be considered first-line therapy in patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis.[25-27]
  - Oral or intranasal antihistamines and cromolyn can be considered alternatives in patients who prefer not to use intranasal corticosteroids.[25-27]
- Other Key Facts:
  - The role of the intranasal antihistamines in the treatment of rhinitis has been well established.
  - In general, intranasal corticosteroids are considered first-line agents for the treatment of rhinitis. Intranasal antihistamines may be considered as alternative agents.[25-27]
  - Generic azelastine hydrochloride 0.1% (Astelin®) is available.[28]
  - The individual components of the azelastine hydrochloride/fluticasone propionate (Dymista®) combination product are available generically.[28]
  - Each nasal antihistamine should be primed before initial use and also when it has not been used for a certain period of time. The number of sprays varies between products, but it is recommended to follow the number of sprays provided or until a fine mist appears.[1-4]
  - Cation should be taken to avoid spraying in the eyes. If Dymista® (azelastine hydrochloride/fluticasone propionate) is sprayed in the eyes, it is recommended that patients should flush their eyes with water for at least 10 minutes.[3]

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Therapeutic Class Overview
Intranasal Calcitonins

Therapeutic Class Overview/Summary:
Osteoporosis is the most common bone disease in humans and is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and consequent susceptibility to fracture.[1] According to the World Health Organization, osteoporosis is defined by a bone mineral density (BMD) at the hip or spine that is less than or equal to 2.5 standard deviations below the expected average for a healthy young person.[2] Utilizing a reference population of young healthy individuals is common when measuring BMD and is known as a T-score.[1] Fractures are the most clinically significant physical manifestation of postmenopausal osteoporosis and low bone mass is the primary indicator of fracture risk.[3] Osteoporotic fractures commonly occur in the wrist, spine, or hip, and can result in complications such as chronic pain, disability, depression, or even death.[1] Osteoporosis and related fractures represent a significant public health and economic burden. The management of osteoporosis is intended to prevent initial or subsequent fractures by maximizing skeletal strength and/or minimizing skeletal trauma, as well as increase the patient's quality of life.[3]

Calcitonin-salmon, a calcitonin derivative, is a polypeptide containing 32 amino acids in the same linear sequence as endogenous calcitonin. Endogenous calcitonin acts primarily on bone; however, direct renal and gastrointestinal effects have also been observed. Calcitonin-salmon appears to have similar actions but has a greater potency and duration of action compared to endogenous calcitonin. The actions of calcitonin on bone and its role in normal human bone physiology are not completely understood, although calcitonin receptors have been discovered in osteoclasts and osteoblasts. Information derived from clinical trials evaluating injectable calcitonin-salmon suggest the agents in this medication class cause marked transient inhibition of the ongoing bone resorptive process.[4,5]

Calcitonin-salmon is currently available as an injection, which is administered either subcutaneously or intramuscularly, or nasal spray. Only the nasal spray formulation will be covered in this review. Miacalcin® (calcitonin-salmon) nasal spray is manufactured by chemical synthesis, and Fortical® (calcitonin-salmon) nasal spray is manufactured by recombinant deoxyribonucleic acid technology and is identical to the synthetic formulations.[4,5] Nasal calcitonin-salmon is only FDA-approved for the treatment of postmenopausal osteroporosis.[4,5] The calcitonins are for use only in postmenopausal women greater than five years postmenopause with low bone mass relative to healthy premenopausal females.[4,5] Currently, synthetic nasal calcitonin-salmon is the only calcitonin available generically.

While not every guideline recommends a preferred medication and/or medication class, the bisphosphonates are generally recognized as first-line therapy for the prevention and treatment of osteoporosis, including postmenopausal and glucocorticoid-induced osteoporosis.[1,3,6-9]

Table 1. Current Medications Available in the Therapeutic Class[4,5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
calcitonin-salmon rDNA origin (Fortical®)	Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females†		-
calcitonin-salmon synthetic (Miacalcin®*)	Treatment of postmenopausal osteoporosis in women greater than five years postmenopause with low bone mass relative to healthy premenopausal females†		a

*Generic available in at least one dosage form or strength.
† Use is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. Use should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.

Evidence-based Medicine

- Overall, there is a lack of substantial clinical trial data for this medication class, as trials are typically small in size and observational in design.[10-13]
- A meta-analysis of 30 clinical trials demonstrated that calcitonins significantly decreased the risk of vertebral fractures compared to control (placebo or calcium and/or vitamin D); however, there was no significant difference in the risk for non-vertebral fractures.[13]
- Nasal calcitonin-salmon was no different than placebo for adverse events other than rhinitis.[10-13]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current clinical guidelines recommend that all drugs FDA-approved for use in osteoporosis are appropriate treatment options, with the bisphosphonates having good quality evidence supporting their use for reducing the risk of vertebral, non-vertebral, and hip fractures.
  - Bisphosphonates are considered first-line[1,3,6-9]
  - Calcitonins are recognized as a potential option for the treatment of osteoporosis, have a fair quality evidence to support their use in reducing vertebral fractures.[6]
  - For postmenopausal osteoporosis, calcitonins are recommended as a last line therapy, and no product is recommended or preferred over another.[3,7,8]
- Other Key Facts:
  - Calcitonin-salmon may also be used off-labeled for cancer pain, treatment of glucocorticoid-induced osteoporosis, and for prophylaxis of fracture of bone in patients with osteoporosis.[14]
  - There are no clinically significant drug interactions associated with the calcitonins.[15]

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Therapeutic Class Overview
Platelet Inhibitors

Therapeutic Class

- **Overview/Summary:** Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. The agents in the class are Food and Drug Administration (FDA)-approved for a variety of indications including treatment and/or prevention of acute coronary syndromes, stroke/transient ischemic attack, and thrombocythemia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action.[1-8] The newest platelet inhibitor to be FDA-approved is vorapaxar (Zontivity®), which is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).[7] Vorapaxar (Zontivity®), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. In addition, vorapaxar is not a prodrug and does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[7] Vorapaxar is available for once-daily dosing in combination with other antiplatelet agents (either clopidogrel and/or aspirin). Clopidogrel and prasugrel are administered once-daily, while ticagrelor is dosed twice daily.[2,4,5]

Table 1. Current Medications Available in the Therapeutic Class[1-8]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Anagrelide (Agrylin®*)	Treatment of thrombocytopenia associated with myeloproliferative disorders†	Capsule: 0.5 mg 1 mg	a
Clopidogrel (Plavix®*)	Recent myocardial infarction, recent stroke, or established peripheral arterial disease, reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome‡	Tablet: 75 mg 300 mg	a
Dipyridamole (Persantine®*)	Prevention of postoperative thromboembolic complications of cardiac valve replacement§	Tablet: 25 mg 50 mg 75 mg	a
Prasugrel (Effient®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention‖	Tablet: 5 mg 10 mg	-
Ticagrelor (Brilinta®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome¶; reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction	Tablet: 90 mg	-
Ticlopidine (Ticlid®*)	Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation#, reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	Tablet: 250 mg	a

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Vorapaxar (Zontivity®)	Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease: Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin)	Tablet: 2.08 mg	-
Combination-Products			
Aspirin/ extended-release dipyridamole (Aggrenox®)	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Capsule: 25/200 mg	-

*Generic available in at least one dosage form or strength.
†To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.
‡For patients with non-ST-segment elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.
§As adjunct to coumarin anticoagulants.
‖Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.
¶Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.
#As adjunct to aspirin.

Evidence-based Medicine

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.[10-15]
- The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PC)I. Prasugrel was noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).[109]
- Approval of prasugrel for use in acute coronary syndromes (ACS) was based on the clinical evidence for safety and efficacy derived from the TRITON-TIMI 38 study (N=13,608). Within the study, prasugrel was significantly more effective compared to clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention. Prasugrel did not demonstrate a mortality benefit and a significantly higher rate of major, minor, life-threatening, and fatal bleeding events was observed with prasugrel.[16]
    - Of note, a benefit with prasugrel was not observed in certain patient subgroups within TRITON-TIMI 38, specifically those who were ≥75 years of age, those weighing <60 kg, and those with a past history of stroke or transient ischemic attack.
- The approval of ticagrelor for use in ACS was based on the clinical evidence for safety and efficacy derived from the PLATO study. Within the trial, hospitalized patients with documented ACS, with or without ST-elevation, were randomized to either ticagrelor or clopidogrel (N=18,624). After 12 months of treatment, ticagrelor was significantly more effective compared to clopidogrel in reducing the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke; without increasing the risk of major bleeding. Ticagrelor demonstrated a mortality benefit compared to clopidogrel.[17]
    - There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.[76]
- Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success (P=0.03), TIMI 3 flow (P=0.06), and lower corrected TIMI frame counts (P=0.008).[77]
- Approval of vorapaxar was based on the results of the TRA2ºP-TIMI 50 trial. The composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or transient ischemic attack (TIA) the vorapaxar group showed a

significant 17% relative risk reduction over the three years of the study (HR, 0.83; 95%CI, 0.76 to 0.90; P<0.001).[78]

- Patients who had a previous stoke were removed from the study after 24 month follow-up assessments. Among the patients with a history of stroke, the rate of intracranial hemorrhage in the vorapaxar group higher (P<0.001), without a history of stroke and was significantly increased as compared with the group without a prior stroke (P=0.049). [78]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Use of the platelet inhibitors, as monotherapy or combination therapy, is based on the specific clinical indication and the patient's risk for thromboembolic events.[24-40]
  - Antiplatelet therapy (aspirin plus extended-release [ER] dipyridamole or clopidogrel >aspirin) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute myocardial infarction, other ACS, or recently placed coronary stent.[24,25]
  - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy aspirin with clopidogrel or ticagrelor or prasugrel monotherapy is recommended in the first year following ACS in patients regardless of PCI status.[24]
    - The guideline recommends ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin in patients post-ACS independent of whether PCI has been conducted.[24]
  - The 2013 guidelines for managing patients with STEMI by American College of Cardiology Foundation and American Heart Association recommend clopidogrel, prasugrel or ticagrelor for one year following PCI, without recommendation for one antiplatelet drug over another.[28]
  - The 2011 European Society of Cardiology guideline for the management of ACS in patients presenting without persisting ST-elevation recommends ticagrelor first-line in patients at moderate to high risk of ischemic events, regardless of treatment strategy and including those pretreated with clopidogrel.[27]
    - If coronary anatomy is known and PCI is planned, prasugrel is recommended.
    - Clopidogrel is recommended in patients who cannot receive prasugrel or ticagrelor.
  - The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous intervention recommends clopidogrel, prasugrel, and ticagrelor as treatment options.[28]
    - Treatment with all agents should be continued for at least one year.
- Other Key Facts:
  - Anagrelide, dipyridamole, and ticlopidine are available generically.

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Therapeutic Class Overview
Urinary Antispasmodics

Therapeutic Class

- **Overview/Summary:** Overactive bladder (OAB) is characterized as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.[1] Urinary incontinence has been shown to greatly reduce quality of life in areas such as mental and general health in addition to physical and social functioning.[2] The urinary antispasmodics that are Food and Drug Administration-approved for the treatment of OAB are listed in Table 1.[3-16] Many of the urinary antispasmodics are anticholinergic compounds that act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and reducing bladder contractions.[3-9,11-16] Mirabegron (Myrbetriq®) is the first β-3 adrenergic receptor agonist to be approved for the treatment of OAB. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle, thereby increasing bladder capacity.[17] The muscarinic receptor antagonists have demonstrated similar safety and efficacy; however, they primarily differ in their receptor selectivity and tolerability profiles. The M2 and M3 muscarinic receptor subtypes are highly concentrated in the bladder and are responsible for detrusor contraction, while M1, M4 and M5 are located throughout the body. Preclinical studies suggest that solifenacin and darifenacin may be "uroselective" for the M3 receptor in the bladder; however, the clinical implications of this suggestion have not been established.[18] The muscarinic receptor antagonists are associated with various adverse events including blurred vision, dry mouth, constipation and urinary retention. Central nervous system adverse events such as dizziness, somnolence and headaches may also occur.[3] The development of extended-release (ER) formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events compared to immediate-release (IR) products. Several urinary antispasmodics are currently available generically in both IR and ER formulations.[19] Because it acts via the beta-3 adrenergic receptor rather than through muscarinic cholinergic receptors, mirabegron may have a better tolerability profile compared to other urinary antispasmodics.[17]

Table 1. Current Medications Available in the Class[3-16]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Darifenacin (Enablex®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 7.5 mg 15 mg	-
Fesoterodine (Toviaz®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 4 mg 8 mg	-
Flavoxate (Urispas®*)	Symptomatic relief of dysuria, urgency, nocturia, suprapubic pain, frequency and incontinence as may occur in cystitis, prostatitis, urethritis and urethrocystitis/urethrotrigonitis	Tablet: 100 mg	a
Mirabegron (Myrbetriq®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release tablet: 25 mg 50 mg	-
Oxybutynin (Ditropan®*, Ditropan XL®*, Gelnique®, Oxytrol®†)	Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (IR), treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency (XL), treatment of pediatric patients aged six years and older with	Extended-release tablet (Ditropan XL®): 5 mg 10 mg 15 mg Gel (Gelnique®): 3% (pump)	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	symptoms of detrusor overactivity associated with a neurological condition (XL)	10% (sachet) Syrup (Ditropan®): 5 mg/5 mL Tablet (Ditropan®): 5 mg Transdermal patch (Oxytrol®): 3.9 mg/24 hours	
Solifenacin (VESIcare®)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency	Tablet: 5 mg 10 mg	-
Tolterodine (Detrol®*, Detrol LA®*)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release capsule (Detrol LA®): 2 mg 4 mg Tablet (Detrol®): 1 mg 2 mg	a
Trospium (Sanctura®*, Sanctura XR®*)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	Extended-release capsule (Sanctura XR®*): 60 mg Tablet (Sanctura®): 20 mg	a

IR=Instant release.
ER, LA, XL and XR=extended-release.
*Generic available in at least one dosage form or strength.
† Available over-the-counter.

Evidence-based Medicine

- The results of a Cochrane systematic review demonstrate that the improvement in quality of life is similar between tolterodine immediate-release (IR) and oxybutynin IR (standardized mean difference [SMD], -0.00; 95% confidence interval [CI], -0.18 to 0.18); however, there is a lower risk of discontinuation (risk ratio [RR], 0.52; 95% CI, 0.40 to 0.66) and dry mouth with tolterodine (RR, 0.65; 95% CI, 0.60 to 0.71). No differences in efficacy were reported. The efficacy between oxybutynin and trospium IR formulations is similar; however, there is a lower risk of withdrawing due to adverse events (RR, 0.66; 95% CI, 0.48 to 0.91) and dry mouth with trospium (RR, 0.64; 95% CI, 0. 52 to 0.77).[20]
- Solifenacin significantly improves quality of life compared to tolterodine (SMD, -0.12; 95% CI, -0.23 to -0.01), and fesoterodine improves quality of life parameters compared to tolterodine extended-release (LA, XL) (SMD, -0.20; 95% CI, -0.27 to -0.14). There was a higher report of cure or improvement in symptoms (RR, 1.25; 95% CI, 1.13 to 1.39) leakage episodes/24 hours (weighted mean difference [WMD], -0.30; 95% CI -0.53 to -0.08) and urgency episodes/24 hours (WMD, -0.43; 95%CI, -0.74 to -0.13) with solifenacin compared to tolterodine. The rates of withdrawal due to adverse events were similar between solifenacin and tolterodine.[20]
- Fesoterodine significantly increases the chance of patient reported cure or improvement in symptoms (RR, 1.11; 95% CI, 1.06 to 1.16), leakage episodes (WMD, -0.19; 95% CI, -0.30 to -0.09), urinary

frequency (WMD, -0.27; 95% CI, -0.47 to -0.06) and urgency episodes/24 hours (WMD, -0.44; 95%CI, -0.72 to -0.16) compared to tolterodine LA. Fesoterodine has a higher risk of withdrawal due to adverse events compared to tolterodine LA (RR, 1.45; 95% CI, 1.07 to 1.98) and higher risk of dry mouth (RR, 1.80; 95% CI, 1.58 to 2.05).[20]

- A meta-analysis comparing oxybutynin and tolterodine IR formulations reported that oxybutynin improved the number of incontinence episodes/24 hours (WMD, 0.41; 95% CI, 0.04 to 0.77) and increased the volume voided per micturition (WMD, 8.24; 95% CI, 2.38 to 14.11) compared to tolterodine. No statistically significant difference was reported between the treatments with regard reduced micturition frequency (WMD, 0.0; 95% CI, -0.38 to 0.38); however, tolterodine was associated with a 46% reduction in the risk of dry mouth compared to oxybutynin (RR, 0.54; 95% CI, 0.48 to 0.61).[21]
- Studies have not consistently demonstrated a lower incidence of adverse events with oxybutynin XL compared to the IR formulation.[22-24]
- Mirabegron was evaluated in three 12-week, placebo-controlled trials of patients with overactive bladder and symptoms of urge urinary incontinence, urgency and urinary frequency. Results from all three studies demonstrated statistically significant improvements in incontinence episodes and micturitions/24 hours across all doses of mirabegron (25, 50 and 100 mg) compared to placebo. In one study using tolterodine as a reference arm, tolterodine ER was not significantly more effective compared to placebo for the primary endpoints. In two studies, both the 100 and 50 mg doses of mirabegron were associated with statistically significant improvements in secondary endpoints compared to placebo. In a third study, the change from baseline in the mean volume voided per micturition was only significant in the mirabegron 50 mg group, but not for the other doses.[25-27]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Behavioral therapies (e.g., bladder training, bladder control strategies, pelvic floor muscle training, fluid management) are considered first-line treatment in all patients with overactive bladder (OAB).[28.29,30]
  - Behavioral therapies may be combined with antimuscarinic therapies.[28.29,30]
  - Oral antimuscarinics are recommended as first-line pharmacologic therapy; no one agent is recommended over another. If adverse events occur, a dose reduction or a switch to a different antimuscarinic medication should be considered.[28.29]
    - § Oxybutynin (IR) should not be recommended to frail older women.[30]
  - If both an immediate-release (IR) and an extended-release (ER) formulation are available, the ER formulations are preferred over IR formulations due to lower rates of dry mouth.[28.29]
  - Transdermal oxybutynin (patch/gel) may be considered if oral agents cannot be tolerated.[28.29]
  - The role of mirabegron in the management if OAB is not clearly defined.[28.29,30]
- Other Key Facts:
  - Trospium has low penetration through the blood brain barrier and gut; however, clinical studies have not demonstrated a lower incidence of adverse events with trospium compared to others within the class.[18]
  - Fesoterodine, a prodrug, is metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.[4,5,16]
  - The oral ER and transdermal formulations may be associated with a lower incidence of dry mouth compared to the IR products.[3-16]
  - Mirabegron is the first beta-3 adrenergic receptor agonist to be approved for the treatment of overactive bladder.[17]

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Therapeutic Class Overview
Angiotensin II receptor blockers (ARBs) – combination products

Therapeutic Class

- **Overview/Summary:** This review will focus on the angiotensin II receptor blocker (ARB) combination products.[1-13] The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[14,15] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[16] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[14,16] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy and remodeling.[14,15] The RAAS plays an important role in the development and progression of heart failure.[15]

  ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[14-17] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (e.g., chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[14,15] The ARBs block the angiotensin II receptor subtype AT1, preventing the negative effects of angiotensin II, regardless of its origin. ARBs do not appear to affect bradykinin. Amlodipine, a nondihydropyridine calcium channel blocker, inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Cardiac and vascular smooth muscle contraction depends on the movement of extracellular calcium ions into cells through specific ion channels. Amlodipine inhibits calcium ion influx and exerts a greater effect on vascular smooth muscle cells compared to cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator, which results in a reduction in peripheral vascular resistance and reduction in blood pressure.[18] HCTZ, a thiazide diuretic, increases the excretion of sodium and chloride by inhibiting their reabsorption in the ascending loop of Henle and the early distal tubules of the kidney. Indirectly, the diuretic action of HCTZ reduces plasma volume, which increases plasma renin activity, aldosterone secretion and subsequently potassium excretion in the urine. The exact antihypertensive mechanism of the thiazide diuretics is unknown, although sodium depletion appears to be an important factor.[18]

Table 1. Current Medications Available in Therapeutic Class[1-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Azilsartan/chlorthalidone (Edarbyclor®)	Hypertension*	Tablet: 40/12.5 mg 40/25 mg	-
Candesartan/hydrochlorothiazide (Atacand HCT®#)	Hypertension†	Tablet: 16/12.5 mg 32/12.5 mg 32/25 mg	a
Eprosartan/hydrochlorothiazide (Teveten HCT®)	Hypertension†	Tablet: 600/12.5 mg 600/25 mg	-
Irbesartan/hydrochlorothiazide (Avalide®#)	Hypertension*	Tablet: 150/12.5 mg 300/12.5 mg	a
Losartan/hydrochlorothiazide (Hyzaar®#)	Hypertension‡, Reduction in the Risk of Stroke in Patients	Tablet: 50/12.5 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with Hypertension and Left Ventricular Hypertrophy§	100/12.5 mg 100/25 mg	
Olmesartan/hydrochlorothiazide (Benicar HCT®)	Hypertension†	Tablet: 20/12.5 mg 40/12.5 mg 40/25 mg	-
Telmisartan/hydrochlorothiazide (Micardis HCT®#)	Hypertension†	Tablet: 40/12.5 mg 80/12.5 mg 80/25 mg	a
Valsartan/hydrochlorothiazide (Diovan HCT®#)	Hypertension*	Tablet: 80/12.5 mg 160/12.5 mg 160/25 mg 320/12.5 mg 320/25 mg	a
Olmesartan/amlodipine (Azor®)	Hypertension*	Tablet: 20/5 mg 40/5 mg 20/10 mg 40/10 mg	-
Olmesartan/amlodipine/ hydrochlorothiazide (Tribenzor®)	Hypertension†	Tablet: 20/5/12.5 mg 40/5/25 mg 40/5/12.5 mg 40/10/12.5 mg 40/10/25 mg	-
Telmisartan/amlodipine (Twynsta®#)	Hypertension*	Tablet: 40/5 mg 40/10 mg 80/5 mg 80/10 mg	a
Valsartan/amlodipine (Exforge®)	Hypertension*	Tablet: 160/5 mg 160/10 mg 320/5 mg 320/10 mg	-
Valsartan/amlodipine/ hydrochlorothiazide (Exforge® HCT)	Hypertension†	Tablet: 160/5/12.5 mg 160/5/25 mg 160/10/12.5 mg 160/10/25 mg 320/10/25 mg	-

*Indicated to treat hypertension in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
†This fixed-dose combination is not indicated for initial therapy.
‡The fixed-dose combination is not indicated for initial therapy, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risks of initiating combination therapy in these patients.
§There is evidence that this benefit does not extend to African American patients.
#Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials assessing the combination angiotensin II receptor blockers (ARBs) in the treatment of hypertension have demonstrated that, in general, dual therapy combinations of ARBs plus either a thiazide diuretic or amlodipine achieve greater reductions in blood pressure and higher blood pressure control rates compared to monotherapy regimens of ARBs, amlodipine or a thiazide diuretic.[25-37]
- A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in systolic and diastolic blood pressure compared to ARB monotherapy.[48]
- A second meta-analysis, conducted by Fogari et al, found that triple combinations of ARBs (olmesartan or valsartan), CCBs (amlodipine), and diuretics (hydrochlorothiazide) at any dose provided more blood pressure reduction in office and 24-hour ambulatory measurements than any dual combination of these molecules (P<.0001 for both).[39]
- Trials assessing triple therapy regimens with an ARB, amlodipine and HCTZ demonstrate significantly greater blood pressure reductions with triple therapy compared to combination and monotherapy.[39-42]
- There are limited head-to-head trials involving these agents, and the trials do not consistently demonstrate superiority of one combination product over another within the class.[43-50]
    - Telmisartan/HCTZ has been shown to significantly improve diastolic and systolic blood pressure when compared to valsartan or losartan in combination with HCTZ in three studies over six to ten weeks.[46,48,49]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - According to the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, Treatment of High Blood Pressure the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker.[19]
    - Current treatment guidelines indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade 2 hypertension may require initial therapy with medications from two different drug classes.[19-22]
    - ARBs are specifically recommended over other classes in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[19-22]
    - It is important to note that certain combinations are not recommended, including concurrent use of an ARB and an ACE-inhibitor.[19,21]
    - Other guidelines highlight the use of antihypertensives in special populations such as pediatrics and kidney disease.[23,24]
- Other Key Facts:
    - The products that are available generically include candesartan/HCTZ, irbesartan/HCTZ, losartan/HCTZ, telmisartan/HCTZ, valsartan/HCTZ, and telmisartan/amlodipine.
    - The only products that are not available generically as a single agent in any dosage for or strength include azilsartan (Edarbi®) and olmesartan (Benicar®).

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Therapeutic Class Review
Angiotensin II Receptor Blockers (ARBs)- Single Entity Agents

Overview/Summary

The angiotensin II receptor blockers (ARBs) are Food and Drug Administration (FDA)-approved for the treatment of hypertension, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, cardiovascular risk reduction in patients unable to take angiotensin converting enzyme (ACE) inhibitors and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.[1] The eight ARBs that are currently available in the United States include azilsartan (Edarbi®), candesartan (Atacand®), eprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan (Benicar®), telmisartan (Micardis®) and valsartan (Diovan®). The only agents in the class that are available generically are losartan (all strengths) and eprosartan (600 mg strength only).[1-9]

The renin-angiotensin-aldosterone system (RAAS) is the most important component in the homeostatic regulation of blood pressure.[10,11] Excessive activity of the RAAS may lead to hypertension and disorders of fluid and electrolyte imbalance.[12] Renin catalyzes the conversion of angiotensinogen to angiotensin I. Angiotensin I is then cleaved to angiotensin II by ACE. Angiotensin II can increase blood pressure by direct vasoconstriction and through actions on the brain and autonomic nervous system.[10,12] In addition, angiotensin II stimulates aldosterone synthesis from the adrenal cortex, leading to sodium and water reabsorption. Angiotensin II exerts other detrimental cardiovascular effects including hypertrophy and remodeling.[10,11] The RAAS plays an important role in the development and progression of heart failure.[11]

ACE inhibitors block the conversion of angiotensin I to angiotensin II, and also inhibit the breakdown of bradykinin, a potent vasodilator associated with dry cough.[10-13] Since angiotensin II may also be generated through other pathways that do not depend upon ACE (e.g., chymase), blockade of angiotensin II by ACE inhibitors is incomplete.[10,11] The ARBs block the angiotensin II receptor subtype AT1, preventing the negative effects of angiotensin II, regardless of its origin. ARBs do not appear to affect bradykinin. A 2011 update from the Agency for Healthcare Research and Quality (AHRQ) on the treatment of essential hypertension reported that ACE inhibitors and ARBs appear to have similar long-term effects on blood pressure among individuals with essential hypertension, and direct renin inhibitors have a greater reduction in blood pressure compared to ramipril and losartan although studies are limited. With regard to mortality and major cardiovascular events, the AHRQ concluded that due to the low number of deaths or major cardiovascular events reported in the comparative studies evaluated, it was difficult to discern any differential effects between the ACE inhibitors and ARBs, while there is insufficient evidence to compare direct renin inhibitors to ACE inhibitors and ARBs in regard to these outcomes.[14]

Treatment guidelines for hypertension indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade two hypertension may require initial therapy with medications from two different drug classes.[15,16] ARBs are recommended in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[15-17]

Treatment guidelines for the management of stable angina indicate that ARBs are recommended in patients with hypertension and those who have an indication for an ACE inhibitor but are intolerant to them, who have heart failure or who have had a myocardial infarction and have a left ventricular ejection fraction of ≤40%. ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction.[18]

Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommend the use of ARBs in patients who are intolerant to ACE inhibitors and who have had a myocardial infarction or have clinical or radiological signs of heart failure or a left ventricular ejection fraction of ≤40%.[19,20] Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and left ventricular ejection fraction ≤40% despite conventional therapy including an ACE inhibitor or ARB as monotherapy.[19] Current treatment guidelines for the management of ST-elevation myocardial infarction recommend ARBs in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%.[21,22]

The National Institute for Health and Clinical Excellence recommends the use of ARBs be reserved for patients post-myocardial infarction who are intolerant to ACE inhibitor therapy. An ACE inhibitor is recommended in patients with a proven myocardial infarction and asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function. Routine use of ARBs after a myocardial infarction is not recommended.[23]

Treatment guidelines for the management of heart failure recommend ARBs, specifically losartan and irbesartan, in patients with type 2 diabetes and nephropathy who are at risk for the development of heart failure. ACE inhibitors and ARBs have been shown to decrease the incidence of end organ disease and clinical events in patients with diabetes. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension.[24-26] ARBs are recommended in patients intolerant to ACE inhibitors who have cardiac structural abnormalities or remodeling who have not developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction. In patients with current or prior symptoms of heart failure, ARBs are recommended in patients who are intolerant to ACE inhibitors and who have reduced ventricular ejection fraction. ARBs may also be a reasonable alternative to ACE inhibitors as first-line therapy in these patients.[24-26] The addition of an ARB may be considered in patients with heart failure who have persistent symptoms despite optimized therapy with an ACE inhibitor and a β-blocker.[27] Individual ARBs may be considered as initial therapy instead of an ACE inhibitor in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction.[27]

Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including either an ACE inhibitor or an ARB. If one class is not tolerated the other should be tried. ACE inhibitors and ARBs are recommended in patients with micro- or macroalbuminuria. In patients with type 2 diabetes, hypertension and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay the progression of nephropathy.[28]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Azilsartan (Edarbi®)	Angiotensin II receptor blocker	-
Candesartan (Atacand®)	Angiotensin II receptor blocker	-
Eprosartan (Teveten®)	Angiotensin II receptor blocker	a *
Irbesartan (Avapro®)	Angiotensin II receptor blocker	-
Losartan (Cozaar®*)	Angiotensin II receptor blocker	a
Olmesartan (Benicar®)	Angiotensin II receptor blocker	-
Telmisartan (Micardis®)	Angiotensin II receptor blocker	-
Valsartan (Diovan®)	Angiotensin II receptor blocker	a

*Generic available in 600 mg strength only.

Indications

Table 2. Food and Drug Administration Approved Indications[1-10]

Generic Name	Cardio-vascular Risk Reduction in Patients Unable to Take ACE Inhibitors	Diabetic Nephropathy in Patients with Type 2 Diabetes and Hypertension	Heart Failure (NYHA Class II to IV)	Hyper-tension	Post-Myo-cardial Infarction	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
Azilsartan				a		
Candesartan			a *	a		
Eprosartan				a		
Irbesartan		a †		a		
Losartan		a †		a		a ‡
Olmesartan				a		
Telmisartan	a §			a		
Valsartan			a ‖	a	a ¶	

ACE=angiotensin converting enzyme, NYHA=New York Heart Association
*To reduce the risk of cardiovascular death and heart failure hospitalization in patients with left ventricular systolic dysfunction. Candesartan has an added effect on these outcomes when used with an angiotensin converting enzyme inhibitor.
†Reduces the rate of progression to nephrophathy in patients with elevated serum creatinine and proteinuria (>300 mg/day).
‡There is evidence that this benefit does not apply to African American patients.
§Reduction of risk of myocardial infarction, stroke or cardiovascular death in patients 55 years of age and older at high risk of developing major cardiovascular events. Use of telmisartan with an angiotensin converting enzyme inhibitor is not recommended. Consider using an angiotensin converting enzyme inhibitor first.
‖Reduction in heart failure hospitalizations. There is no evidence that valsartan provides added benefit when used with adequate doses of an angiotensin converting enzyme inhibitor.
¶In clinically stable patients with left ventricular failure or dysfunction following myocardial infarction, to reduce the risk of cardiovascular mortality.

Pharmacokinetics

Azilsartan, candesartan and olmesartan are prodrugs. Azilsartan medoxomil is a prodrug which is hydrolyzed to azilsartan in the gastrointestinal tract during absorption. Candesartan cilexetil is the esterified prodrug of candesartan. It is thought to be completely metabolized to CV-11974 during absorption from the intestinal wall.[10] Olmesartan medoxomil is rapidly and completely deesterified to the active olmesartan during absorption from the intestinal wall.[10] Information regarding metabolism of these medications in Table 3 refer to metabolism of the active drugs azilsartan, candesartan and olmesartan, respectively.

Table 3. Pharmacokinetics[1-10]

Generic Name	Bioavailability (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Azilsartan	60	CYP2C9	No	Feces (55); renal (42)	11
Candesartan	15	CYP2C9	No	Feces (67); renal (33)	9
Eprosartan	13	Glucuronidation	No	Feces (90); renal (7)	6
Irbesartan	60 to 80	CYP2C9	No	Feces (80); renal (20)	11 to 15
Losartan	33	CYP2C9; CYP3A4	Yes; 5-carboxylic acid (E-3174)	Feces (60); renal (35)	2 (6 to 9)*
Olmesartan	26	Deesterification†	No	Feces (50 to 65); renal (35 to 50)	13

Generic Name	Bioavailability (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Telmisartan	42 to 58	Conjugation	No	Feces (>97)	24
Valsartan	25	Minimal; enzyme unknown	No	Feces (83); renal (13)	6

*Metabolite.
†Deesterification is responsible for converting the prodrug of olmesartan medoxomil to active olmesartan. Olmesartan does not undergo any further metabolism.

Clinical Trials

Clinical trials assessing the single entity angiotensin II receptor blockers (ARBs) in the treatment of hypertension have demonstrated efficacy in lowering systolic and diastolic blood pressure.[29-49] Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another.[29-33, 39,40,43,46] A meta-analysis by Conlin et al found that the absolute weighted-average reductions in systolic and diastolic blood pressure associated with ARB monotherapy were comparable for all ARBs.[46] Head-to-head trials comparing therapy with ARBs and angiotensin converting enzyme (ACE) inhibitors have generally demonstrated no significant differences between classes.[35,42] Comparisons of ARBs with other blood pressure lowering agents have not consistently demonstrated superiority of ARBs over other agents from different classes.[36,45]

Azilsartan is indicated for the treatment of hypertension, either alone or in combination with other drugs, and is the ARB most recently approved by the Food and Drug Administration. In a study by White et al (N=1,291), azilsartan 80 mg was significantly more effective in lowering mean 24-hour systolic blood pressure over 6 weeks (-14.3 mm Hg) compared to patients receiving either valsartan 320 mg (-10.0 mm Hg; *P*<0.001) or 40 mg of olmesartan (-11.7 mm Hg; *P*=0.009).[29] A similar study including 1,275 patients with primary hypertension also reported azilsartan 80 mg to be significantly more effective than olmesartan 40 mg in reducing mean 24-hour systolic blood pressure after 6 weeks of treatment (-14.6 vs. -12.6 mm Hg; *P*=0.038).[30] In a 24-week study, patients who were randomized to either 40 mg or 80 mg of azilsartan experienced significant reductions in 24-hour mean systolic blood pressure compared to valsartan 320 mg (-14.9 and -15.3 mm Hg vs -11.3 mm Hg for azilsartan 40 mg, 80 mg and valsartan 320 mg, respectively; *P*<0.001 for both comparisons).[31]

Telmisartan is indicated to reduce cardiovascular risk in patients unable to take ACE inhibitors. The ONTARGET trial compared telmisartan and ramipril monotherapy and in combination with each other and demonstrated no significant difference between any group in death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure.[50] The TRANSCEND trial compared telmisartan and placebo and showed no significant difference between groups in death from cardiovascular causes, myocardial infarction, stroke or heart failure hospitalizations. The composite endpoint of death from cardiovascular causes, myocardial infarction and stroke occurred in significantly fewer patients in the telmisartan group, but this significance was lost after adjustment for multiplicity of comparisons and overlap with the primary outcome.[51]

Losartan is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. The efficacy of losartan was demonstrated in the LIFE trial and its corresponding sub-analyses. Losartan was compared to therapy with atenolol (hydrochlorothiazide could be added to primary regimens if needed for blood pressure control). Results demonstrated a 24.9% relative risk reduction in stroke in patients treated with losartan-based regimens as compared to atenolol-based regimens.[52] However, a post-hoc analysis in African American patients showed an increase in the composite of cardiovascular death, myocardial infarction and stroke in losartan-treated patients compared to atenolol.[53]

Candesartan and valsartan are indicated to treat heart failure. Trials demonstrated the efficacy of candesartan alone and in combination with ACE inhibitor therapy compared to placebo in reducing the risk of all-cause mortality, cardiovascular death and/or heart failure hospitalization.[54-57] When compared to therapy with an enalapril in the RESOLVD trial, candesartan was not significantly better in improving six-

minute walking distance, New York Heart Association (NYHA) functional class or quality of life.[54] Losartan has also been evaluated in patients with heart failure and, when compared to captopril, no significant difference was observed in renal function or all-cause mortality.[58,59] However, there was a significantly lower risk of sudden death and resuscitated cardiac arrest.[59] Trials evaluating the efficacy of valsartan compared to placebo in the Val-HeFT trial show no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, heart failure hospitalizations and morbidity and mortality.[60]

Valsartan is indicated to reduce cardiovascular mortality in patients post-myocardial infarction with left ventricular failure or dysfunction. The VALIANT trial compared valsartan with captopril and combination therapy with valsartan plus captopril. No significant differences in all-cause mortality, cardiovascular death, reinfarction or heart failure hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy.[61] Losartan has also been evaluated in patients post-myocardial infarction compared to and in combination with captopril. Results are similar to results observed in the VALIANT trial.[62]

Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension. Through the IDNT and RENAAL trials, irbesartan and losartan reduced the rate of progression of nephropathy (as measured by occurrence of doubling of serum creatinine or end stage renal disease) in type 2 diabetics with hypertension and diabetic nephropathy with elevated serum creatinine and proteinuria.[63,64] However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan and valsartan.[65-69]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension				
White et al[29] Azilsartan 20 or 40 mg QD for 2 weeks, followed by forced titration to 40 to 80 mg QD for 4 weeks vs olmesartan 20 mg QD for 2 weeks, followed by forced titration to 40 mg QD for 4 weeks vs valsartan 160 mg QD for 2 weeks, followed by forced titration to 320 mg QD for 4 weeks vs placebo	AC, DB, MC, PC, RCT Patients 18 years of age and older with HTN (clinic SBP ≥150 and ≤180 mm Hg and 24-hour mean SBP ≥130 and ≤170 mm Hg	N=1,291 6 weeks	Primary: Change from baseline in 24-hour mean SBP Secondary: Change from baseline in trough, seated and clinic SBP, changes from baseline in 24-hour mean and clinic DBP	Primary: All active treatment arms lowered 24-hour mean SBP significantly compared to placebo (P<0.001). Changes from baseline in 24-hour mean SBP were significantly greater with azilsartan 80 mg compared to olmesartan 40 mg and valsartan 320 mg (P≤0.009). Azilsartan 40 mg was non-inferior to olmesartan 40 mg (P=0.136). Secondary: Clinic SBPs were significantly lower for both doses of azilsartan compared to olmesartan 40 mg and valsartan 320 mg (P≤0.018). Changes in 24-hour and clinic DBP were significantly lower for azilsartan 80 mg compared to olmesartan 40 mg and valsartan 320 mg (P≤0.011). A significant difference was also observed between azilsartan 40 mg and valsartan 320 mg (P≤0.020). No significant difference was observed between azilsartan 40 mg and olmesartan 40 mg (P≥0.17).
Bakris et al[30] Azilsartan 20, 40 or 80 mg QD vs olmesartan 40 mg QD	DB, MC, PC, PG, RCT Patients 18 years of age and older with primary HTN	N=1,275 6 weeks	Primary: Change in 24-hour mean SBP Secondary: Change in trough clinic SBP, 24-hour mean DBP, trough	Primary: The change in 24-hour mean SBP was significantly greater in the azilsartan 80 mg group compared to the olmesartan 40 mg group (P=0.038). No significant difference was observed in the azilsartan 20 and 40 mg groups compared to the olmesartan 40 mg group (P≥0.352).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			clinic DBP, daytime and nighttime mean ABPM, mean ABPM at 0 to 12 hours after dosing, mean ABPM at trough (22 to 24 hours after dosing), proportion of responders	Secondary: The change in trough clinic SBP was significantly greater in the azilsartan 80 mg group compared to the olmesartan 40 mg group (*P*=0.043). No significant difference was observed in trough clinic SBP in the azilsartan 20 and 40 mg groups compared to the olmesartan 40 mg group (*P*≥0.662). Changes in 24-hour mean and clinic DBP were significantly greater in the azilsartan 80 mg group compared to the olmesartan 40 mg group (*P*=0.044). There was a trend for greater reduction of ABPM parameters in the azilsartan 80 mg group compared to the olmesartan 40 mg group (*P* values not reported). No significant difference was observed in proportion of responders between azilsartan 80 mg and olmesartan 40 mg (*P*=0.402).
Sica et al[31] Azilsartan 20 mg force titrated to 40 mg QD after 2 weeks vs azilsartan 20 mg force titrated to 80 mg QD after 2 weeks vs valsartan 80 mg QD force titrated to 320 mg	AC, DB, MC, PG, RCT Patients ≥18 years of age with hypertension were included if their clinic SBP was >150 mm Hg and <180 mm Hg and 24-hour mean SBP was ≥130 mm Hg and ≤170 mm Hg.	N=984 24 weeks	Primary: Change from baseline to week 24 in 24-hour mean SBP by ABPM Secondary: Change from baseline to week 24 in trough sitting clinic SBP, 24-hour mean DBP by ABPM, trough sitting clinic DBP and the proportion of patients who	Primary: After 24 weeks of treatment, the changes from baseline in 24-hour mean SBP were significantly greater with azilsartan 40 mg (-14.9 mm Hg) and 80 mg (-15.3 mm Hg) compared to valsartan 320 mg (-11.3 mm Hg; *P*<0.001 for both comparisons). Secondary: After 24 weeks of treatment, the changes from baseline in 24-hour sitting clinic SBP, were significantly greater with azilsartan 40 mg (-14.9 mm Hg) and 80 mg (-16.9 mm Hg) compared to valsartan 320 mg (-11.6 mm Hg; *P*<0.015 for both comparisons). Patients randomized to azilsartan 40 mg or 80 mg experienced greater reductions in mean 24-hour DBP compared to valsartan 320 mg (-2.16 mm Hg; 95% CI, -3.44 to -0.88 and -2.69 mm Hg; 95% CI, -3.99 to -1.40 for the 40 mg and 80 mg doses, respectively; *P*<0.001 for both

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD after 2 weeks			achieved a BP response, which was defined as a clinic SBP <140 mm Hg and/or a reduction of ≥20 mm Hg from baseline, or clinic DBP <90 mm Hg and /or a reduction of ≥10 mm Hg from baseline	comparisons). Compared to valsartan 320 mg, the mean reduction in clinic DBP was significantly greater for the patients receiving azilsartan 40 mg (-2.52 mm Hg; 95% CI, -4.06 to -0.98; *P*=0.001) or 80 mg (-2.76 mm Hg; 95% CI, -4.32 to -1.21; *P*<0.001). The percentage of patients who achieved a clinic SBP of <140 mm Hg and/or a reduction of ≥20 mm Hg was significantly greater with azilsartan 40 mg (56%; *P*=0.016) and 80 mg (59%; *P*=0.002) compared to patients who received valsartan 320 mg.
Baguet et al[32] Candesartan 8 mg QD vs losartan 50 mg QD vs placebo	DB, RCT Patients with mild- to moderate essential HTN (DBP 95 to 115 mm Hg)	N=256 6 weeks	Primary: Change in mean ambulatory DBP from baseline to the 0 to 24 hour period after the last dose of study medication Secondary: Change in mean ambulatory SBP from baseline to the 0 to 24 hour period after the last dose of study medication, change in DBP and SBP during the daytime and nighttime, change in DBP and SBP between 12 and 24 hours after dosing	Primary: At the end of the six weeks, the mean change in DBP between the baseline and the 0 to 24 hour period after the last dose of study medication was greater in patients receiving candesartan 8 mg compared to losartan (-7.3 vs -5.1 mm Hg; *P*<0.05) or placebo (0.3 mm Hg; *P*<0.001). Secondary: The mean change in SBP between the baseline and the 0-24 hour period after the last dose of study medication was greater in patients receiving candesartan (-10.8 mm Hg) or losartan (-8.8 mm Hg) than placebo (1.2 mm Hg; *P*<0.001). Candesartan was associated with a greater reduction in DBP and SBP relative to placebo, when compared to losartan during both the daytime and nighttime, and between 12 and 24 hours after dosing (*P*<0.001). Both active treatments were well tolerated.
Baguet et al[33]	MA	N=10,818	Primary: Weighted average	Primary: Data did not reflect outcomes from direct, head-to-head comparative

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Antihypertensive drugs (candesartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan, HCTZ, indapamide SR, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril and aliskiren) Drugs were used as monotherapy, either at a fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.	Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	8 to 12 weeks	reductions in SBP and DBP Secondary: Not reported	trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), CCBs (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (*P* values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), CCBs (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (*P* values were not reported). The weighted average reductions of SBP and DBP for each drug class were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. CCBs: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Robles et al[34] (ESTEPP) Eprosartan 600 mg QD	MC, OL, PRO Patients with mild- to moderate HTN with and without diabetes, mean age 65 years for patients with diabetes and 63 years for patients without diabetes	N=549 16 weeks	Primary: Changes in BP, compliance, adverse effects Secondary: Not reported	Primary: BP decreased significantly (*P*<0.0001) in both diabetic and nondiabetic patients (SBP, 25.9 vs 26.0 mm Hg, DBP, 12.5 vs 13.2 mm Hg, MAP, 16.9 vs 17.5 mm Hg and pulse pressure, 13.4 vs 12.8 mm Hg). Pulse pressure/MAP ratio showed a significant reduction in diabetics and nondiabetics. Treatment compliance did not differ between the groups (diabetics, 98.0% vs nondiabetics, 92.2%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The adverse effect rate was 7.0% in diabetic patients and 2.8% in nondiabetics. Secondary: Not reported
Ruilope et al[35] Eprosartan 600 mg QD (titration to 800 mg QD was allowed after 3 weeks) vs enalapril 5 mg QD (titration to 10 mg followed by 20 mg was allowed every 3 weeks)	DB, MC, PG, RCT Patients greater than 65 years of age with essential HTN, either newly diagnosed or for whom a change in existing antihypertensive medication is indicated due to poor control	N=334 12 weeks	Primary: Mean change from baseline in sitting SBP Secondary: Normalization rate for sitting SBP and DBP, response rate for sitting SBP and DBP, mean change from baseline in DBP	Primary: No significant difference between groups in change from baseline in sitting SBP was observed (*P*=0.76). Secondary: No significant difference between groups in change from baseline in sitting DBP was observed (*P*=0.84). BP response rates for SBP and DBP were significantly greater for eprosartan at week three ($P \leq 0.033$) but the significant difference had disappeared by endpoint ($P \geq 0.49$). Normalization rates for SBP were low in both groups (*P* value not reported). Normalization rates for DBP were higher in both groups than SBP normalization rates (*P* value not reported).
Flack et al[36] Losartan 50 mg QD vs eplerenone 50 mg QD vs placebo	DB, MC, PG, RCT Patients 18 years of age and older, with mild to moderate HTN, with SBP <180 mm Hg and DBP 95 to 109 mm Hg (off medication) or if patients were receiving antihypertensive	N=551 16 weeks	Primary: Mean change from baseline in DBP at 16 weeks Secondary: Mean change from baseline at 16 weeks in SBP, SBP and DBP within and between racial groups, response	Primary: At 16 weeks, eplerenone-treated patients exhibited significantly greater mean changes in DBP from baseline compared to either losartan- or placebo-treated patients (*P*<0.001). Secondary: At 16 weeks, eplerenone-treated patients exhibited significantly greater mean changes in SBP from baseline compared to either losartan- or placebo-treated patients (*P*<0.001). At 16 weeks, eplerenone-treated African American patients exhibited significantly greater mean changes in SBP and DBP from baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doses of study medications were increased if BP remained uncontrolled.	therapy their BP was <140/90 mm Hg		rate (percentage of patients with DBP <90 mm Hg or DBP ≥90 but ≥10 mm Hg below baseline), urinary albumin/creatinine ratio, effect of eplerenone in patients with various baseline renin and aldosterone levels, adverse effects	compared to the placebo-treated African American patients (*P*<0.001). At 16 weeks, eplerenone-treated African American patients exhibited significantly greater mean changes in SBP and DBP from baseline compared to the losartan-treated African American patients (*P*≤0.001). At 16 weeks, eplerenone-treated white patients exhibited significantly greater mean changes in SBP and DBP from baseline compared to the placebo-treated white patients (*P*=0.001). However, the difference in SBP and DBP lowering effects was not significant different between eplerenone- and losartan-treated white patients (*P*=0.126, *P*=0.068, respectively). Significantly greater percentage of eplerenone-treated patients exhibited a positive response to therapy compared to either placebo- (64.5 vs 41.2%; *P*<0.001) or losartan-treated patients (64.5 vs 48.3%; *P*=0.003). Eplerenone-treated patients (regardless of race) exhibited significant improvement in urinary albumin/creatinine ratio from baseline compared to placebo-treated patients (*P*=0.003). However, the difference in urinary albumin/creatinine ratio change from baseline was not significantly different between eplerenone- and losartan-treated patients (*P*=0.652). Compared to losartan therapy, eplerenone therapy was more effective in lowering SBP and DBP in patients with low to moderate baseline renin levels (*P*<0.05). However, the difference was not significant in patients with high baseline renin levels (*P* value not reported). Compared to losartan therapy, eplerenone therapy was more effective in lowering SBP in patients with low or high baseline aldosterone levels (*P*<0.05). However, the difference was not significant in patients with moderate baseline aldosterone levels (*P* value not reported). Compared to losartan therapy, eplerenone therapy was more effective

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in lowering DBP in patients with low baseline aldosterone levels (*P*<0.05). However, the difference was not significant in patients with moderate to high baseline aldosterone levels (*P* value not reported). There were no significant differences in the incidence of adverse events noted in eplerenone-, placebo- or losartan-treated patients (*P* value not reported). The reported incidence of gynecomastia, breast pain, menstrual abnormalities, impotence, hyperkalemia and decreased libido in eplerenone-treated patients was low and comparable to losartan- and placebo-treated patients.
Ribeiro et al[37] LAMHYST Amlodipine 5 mg QD (option to increase to 10 mg at 6 weeks) vs losartan 50 mg QD (option to increase to 100 mg at 6 weeks)	DB, DD, PG, PRO, RCT Flexible-dose escalation study Males and females 18 to 79 years of age with diagnosis of mild (>95 but <115 mm Hg) to moderate essential HTN and not taking an antihypertensive medication (within last 4 weeks)	N=194 12 weeks, with 2 days placebo treatment, mimicking a drug holiday after 12 weeks on treatment	Primary: Difference between treatment groups in mean change in ambulatory BP monitoring for last nine hours of treatment and during drug holiday Secondary: Not reported	Primary: After 12 weeks, mean reductions in SBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; *P*<0.001). Mean reductions in DBP were significantly larger in the amlodipine group than the losartan group (–18.1 vs –10.1 mm Hg; *P*<0.05). Mean increases in SBP were similar between the groups during the two-day drug holiday (*P*>0.05). After the two-day drug holiday, SBP was lower than baseline in both groups (*P*<0.001), with the amlodipine group SBP remaining significantly lower (*P*<0.01). Mean increases in DBP were similar between the groups during the two-day drug holiday (*P*>0.05). After the two-day drug holiday, DBP was lower than baseline in both groups (*P*=0.0001), with the amlodipine group DBP remaining significantly lower (*P*<0.05). Secondary: Not reported
Van Bortel et al[38] Losartan 50 mg QD	DB, MC, PG, RCT Patients <70 years of age with a DBP 95 to	314 12 weeks	Primary: Effects on BP and overall QOL	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced SBP compared to baseline (*P*<0.0001 for both), but the agents were not significantly different from each other (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs nebivolol 5 mg QD All patients entered a SB 2 week placebo run in period. If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy.	114 mm Hg		Secondary: Comparison of different aspects of QOL	Both agents also significantly decreased DBP compared to baseline (*P*<0.0001), but nebivolol significantly reduced DBP compared to losartan (*P*<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (*P*<0.007), but the agents were not significantly different from each other (*P* value not reported). Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the two treatments (*P* values not reported). Questions inquired about headaches, lightheadedness, sleepiness, flushing and sexual function.
Oparil et al[39] Olmesartan 20 mg QD vs irbesartan 150 mg QD, losartan 50 mg QD or valsartan 80 mg QD	DB, MC, PG, RCT Patients 18 years of age and older with essential HTN (cuff DBP ≥100 and ≤115 mm Hg and mean daytime DBP ≥90 and <120 mm Hg)	N=588 8 weeks	Primary: Change in seated cuff DBP at week eight compared to olmesartan Secondary: Change in seated cuff SBP at week eight, 24-hour DBP and SBP, adverse events	Primary: The mean reductions in seated cuff DBP at week eight were significantly greater with olmesartan (11.5 mm Hg) than with irbesartan (9.9 mm Hg; *P*=0.0412), losartan (8.2 mm Hg; *P*=0.0002) and valsartan (7.9 mm Hg; *P*<0.0001). The clinical significance of a few mm Hg DBP difference between the groups is unknown. Secondary: Reductions of cuff SBP were not significantly different among the four ARBs and ranged from 8.4 to 11.3 mm Hg. The reduction in mean 24-hour DBP with olmesartan (8.5 mm Hg) was significantly greater than reductions with losartan and valsartan (6.2 and 5.6 mm Hg, respectively) and showed a trend toward significance when compared to irbesartan (7.4 mm Hg; *P*=0.087). The reduction in mean 24-hour SBP with olmesartan (12.5 mm Hg) was significantly greater than the reductions with losartan and valsartan (9.0 and 8.1 mm Hg, respectively) and equivalent to the reduction with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				irbesartan (11.3 mm Hg). All drugs were well tolerated with the incidence of adverse events reported in 30.6% of patients in the olmesartan group, 35.6% for irbesartan, 32.0% for losartan and 44.8% for valsartan.
Brunner et al[40] Olmesartan 20 mg QD vs candesartan 8 mg QD	DB, RCT Patients with mainly mild- to moderate HTN	N=635 8 weeks	Primary: 24-hour antihypertensive efficacy (with emphasis on BP control during the early morning period), proportion of patients who achieved various ABPM goals (SBP/DBP <125/80 mm Hg) Secondary: Not reported	Primary: After eight weeks, significantly greater proportions of patients treated with olmesartan achieved 24-hour and daytime ABPM goals (25.6 and 18.3%, respectively) compared to candesartan (14.9%; *P*<0.001 and 9.6%; *P*=0.002, respectively). During the last four hours of 24-hour ABPM, the proportion of patients who achieved goals was significantly greater with olmesartan (33.3%) than candesartan (22.9%; *P*<0.001). Similarly, during the last two hours of 24-hour ABPM, the proportion of patients who achieved these BP goals was higher with olmesartan (26.9 and 19.9%) compared to candesartan (19.6%; *P*=0.028 and 14.3%; *P*=0.061). Secondary: Not reported
Weir et al[41] Olmesartan 20 mg for 4 weeks, then OM 40 mg for 4 weeks vs losartan 50 mg for 4 weeks, then LOS 100 mg for 4 weeks	AC, DB, MC, PRO, RCT Patients ≥18 but <100 years of age with mean SeDBP ≥95 and ≤115 mm Hg and mean SeSBP ≤180 mm Hg when measured at 2 consecutive qualification study visits during the	N=941 8 weeks	Primary: Mean change from baseline in trough SeDBP at week eight Secondary: Change from baseline in mean trough SeSBP at weeks four and eight, SeDBP at week four,	Primary: After eight weeks of treatment, patients randomized to receive olmesartan experienced a greater reduction from baseline in SeDBP compared to patients receiving losartan (-9.7 vs -7.1 mm Hg; *P*<0.0001). Secondary: At week four, olmesartan treatment was associated with a greater reduction from baseline in SeSBP compared to losartan (-12.0 vs -8.5 mm Hg; *P*=0.0001). At week eight, olmesartan treatment was associated with a greater reduction form baseline in SeSBP compared to losartan (-13.6 vs -9.7

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	placebo run-in phase		percentage of patients achieving the SeBP goal of <140/90 mm Hg at weeks four and eight, the change from baseline in mean 24-hour ambulatory SBP and DBP at weeks four and eight, and the percentage of patients achieving the mean 24-hour ambulatory BP target of <130/80 mm Hg at weeks four and eight.	mm Hg; *P*=0.0001). A significantly greater percentage of patients receiving olmesartan achieved the SeBP goal of <140/90 mm Hg at week four and eight, respectively, compared to losartan (26.5 vs 14.3% and 31.6 vs 19.5%; *P*<0.0001 for both comparisons). At week eight, there was a significant reduction in mean 24-hour ambulatory DBP for patients receiving olmesartan therapy compared to losartan (-2.4 mm Hg; *P*=0.02) and SBP (-3.6 mm Hg; *P*=0.02). At week four, there was no significant difference in 24-hour ambulatory BP for patients receiving olmesartan therapy compared to losartan (−7.37 vs −5.90 mm Hg; *P* value not reported). There was no significant difference in the percentage of patients achieving the 24-hour ambulatory BP target of <130/80 mm Hg for patients receiving olmesartan compared to losartan at week 4 (30.5 vs 19.5%; *P*=0.14), week eight (34.9 vs 25.5%; *P*=0.13), or at any time during treatment (42.3 vs 28.5%; *P*=0.05).
Karlberg et al[42] (TEES) Telmisartan 20 to 80 mg QD vs enalapril 5 to 20 mg QD HCTZ 12.5 or 25 mg QD could be added to either group as needed to reach DBP goal (≤90 mm Hg).	DB, DD, MC, PG, RCT Patients 65 years of age and older with mild- to moderate HTN	N=278 26 weeks	Primary: Change from baseline in supine SBP and DBP Secondary: Proportion of responders, safety	Primary: Both treatments had similar rates of HCTZ use. Both treatments showed comparable decreases in BP. Mean changes in DBP were -12.8 mm Hg for telmisartan and -11.4 mm Hg for enalapril (*P*=0.074). Mean changes in SBP were -22.1 mm Hg for telmisartan and -20.1 mm Hg for enalapril (*P*=0.350). Secondary: Overall, 63 and 62% of patients responded to telmisartan and enalapril, respectively, with a DBP of <90 mm Hg. Both regimens provided effective BP lowering over the 24-hour dosing interval, as determined by ambulatory BP monitoring. Both regimens were well tolerated; however, the enalapril group had a higher incidence of cough than the telmisartan group (15.8 vs 6.5%; *P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported).
Xi et al[43] Telmisartan vs losartan Regimens varied.	MA Patients with HTN	N=1,832 Duration varied	Primary: Reduction in DBP and SBP Secondary: Therapeutic response of DBP and SBP, tolerability	Primary: Use of telmisartan resulted in a significant reduction in clinic DBP (WMD, 1.52; 95% CI, 0.85 to 2.19) and SBP (WMD, 2.77; 95% CI, 1.90 to 3.63) when compared to losartan. Secondary: There was also a significant reduction in 24-hour mean ambulatory DBP (WMD, 2.49; 95% CI, 0.56 to 4.42) and SBP (WMD, 2.47; 95% CI, 0.40 to 4.55) with telmisartan as compared to losartan. There was a significant increase in therapeutic response of DBP (RR, 1.14; 95% CI, 1.04 to 1.23) and SBP response (RR, 1.10; 95% CI, 1.01 to 1.20) with telmisartan as compared to losartan. Both telmisartan and losartan were well tolerated.
Williams et al[44] (PRISMA I and PRISMA II pooled analysis) Telmisartan 40 mg QD for 2 weeks, followed by forced titration to 80 mg QD for 12 weeks vs ramipril 2.5 mg QD for 2 weeks, followed by forced titration to 5 mg QD for 6 weeks then 10 mg QD for 6 weeks	Blinded endpoint, OL, PRO, RCT (PROBE) Patients 18 years of age and older with mild- to moderate HTN	N=1,613 14 weeks	Primary: Change from baseline in mean ambulatory BP during the final six hours of the 24-hour dosing interval Secondary: Change from baseline in mean ambulatory BP during the 24-hour dosing interval, morning, daytime and nighttime ambulatory BP, 24-hour BP load, treatment response,	Primary: A significantly greater reduction in mean ambulatory BP during the last six hours of the 24-hour dosing interval was observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001). Secondary: Significantly greater reductions in mean 24-hour, morning, daytime, nighttime and 24-hour BP load were observed with telmisartan 80 mg compared to ramipril 5 mg and 10 mg (P<0.0001). Significantly greater reductions in treatment response and BP control rates were observed with telmisartan 80 mg compared to ramipril 5 and 10 mg (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			BP control	
Karotsis et al[45] Valsartan 80 mg QD vs chlorthalidone 12.5 mg QD vs felodipine 5 mg QD vs lisinopril 10 mg QD All patients also received diltiazem 240 mg QD.	RCT Patients 25 to 79 years of age with uncontrolled HTN(average office BP >140/90 mm Hg for all or >153/85 mm Hg for diabetics or patients <65 years of age, confirmed on 2 office visits ≥1 week apart) after ≥4 weeks of OL monotherapy with diltiazem at 240 mg QD	N=211 8 weeks	Primary: BP Secondary: Not reported	Primary: There was a significant decline in both office and home SBP and DBP during the trial with all treatments. The antihypertensive effect was more pronounced and reached significance when home BP monitoring was used in comparison to office BP without the white-coat effect (*P*<0.001 for all BP changes). With or without the white-coat effect, BP still declined and the differences were significant (*P*<0.0001 for all BP changes). Secondary: Not reported
Conlin et al[46] (PREVAIL) Candesartan 8 to 16 mg/day, irbesartan 150 to 300 mg/day, losartan 50 to 100 mg/day and valsartan 80 to 160 mg/day vs another ARB vs	MA Patients with HTN	N=11,281 Duration varied	Primary: Weighted average for SBP and DBP reduction with ARB monotherapy, dose titration, and with the addition of low-dose HCTZ were calculated; responder rates Secondary: Not reported	Primary: The absolute weighted-average reductions in DBP (8.2 to 8.9 mm Hg) and SBP (10.4 to 11.8 mm Hg) for ARB monotherapy were comparable for all ARBs (*P* value not reported). Responder rates for ARB monotherapy were 48 to 55%. Dose titration resulted in slightly greater BP reduction and an increase in responder rates of 53 to 63% (*P* value not reported). ARB and HCTZ combinations produced substantially greater reductions in SBP (16.1 to 20.6 mm Hg) and DBP (9.9 to 13.6 mm Hg) than ARB monotherapy (*P* value not reported). Responder rates for ARB and HCTZ combinations were 56 to 70% (*P* value not reported). The authors concluded that candesartan, irbesartan, losartan and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ARB plus low-dose HCTZ				valsartan produced comparable antihypertensive efficacy when administered at their recommended doses, a near flat dose response when titrating from starting to maximum recommended dose, and substantial potentiation of the antihypertensive effect with addition of HCTZ. Secondary: Not reported
Van Bortel et al[47] ARB, ACE inhibitor, β-blocker, CCB or placebo vs nebivolol	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; *P*=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; *P*=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; *P*=0.283), CCBs (OR, 1.19; 95% CI, 0.83 to 1.70; *P*=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; *P*=0.212). Overall, a higher percentage of patients obtained normalized BP with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; *P*=0.012). A higher percentage of patient receiving nebivolol obtained normalized BP compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; *P*=0.004) and CCBs (OR, 1.96; 95% CI, 1.05 to 1.96; *P*=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; *P*=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; *P*<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; *P*=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; *P*=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; *P*=0.007) and CCBs (OR, 0.49; 95% CI 0.33 to 0.72; *P*<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Lindholm et al[48] β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol or propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide, captopril, diltiazem, enalapril, felodipine, HCTZ, isradapine, lacidipine, lisinopril, losartan or verapamil) or placebo	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; *P*=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; *P*<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (*P* value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; *P*=0.14). Secondary: Not reported
Wiysonge et al[49] Other antihypertensive therapies (i.e., placebo, diuretics, CCBs or renin-angiotensin system inhibitors) vs β-blockers (atenolol,	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; *P* value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; *P* value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; *P* value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to CCBs (RR, 1.07; 95% CI, 1.00 to 1.14; *P*=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metoprolol, oxprenolol* or propranolol)				therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to CCBs (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), CCBs (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly worse than that of CCBs (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to CCBs (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Cardiovascular Risk Reduction				
Lithell et al[70] (SCOPE) Candesartan 16 mg QD vs placebo in addition to	DB, MC, PC, PG, RCT Patients 70 to 89 years of age with mild-to-moderate HTN (SBP 160 to 179 mm Hg and/or DBP	N=4,964 3.7 years	Primary: First major coronary event including cardiovascular death, nonfatal MI or nonfatal stroke Secondary:	Primary: Results showed no significant difference in the primary end point between candesartan and placebo (*P*=0.19). Secondary: Candesartan treatment reduced nonfatal stroke by 27.8% (*P*=0.04) and all stroke by 23.6% (*P*=0.056) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
conventional therapy (diuretics, ACE inhibitors, β-blockers, CCBs)	90 to 99 mm Hg) and MMSE scores ≥24		Cardiovascular death, nonfatal and fatal stroke and MI, cognitive function	There were no significant differences in MI and cardiovascular mortality. Mean MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the control group (*P*=0.20). The proportion of patients who had a significant cognitive decline or developed dementia was not different in the two groups.
Ogihara et al[71] CASE-J Candesartan 4 to 12 mg QD vs amlodipine 2.5 to 10 mg QD	AC, MC, OL, PG, PRO, RCT Patients with high risk HTN (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70 years old or SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old), with either type 2 diabetes, history of stroke or ischemic attack, LVH, proteinuria or serum creatinine ≥1.3 mg/dL	N=4,703 Up to 4 years	Primary: First fatal/nonfatal cardiovascular event (composite of sudden death, cerebrovascular events, cardiac events including heart failure, angina pectoris, acute MI, renal events, including serum creatinine increases, vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion Secondary: All-cause death, new-onset diabetes, discontinuation due to adverse events	Primary: One hundred thirty four patients experienced a cardiovascular event in each treatment group (HR, 1.00; 95% CI, 0.78 to 1.27; *P*=0.969). Secondary: All-cause death rates did not differ between groups, 73 deaths in the candesartan group and 86 deaths in the amlodipine group (*P* value not reported). New-onset diabetes occurred in significantly fewer patients in the candesartan group than the amlodipine group (HR, 0.64; 95% CI, 0.43 to 0.97; *P*=0.033). One hundred twenty five (5.4%) patients in the candesartan group and 134 (5.8%) patients in the amlodipine group discontinued due to adverse events (*P* value not reported).
ONTARGET Investigators[50] Telmisartan 80 mg QD	DB, MC, PC, RCT Men and women with coronary, peripheral,	N=25,620 56 months (median	Primary: Death from cardiovascular causes, MI, stroke	Primary: The primary outcome occurred in 16.5, 16.7 and 16.3% of patients receiving ramipril, telmisartan and combination therapy, respectively (*P*=0.83 for telmisartan compared to ramipril and *P*=0.38 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ramipril 10 mg QD vs telmisartan 80 mg QD plus ramipril 10 mg QD	or cerebrovascular disease or diabetes with end-organ damage	follow-up)	or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, MI or stroke; heart failure; worsening or new angina; new diagnosis diabetes mellitus; new atrial fibrillation; renal impairment; revascularization procedures	combination therapy compared to ramipril). Secondary: The composite of death from cardiovascular causes, MI or stroke occurred in 14.1% of patients in the ramipril group and 13.9% of patients in the telmisartan group (RR, 0.99; 95% CI, 0.91 to 1.07; *P*=0.001 for noninferiority). Combination therapy was not significantly better than ramipril alone (RR, 0.99; 95% CI, 0.92 to 1.07). There were no significant differences in the rates of secondary outcomes, except for renal dysfunction, which occurred in 10.2% of patients receiving ramipril, 10.6% of patients receiving telmisartan and 13.5% of patients receiving combination therapy (*P*<0.001 vs ramipril; *P* value not reported vs telmisartan). As compared to the ramipril group, the telmisartan group had lower rates of cough (1.1 vs 4.2%; *P*<0.001) and angioedema (0.1 vs 0.3%; *P*=0.01) and a higher rate of hypotensive symptoms (2.6 vs 1.7%; *P*<0.001); the rate of syncope was the same in the two groups (0.2%). As compared to the ramipril group, combination therapy had an increased risk of hypotensive symptoms (4.8 vs 1.7%; *P*<0.001), syncope (0.3 vs 0.2%; *P*=0.03) and renal dysfunction (13.5 vs 10.2%; *P*<0.001).
TRANSCEND Investigators[51] Telmisartan 80 mg QD vs placebo	DB, MC, PC, RCT Men and women with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage and intolerance to ACE inhibitors	N=5,926 56 months (median follow-up)	Primary: Death from cardiovascular causes, MI, stroke or hospitalization for heart failure Secondary: Composite of death from cardiovascular causes, MI or	Primary: No significant difference was observed between the telmisartan group and the placebo group in death from cardiovascular causes, MI, stroke or hospitalization for heart failure (*P*=0.216). Secondary: The composite of death from cardiovascular causes, MI or stroke occurred in significantly fewer patients in the telmisartan group compared to placebo (*P*=0.048), but this difference was not statistically significant after adjustment for multiplicity of comparisons and overlap with the primary outcome (*P*=0.068, adjusted).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			stroke; heart failure; development of diabetes mellitus; atrial fibrillation; revascularization	No significant differences were observed between groups in other secondary outcomes.
Julius et al[72] (VALUE) Valsartan 80 to 160 mg QD vs amlodipine 5 to 10 mg QD	DB, PG, RCT Patients 50 years of age and older with treated or untreated HTN and history of CVD, stroke or diabetes; previous medications were discontinued at trial onset	N=15,245 4.2 years (mean)	Primary: Time to first cardiac event (cardiac morbidity and mortality) Secondary: Fatal and nonfatal MI, fatal and nonfatal heart failure and fatal and nonfatal stroke, all-cause mortality, new onset diabetes	Primary: There were no differences in the primary composite end point between the valsartan and amlodipine groups (10.6 vs 10.4%; *P*=0.49). Secondary: There was a higher incidence of MI (4.8 vs 4.1%; *P*=0.02) in patients receiving valsartan than amlodipine. There was no difference in the incidence of heart failure (4.6 vs 5.3%; *P*=0.12), stroke (4.2 vs 3.7%; *P*=0.08) and all-cause mortality (11.0 vs 10.8%; *P*=0.45) between valsartan- and amlodipine-treated patients. New onset diabetes occurred less with valsartan (13.1%) vs amlodipine (16.4%; *P*<0.001). Limited benefit of valsartan vs amlodipine was attributed to the differences in BP lowering. Combined target BP (<140/90 mm Hg) was achieved in 58 and 62% of patients receiving valsartan and amlodipine, respectively.
Blood Pressure Lowering Treatment Trialists' Collaboration[73] ARBs (9 trials) vs ACE inhibitors (17 trials)	MA (RCT published by the end of 2004) Patients with high BP, diabetes, history of CHD or cerebrovascular disease	N=146,838 (26 trials) Duration varied	Primary: Nonfatal MI or death from CHD, including sudden death; heart failure causing death or requiring hospitalization; nonfatal stroke or death from cerebrovascular disease	Primary: From a total of 146,838 individuals with high BP or an elevated risk of cardiovascular disease, major cardiovascular events were documented in 22,666 patients during follow-up. The analyses showed comparable BP-dependent reductions in risk with ACE inhibitors and ARBs (*P*≥0.3 for all three outcomes). ACE inhibitors produced a BP-independent reduction in the relative risk of CHD of approximately 9% (95% CI, 3 to 14). No similar effect was detected for ARBs, and there was some evidence of a difference between ACE inhibitors and ARBs in this regard (*P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	For both stroke and heart failure, there was no evidence of any BP-independent effects of either ACE inhibitors or ARBs. Secondary: Not reported The authors concluded that there are similar BP-dependent effects of ACE inhibitors and ARBs for the risks of stroke, CHD and heart failure. For ACE inhibitors but not ARBs, there is evidence of BP-independent effects on the risk of major coronary disease events.
Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy				
Dahlöf et al[52] (LIFE) Losartan 50 to 100 mg/day plus HCTZ 12.5 to 25 mg/day if needed for BP control vs atenolol 50 to 100 mg/day, plus HCTZ 12.5 to 25 mg/day if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revasculari-zation procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference; *P*=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference; *P*=0.37). Mean arterial pressure was 102.2 and 102.4 mm Hg, respectively (*P* value not significant). Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 vs -1.8 beats/minute, respectively; *P*<0.0001). Compared to atenolol, the primary composite endpoint occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.021). While there was no difference in the incidence of cardiovascular mortality (*P*=0.206) and MI (*P*=0.491), losartan treatment resulted in a 24.9% RRR in stroke compared to atenolol (*P*=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (*P*=0.001). There was no significant difference among the other secondary end points between the two treatment groups. Note: At end point or end of follow-up, 18 and 26% of patients on

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16 and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al[53] (LIFE Black Subset) Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years of age with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=523 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: Not reported	Primary: Compared to atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; *P*=0.033). Hazard ratios favored atenolol across all parameters (*P*=0.246 for cardiovascular mortality, *P*=0.140 for MI and *P*=0.030 for stroke). In African American patients, BP reduction was similar in both groups, and regression of electrocardiographic-LVH was greater with losartan. Secondary: Not reported
Lindholm et al[74] (LIFE Diabetic Subset) Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years of age with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (*P*=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (*P*=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (*P*=0.002). Mean BP fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; *P*=0.002).
Kjeldsen et al[75] (LIFE Isolated Systolic	DB, DD, PG, RCT	N=1,326	Primary: Composite of	Primary: Compared to atenolol, losartan resulted in a trend towards a 25%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypertension Subset) Losartan 50 to 100 mg QD with HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, with HCTZ 12.5 to 25 mg QD if needed for BP control	Patients 55 to 80 years of age with isolated systolic HTN (SBP of 160 to 200 mm Hg and DBP <90 mm Hg) and LVH	≥4 years	cardiovascular death, MI and stroke Secondary: All-cause mortality	reduction in the primary end point (*P*=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (*P*=0.01) and 40% risk reduction in stroke compared to atenolol (*P*=0.02). There was no difference in the incidence of MI. BP was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms. Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; *P*<0.046).
Fossum et al[76] (ICARUS, a LIFE substudy) Losartan 50 to 100 mg QD plus HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, plus HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=81 3 years	Primary: Amount and density of atherosclerotic lesions in the common carotid arteries and carotid bulb Secondary: Not reported	Primary: The amount of plaque decreased in the losartan group and increased in the atenolol group, though the difference between groups was not statistically significant (*P*=0.471). Patients in the atenolol group had a greater increase in plaque index compared to the losartan group, though the difference between groups was not statistically significant (*P*=0.742) Secondary: Not reported
Kizer et al[77] (LIFE substudy) Losartan 50 to 100 mg QD plus HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm	N=9,193 ≥4 years	Primary: Reduction in the risk of different stroke subtypes and neurological deficits Secondary:	Primary: The risk of fatal stroke was significantly decreased in the losartan group compared to the atenolol group (*P*=0.032). The risk of atherothrombotic stroke was significantly decreased in the losartan group compared to the atenolol group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atenolol 50 to 100 mg QD, plus HCTZ 12.5 to 25 mg QD if needed for BP control	Hg) and LVH		Not reported	Comparable risk reductions were observed for hemorrhagic and embolic stroke but did not reach statistical significance. The risk of recurrent stroke was significantly reduced in the losartan arm compared to the atenolol arm (*P*=0.017). The number of neurological deficits per stroke was similar (*P*=0.68), but there were fewer strokes in the losartan group for nearly every level of stroke severity. Secondary: Not reported
Wachtell et al[78] (LIFE substudy) Losartan 50 to 100 mg QD plus HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, plus HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=8,851 (patients in LIFE with no baseline history of AF but at risk for AF) ≥4 years	Primary: Incidence of new-onset AF and outcome Secondary: Not reported	Primary: Significantly fewer patients in the losartan group experienced new-onset AF compared to the atenolol group (*P*<0.001). Randomization to losartan treatment was associated with a 33% lower rate of new onset AF independent of other risk factors (*P*<0.001). Patients in the losartan group had a 40% lower rate of composite events consisting of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI (*P*=0.03). Significantly fewer strokes occurred in the losartan group compared to the atenolol group (*P*=0.01), and there was a trend toward fewer MIs in the losartan group (*P*=0.16). There was no significant difference in cardiovascular mortality between groups. In contrast, the atenolol group experienced significantly fewer hospitalizations for heart failure (*P*=0.004) and a trend toward fewer sudden cardiac deaths (*P*=0.07). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Wachtell et al[79] (LIFE substudy) Losartan 50 to 100 mg QD plus HCTZ 12.5 to 25 mg QD if needed for BP control vs atenolol 50 to 100 mg QD, plus HCTZ 12.5 to 25 mg QD if needed for BP control	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and LVH	N=342 (LIFE patients with AF at the start of the LIFE study) ≥4 years	Primary: Cardiovascular morbidity and mortality Secondary: Not reported	Primary: Patients with a history of AF had significantly higher rates of cardiovascular and all-cause mortality, fatal and non-fatal stroke, heart failure, revascularization and sudden cardiac death compared to patients without AF ($P<0.001$). Patients with a history of AF had similar rates of MI and hospitalization for angina pectoris ($P\geq0.209$). The primary composite endpoint of cardiovascular mortality, stroke and MI occurred in significantly fewer patients in the losartan group compared to the atenolol group ($P=0.009$). The difference in MI between groups was not significant. Treatment with losartan trended toward lower all-cause mortality ($P=0.09$) and fewer pacemaker implantations ($P=0.065$). Secondary: Not reported
Heart Failure				
Pfeffer et al[54] (CHARM Overall Programme) Candesartan 32 mg QD (±ACE inhibitor) vs placebo (±ACE inhibitor)	DB, PC, PG, RCT Summary of all CHARM sub-studies	N=7,599 37.7 months	Primary: All-cause mortality (Overall Programme) and cardiovascular death or hospital admission for CHF (all of the component trials) Secondary: Not reported	Primary: In the overall analysis, candesartan 32 mg daily resulted in an 18% decreased risk of all-cause mortality compared to placebo (23 vs 25%; unadjusted HR, 0.91; 95% CI, 0.83 to 1.00; $P=0.055$; covariate adjusted HR, 0.90; 95% CI, 0.82 to 0.99; $P=0.032$). Annual mortality rates were 8.1 and 8.8% for patients treated with candesartan and placebo, respectively. The lower mortality in patients treated with candesartan vs placebo was attributed to fewer cardiovascular deaths (18 vs 20%; unadjusted HR, 0.88; 95% CI, 0.79 to 0.97; $P=0.012$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Hospital admissions for CHF were significantly fewer in patients treated with candesartan than placebo (20 vs 24%; *P*<0.0001). Secondary: Not reported
McMurray et al[55] (CHARM-Added) Candesartan 32 mg QD in patients already taking ACE inhibitors vs placebo in patients already taking ACE inhibitors	DB, MC, PC, RCT Patients 18 years of age and older with LVEF ≤40%, NYHA Class II to IV heart failure and treatment with an ACE inhibitor at a constant dose for 30 days or longer	N=2,548 41 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg daily when added to ACE inhibitors resulted in a 15% reduction in the primary end point (*P*=0.011), 16% decrease in cardiovascular deaths (*P*=0.029) and 17% reduction in heart failure hospitalizations (*P*=0.014). Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, MI, stroke or coronary revascularization in the candesartan group (42.9%) compared to placebo (46.9%; *P*=0.015).
Granger et al[80] (CHARM-Alternative) Candesartan 32 mg QD vs placebo	DB, PC, RCT Patients 18 years of age and older with LVEF ≤40%, NYHA Class II to IV heart failure and intolerance to ACE inhibitors	N=2,028 33.7 months	Primary: Composite of cardiovascular death and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary revascularization	Primary: Compared to placebo, candesartan 32 mg daily resulted in a 30% reduction of the composite end point (*P*<0.0001). A 20% decrease in cardiovascular death (*P*=0.02) and 39% reduction in heart failure hospitalizations (*P*<0.0001) were noted in patients treated with candesartan compared to placebo. Study drug discontinuation rates were similar in the candesartan (30%) and placebo (29%) groups. Secondary: Fewer patients experienced cardiovascular death, hospital admission for CHF, MI, stroke or coronary revascularization in the candesartan group (39.1%) compared to placebo (44.9%; *P*<0.0001).
Yusuf et al[56] (CHARM-Preserved)	DB, PC, RCT Patients 18 years of	N=3,025 36.6 months	Primary: Composite of cardiovascular death	Primary: Compared to placebo, candesartan 32 mg daily resulted in an insignificant 14% trend towards lower incidence of the primary end

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Candesartan 32 mg QD vs placebo	age and older with preserved ejection fraction (>40%) and symptomatic heart failure		and hospitalization for heart failure Secondary: Composites of primary end point and MI, nonfatal stroke and coronary revascularization	point (*P*=0.051). Candesartan significantly reduced the risk of heart failure hospitalization (16%; *P*=0.047) but did not significantly decrease the risk of cardiovascular death (*P*=0.635). Secondary: The composite of cardiovascular death, hospitalization for CHF, MI and stroke was significantly lower in the candesartan group compared to placebo (25.6 vs 28.4%; *P*=0.037). There was no significant difference in the composite of cardiovascular death, hospital admission for CHF, MI, stroke or coronary revascularization in the candesartan group (30.4%) compared to placebo (32.9%; *P*=0.130).
McKelvie et al[57] (RESOLVD Pilot Study) Candesartan 4 to 16 mg QD vs enalapril 10 mg BID vs candesartan 4 to 8 mg QD plus enalapril 10 mg BID	DB, MC, PG, RCT Patients with CHF (NYHA Class II to IV), a 6-minute walk distance of 500 meters or less and an ejection fraction <40%	N=768 43 weeks	Primary: Change in 6-minute walk distance Secondary: Change in NYHA functional class, quality of life, ejection fraction, ventricular volumes, neurohormone levels, safety	Primary: There were no significant differences among the groups with regards to the six-minute walk distance over the 43 week study period (*P* value not reported). Secondary: There were no significant differences among the groups with regards to the NYHA functional class or quality of life at 18 or 43 weeks (*P* values not reported). Ejection fraction increased more with candesartan plus enalapril than monotherapy with either agent; however, the difference was not statistically significant (*P* value not significant). End-diastolic volumes (*P*<0.01) and end-systolic volumes (*P*<0.05) increased less with combination therapy than with monotherapy with either agent. Aldosterone decreased with combination therapy at 17, but not 43, weeks compared to candesartan or enalapril (*P*<0.05). Brain natriuretic peptide decreased with combination therapy compared to candesartan and enalapril alone (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				BP decreased with combination therapy compared to candesartan or enalapril alone (*P*<0.05). Compared to enalapril, potassium levels decreased with candesartan use (*P*<0.05) and increased with candesartan plus enalapril (*P*<0.05). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups. There were no significant differences in creatinine, mortality or hospitalizations for CHF or any cause among the three groups.
Pitt et al[58] (ELITE) Losartan 50 mg QD vs captopril 50 mg TID	DB, MC, PG, RCT Patients 65 years of age and older with symptomatic heart failure (NYHA Class II to IV and LVEF ≤40%) and no history of prior ACE inhibitor therapy	N=722 1 year	Primary: Change in renal function Secondary: Composite of death and/or hospital admission for heart failure, all-cause mortality, admission for heart failure, NYHA class, admission for MI or unstable angina	Primary: No difference between losartan and captopril was reported in the rate of persistent rise in serum creatinine concentrations (10.5% for both groups). Secondary: Death and/or hospital admission for heart failure was recorded in 9.4% of patients receiving losartan and 13.2% for patients receiving captopril (risk reduction, 32%; 95% CI, -4 to 55; *P*=0.075). This risk reduction was primarily due to a decrease in all-cause mortality (4.8 vs 8.7%; risk reduction, 46%; 95% CI, 5 to 69; *P*=0.035). Admissions with heart failure were the same in both groups (5.7%), as was improvement in NYHA functional class from baseline. Admission to the hospital for any reason was less frequent with losartan than with captopril treatment (22.2 vs 29.7%; *P*=0.014). More patients discontinued therapy due to adverse events with captopril (20.8%) than losartan (12.2%; *P*=0.002).
Pitt et al[59] (ELITE II) Losartan 50 mg QD vs	DB, MC, PG, RCT Patients 60 years of age and older with symptomatic heart failure (NYHA Class	N=3,152 555 days (mean follow-up)	Primary: All-cause mortality Secondary: Composite of sudden cardiac	Primary: No significant difference in all-cause mortality was reported between losartan (17.7%) and captopril (15.9%; HR, 1.13; 95% CI, 0.95 to 1.35; *P*=0.16). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
captopril 50 mg TID	II to IV and LVEF ≤40%) and no history of prior ACE inhibitor therapy		death or resuscitated cardiac arrest	Sudden death or resuscitated cardiac arrest was observed in 9.0% of patients receiving losartan and 7.3% of patients receiving captopril (HR, 1.25; 95% CI, 0.98 to 1.60; *P*=0.08). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse events (9.7 vs 14.7%; *P*<0.001), including cough (0.3 vs 2.7%). Note: The ELITE II trial was a larger follow-up trial to the ELITE I trial to confirm the secondary end point from the ELITE I trial which reported a greater reduction in all-cause mortality with losartan compared to captopril.
Cohn et al[60] (Val-HeFT) Valsartan 160 mg BID vs placebo	DB, PC, RCT Patients 18 years of age and older with a cardiovascular history and NYHA Class II to IV heart failure	N=5,010 2 years	Primary: Mortality and composite end point of morbidity and mortality Secondary: Change in NYHA class, ejection fraction, signs and symptoms of heart failure, quality of life	Primary: Compared to placebo, valsartan resulted in no significant differences in all-cause mortality. Patients treated with valsartan experienced a 13% decrease in the composite end point (*P*=0.009) and 27% decrease in heart failure hospitalizations (*P*<0.001). Secondary: Treatment with valsartan resulted in significant improvements in NYHA functional class, ejection fraction, signs and symptoms of heart failure and quality of life as compared to placebo (*P*<0.01). In a post hoc analysis of the combined end point and mortality in subgroups defined according to baseline treatments with ACE inhibitors or β-blockers, valsartan had a favorable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.
Lee et al[81] ARBs vs	MA Patients with chronic heart failure and high-risk acute MI	N=38,080 Duration varied	Primary: All-cause mortality and heart failure hospitalizations	Primary: ARBs were associated with reduced all-cause mortality (OR, 0.83) and heart failure hospitalizations (OR, 0.64) vs placebo. There was no difference in all-cause mortality (OR, 1.06) and heart

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo (+/-ACE inhibitor) vs ACE inhibitor monotherapy			Secondary: Not reported	failure hospitalization (OR, 0.95) between ARBs and ACE inhibitors. When ARBs were combined with ACE inhibitors, all-cause mortality was not reduced (OR, 0.97), but heart failure hospitalizations were reduced (OR, 0.77) compared to treatment with ACE inhibitors alone. Two RCT comparing ARBs with ACE inhibitors in patients with high-risk acute MI did not reveal differences in all-cause mortality or heart failure hospitalization. Secondary: Not reported
Post–Myocardial Infarction				
Dickstein et al[62] (OPTIMAAL) Losartan 50 mg QD vs captopril 50 mg TID	DB, MC, PG, RCT Patients 50 years of age and older with an acute MI and signs or symptoms of heart failure during the acute phase or a new Q-wave anterior infarction or reinfarction	N=5,477 2.7 years (mean)	Primary: All-cause mortality Secondary: Composite of sudden cardiac death or resuscitated cardiac arrest	Primary: No significant difference in all-cause mortality was reported between patients receiving losartan and captopril (18 vs 16%, respectively; RR, 1.13; 95% CI, 0.99 to 1.28; *P*=0.07). Secondary: No significant difference in sudden cardiac death or resuscitated cardiac arrest was reported between patients receiving losartan and captopril (9 vs 7%; RR, 1.19; 95% CI, 0.98 to 1.43; *P*=0.07). Losartan was significantly better tolerated than captopril, with fewer patients discontinuing study medication (17 vs 23%; *P*<0.0001).
Pfeffer et al[61] (VALIANT) Valsartan 160 mg BID vs captopril 50 mg TID vs	DB, MC, RCT Men and women 18 years of age and older with an acute MI that was complicated by clinical or radiologic signs of heart failure and/or evidence of	N=14,703 24.7 months	Primary: All-cause mortality Secondary: Death from cardiovascular causes, recurrent MI, hospitalization for heart failure	Primary: No significant difference in all-cause mortality was reported between valsartan monotherapy and captopril monotherapy (*P*=0.98). No significant difference in all-cause mortality was observed between valsartan plus captopril combination therapy and captopril monotherapy (*P*=0.73). Secondary: The rate of death from cardiovascular causes, reinfarction or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination valsartan 80 mg BID and captopril 50 mg TID	left ventricular systolic dysfunction			hospitalization for heart failure was not significantly different between valsartan and captopril monotherapy (*P*=0.20). The rate of death from cardiovascular causes, reinfarction or hospitalization for heart failure was not significantly different between valsartan and captopril combination therapy and captopril monotherapy (*P*=0.37). Combination therapy had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group and cough, rash and taste disturbance were more common in the captopril group.
Renal Dysfunction				
Mogensen et al[65] (CALM) Candesartan 16 mg QD vs lisinopril 20 mg QD vs candesartan 16 mg QD plus lisinopril 20 mg QD Patients received 12 weeks monotherapy followed by an additional 12 weeks of monotherapy or combination therapy.	DB, DD, MC, PG, RCT Patients 30 to 75 years of age with HTN, type 2 diabetes and microalbuminuria	N=199 24 weeks	Primary: BP and urinary albumin:creatinine ratio Secondary: Not reported	Primary: At 12 weeks, mean reductions in DBP were 9.7 (*P*<0.001) and 9.5 mm Hg (*P*<0.001), respectively, and in urinary albumin:creatinine ratio were 46 (*P*<0.001) and 30% (*P*<0.001) for lisinopril and candesartan, respectively. Compared to either agent alone, at 24 weeks the combination of lisinopril plus candesartan resulted in 16.3 mm Hg reduction in mean DBP vs 10.4 mm Hg for candesartan alone (*P*<0.001) and 10.7 mm Hg for lisinopril alone (*P*<0.001). The reduction in urinary albumin:creatinine ratio with combination treatment (50%) was greater than with lisinopril alone (39%; *P*<0.001) and candesartan alone (24%; *P*=0.05). All treatments were generally well tolerated. Secondary: Not reported
Lewis et al[63] (IDNT)	DB, MC, PC, PRO, RCT	N=1,715	Primary: Composite of risk of	Primary: Compared to placebo, irbesartan 300 mg daily resulted in a 20% lower

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Irbesartan 300 mg QD vs amlodipine 10 mg QD vs placebo	Patients 30 to 70 years of age, with type 2 diabetes mellitus, HTN and nephropathy	2.6 years	doubling serum creatinine, ESRD or death from any cause Secondary: Composite of death from cardiovascular causes, nonfatal MI, heart failure requiring hospitalization, permanent neurologic deficit caused by a cerebrovascular event or lower limb amputation	relative risk of the composite primary outcome (*P*=0.02). Irbesartan treatment was associated with a 33% lower risk of doubling serum creatinine (*P*=0.003) and 23% trend towards lower risk of ESRD (*P*=0.07) compared to placebo. There was no significant difference in risk of death from any cause for irbesartan compared to placebo (*P*=0.57). Compared to amlodipine, irbesartan treatment resulted in a 23% lower risk of composite primary outcome (*P*=0.006). Irbesartan treatment was associated with a 37% lower risk of doubling serum creatinine vs amlodipine (*P*<0.001) and 23% trend towards lower risk of ESRD vs amlodipine (*P*=0.07). There was no significant difference in risk of death from any cause (*P*=0.80). Secondary: There were no significant differences in the secondary cardiovascular composite end point (*P*=0.40 and *P*=0.79 for irbesartan vs placebo and amlodipine, respectively).
Parving et al[82] (IRMA2) Irbesartan 150 or 300 mg QD vs placebo	DB, MC, PC, RCT Patients with HTN, type 2 diabetes mellitus and microalbuminuria	N=590 2 years	Primary: Time to onset of diabetic nephropathy Secondary: Changes in level of albuminuria and creatinine clearance and restoration of normoalbuminuria	Primary: The primary end point was reached in 5.2% of patients in the irbesartan 300 mg group (*P*<0.001) and 9.7% of patients in the irbesartan 150 mg group (*P*=0.08) compared to 14.9% of patients receiving placebo. Secondary: Irbesartan reduced the level of urinary albumin excretion by 38% in patients receiving the 300 mg dose and 24% in patients receiving the 150 mg dose vs 2% for placebo (*P*<0.001 for the combined irbesartan groups vs placebo and *P*<0.001 for the 300 vs 150 mg doses). There was no significant difference in the decline in creatinine clearance among the three groups. Restoration of normoalbuminuria was observed in 34% of patients receiving irbesartan 300 mg (*P*=0.006), 24% of patients receiving irbesartan 150 mg (*P* value not reported) and 21% with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Brenner et al[64] (RENAAL) Losartan 50 to 100 mg QD vs placebo	DB, PC, RCT Patients 31 to 70 years of age with HTN, type 2 diabetes mellitus and nephropathy on conventional antihypertensive therapy	N=1,513 3.4 years	Primary: Composite of risk of doubling of serum creatinine, ESRD or death from any cause Secondary: Composite of morbidity and mortality from cardiovascular causes, proteinuria, rate of progression of renal disease	Primary: Compared to placebo, losartan resulted in a 16% reduction of composite primary end point (*P*=0.02). Losartan treatment produced a 25% reduction of doubling serum creatinine vs placebo (*P*=0.006) and 28% reduction in ESRD vs placebo (*P*=0.002). No differences in mortality were reported (*P*=0.88). Secondary: There was no significant difference between the losartan and placebo groups in the composite end point of morbidity and mortality from cardiovascular causes (no *P* value reported). Losartan treatment led to an average reduction in the level of proteinuria by 35% (*P*<0.001 vs placebo). Losartan reduced the rate of decline in renal function by 18% (*P*=0.01 vs placebo).
Hou et al[66] (ROAD) Losartan 50 mg QD vs individual uptitration (50 to 200 mg/day with median dose of 100 mg/day) vs benazepril 10 mg QD vs individual uptitration (10 to 40 mg/day with median dose of 20 mg/day)	OL, PRO, RCT Patients aged 18 to 70 years of age with proteinuria and chronic renal insufficiency who did not have diabetes	N=360 3.7 years (median follow-up)	Primary: Time to composite of doubling of serum creatinine, ESRD or death Secondary: Changes in level of proteinuria, rate of progression of renal disease	Primary: Compared to the conventional dosages, optimal antiproteinuric dosages of benazepril and losartan that were achieved through uptitration were associated with a 51 and 53% reduction in the risk for the primary end point (*P*=0.028 and *P*=0.022, respectively). There was no statistically significant difference between benazepril and losartan in the overall relative risk reduction at their respective optimal antiproteinuric dosages or at conventional dosages (*P* values not reported). Secondary: Optimal antiproteinuric dosages of benazepril and losartan at comparable BP control, achieved a greater reduction in both proteinuria and the rate of decline in renal function compared to their conventional dosages.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Uptitration was performed to optimal antiproteinuric and tolerated dosages, and then these dosages were maintained.				There was no significant difference in proteinuria reduction between benazepril and losartan at both conventional and optimal antiproteinuric dosages (*P* values not reported). Changes in renal function were similar between benazepril and losartan arms at both conventional and optimal antiproteinuric doses (*P*>0.05). There was no significant difference for the overall incidence of major adverse events between groups that were given conventional and optimal dosages in any of the treatment arms (*P* values not reported).
Parving et al[83] (AVOID) Losartan 100 mg daily plus aliskiren 150 mg daily for 3 months, followed by 300 mg for an additional 3 months vs losartan 100 mg plus placebo	DB, MC, PC, RCT Hypertensive patients who were 18 to 85 years of age with type 2 diabetes and nephropathy	N=599 6 months	Primary: Reduction in albumin:creatinine ratio at six months Secondary: BP reductions, adverse events	Primary: Treatment with aliskiren 300 mg daily as compared to placebo reduced the mean urinary albumin:creatinine ratio by 20% (95% CI, 9 to 30; *P*<0.001), with a reduction of 50% or more in 24.7% of the patients who received aliskiren as compared to 12.5% of those who received placebo (*P*<0.001). Secondary: A small difference in BP was seen between the treatment groups by the end of the study period with SBP and DBP pressures 2 and 1 mm Hg lower, respectively, in the aliskiren group (*P*=0.07 and *P*=0.08, respectively). The total numbers of adverse and serious adverse events were similar in the groups.
Barnett et al[67] (DETAIL) Telmisartan 80 mg QD vs enalapril 20 mg QD	DB, MC, PG, RCT Patients aged 35 to 80 years of age with type 2 diabetes and HTN	N=250 5 years	Primary: Change in the GFR Secondary: Annual changes in GFR, serum creatinine level, urinary albumin excretion and BP; rates of ESRD and cardiovascular	Primary: After five years, GFR decreased by 17.9 mL/minute/1.73 m^2 with telmisartan compared to 14.9 mL/min/1.73 m^2 with enalapril (mean difference, -3.0 mL/min/1.73 m^2; 95% CI, -7.6 to 1.6). Therefore, the changes in GFR were comparable between the groups (*P* value not reported). Secondary: The effects of the two agents on the secondary end points were not significantly different after five years.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			events; all-cause mortality	
Galle et al[68] Telmisartan 80 mg QD vs valsartan 160 mg QD Additional antihypertensive therapy was permitted.	DB, MC, PG, PRO, RCT Hypertensive patients (SBP/DBP >130/80 mm Hg) with type 2 diabetes, proteinuria and serum creatinine ≤3.0 mg/dL	N=885 12 months	Primary: Change from baseline in the 24-hour proteinuria Secondary: Changes in 24-hour albuminuria, estimated GFR and inflammatory parameters	Primary: Telmisartan and valsartan produced comparable reductions in 24-hour urinary protein excretion rates: geometric mean reduction was 33% for both telmisartan and valsartan. Secondary: No significant differences between treatments were seen in changes from baseline in 24-hour urinary albumin excretion rate and GFR at 12 months. With both treatments, greater renoprotection was seen among patients with better BP control. No significant changes in C-reactive protein were noted for either group at 12 months.
Viberti et al[69] (MARVAL) Valsartan 80 mg QD vs amlodipine 5 mg QD A target BP of 135/85 mm Hg was aimed for by dose-doubling followed by the addition of bendrofluazide* and doxazosin whenever needed.	AC, DB, RCT Patients 35 to 75 years of age with type 2 diabetes mellitus and microalbuminuria, with or without HTN	N=332 24 weeks	Primary: Change in UAER; proportion of patients who returned to normal albuminuria Secondary: Proportion of patients returning to normoalbuminuria	Primary: Valsartan resulted in a UAER reduction of 44% at 24 weeks compared to baseline vs an 8% reduction with amlodipine (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive groups. Over the study period, BP reductions were similar between the two treatments and at no time point was there a between-group significant difference in BP values in either the hypertensive or the normotensive subgroup. Secondary: The proportion of patients returning to normal albuminuria was greater with valsartan (29.9%) vs amlodipine (14.5%; P=0.001).
Casas et al[84]	MA	N=127 studies	Primary: Doubling of serum	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ACE inhibitor or ARBs compared to placebo vs ACE inhibitor or ARBs compared to other antihypertensive drugs (β-blockers, α-adrenergic blocking agents, CCB's, or combinations) Specific agents and doses were not specified.	Studies in adults that examined the effect of any drug treatment with a BP- lowering action on progression of renal disease	4.2 years (mean)	creatinine, ESRD Secondary: Serum creatinine, urine albumin excretion, GFR	reduction in the risk of doubling of creatinine vs other antihypertensives (*P*=0.07), with no differences in the degree of change of SBP or DBP between the groups. A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (*P*=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (*P*=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitors or ARBs were reported when these agents were compared to other antihypertensives (*P*=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR (no *P* value reported). Conclusion: Benefits of ACE inhibitors or ARBs on renal outcomes compared to placebo are probably due to a BP-lowering effect. In diabetic patients, additional renoprotective effects of ACE inhibitors or ARBs beyond BP lowering remain unproven and there is uncertainty about the greater renoprotection seen in nondiabetic renal disease.
Strippoli et al[85] ARBs vs placebo (4 trials; irbesartan 75 to 300 mg/day [2 trials] and losartan 50 to 100 mg/day [2 trials]) or	MA of 43 RCT (to September 2003) Patients with diabetic nephropathy	N=43 trials Duration at least 6 months, range 6 to 63.6 months	Primary: All-cause mortality, renal outcomes (ESRD, doubling of serum creatinine, microalbuminuria to macroalbuminuria) Secondary:	Primary: ACE inhibitors significantly reduced all-cause mortality compared to placebo or no treatment (RR, 0.79; 95% CI, 0.63 to 0.99; *P*=0.04). There was a nonsignificant trend for reduction in ESRD (*P*=0.07) and doubling of serum creatinine (*P*=0.08) with ACE inhibitors compared to placebo or no treatment. ACE inhibitors significantly reduced the risk of progression from microalbuminuria to macroalbuminuria (*P*=0.0007) and increased regression back to normoalbuminuria (*P*<0.0001) compared to placebo or no treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ACE inhibitors vs placebo (36 trials; benazepril 10 mg/day, captopril 37.5 to 100 mg/day, cilazapril* 2.5 to 5 mg/day, enalapril 5 to 40 mg/day, fosinopril 10 mg/day, imidapril* 5 mg/day, lisinopril 2.5 to 20 mg/day, perindopril 2 to 8 mg/day and ramipril 1.25 to 10.0 mg/day) or ACE inhibitors vs ARBs (3 trials; enalapril 5 to 10 mg/day vs losartan 50 mg/day [2 trials] and captopril 75 mg/day vs valsartan 80 to 160 mg/day)			Not reported	ARBs did not significantly reduce all-cause mortality compared to placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17; *P*=0.95). ARBs significantly reduced the risk of ESRD (*P*=0.001) and doubling of serum creatinine (*P*=0.004). ARBs significantly decreased the risk of progression to macroalbuminuria (*P*=0.001) and increased regression to normoalbuminuria (*P*=0.02) compared to placebo or no treatment. The three trials that compared ACE inhibitors to ARBs did not report on all-cause mortality, ESRD or doubling of serum creatinine. Progression from microalbuminuria to macroalbuminuria was reported in one trial (N=92) and there was no significant difference in risk, with the point estimate favoring ACE inhibitors (RR, 0.16; 95% CI, 0.02 to 1.44; *P* value not reported). Regression from microalbuminuria to normoalbuminuria in one trial showed a nonsignificant difference in the risk (*P* value not reported). Secondary: Not reported
Strippoli et al[86] ARBs vs placebo (4 trials) or ACE inhibitors vs placebo (38 trials) or	MA Patients with diabetic kidney disease	N=12,067 Duration at least 6 months	Primary: All-cause mortality, ESRD, doubling of serum creatinine concentration, progression from micro- to macroalbuminuria, regression from micro- to normoalbuminuria, drug-related toxicity	Primary: There was no significant difference in the risk of all-cause mortality for ACE inhibitors vs placebo or no treatment (RR, 0.91; 95% CI, 0.71 to 1.17) and ARBs vs placebo or no treatment (RR, 0.99; 95% CI, 0.85 to 1.17). No statistically significant reduction in the risk of all-cause mortality was found in the three trials that compared ACE inhibitors with ARBs (RR, 0.92; 95% CI, 0.31 to 2.78). A subgroup analysis of trials showed a significant reduction in the risk of all-cause mortality with the use of full-dose ACE inhibitors (RR, 0.78; 95% CI, 0.61 to 0.98), but not when using half or less than half the maximum tolerable dose of ACE inhibitors (RR, 1.18; 95% CI, 0.41 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ARBs vs ACE inhibitors (7 trials)			(including cough, headache, hyperkalemia, impotence and pedal edema) Secondary: Not reported	3.44). There was a significant reduction in the risk of ESRD with ACE inhibitors and ARBs compared to placebo or no treatment (RR, 0.60; 95% CI, 0.39 to 0.93 and RR, 0.78; 95% CI, 0.67 to 0.91, respectively). There was a significant reduction in the risk of doubling of serum creatinine concentration with ACE inhibitors and ARBs (RR, 0.68; 95% CI, 0.47 to 1.00 and RR, 0.79; 95% CI, 0.67 to 0.93, respectively). ACE inhibitors and ARBs significantly reduced the risk of progression from micro- to macroalbuminuria (RR, 0.45; 95% CI, 0.29 to 0.69 and RR, 0.49; 95% CI, 0.32 to 0.75, respectively). ACE inhibitors and ARBs significantly increased the regression from micro- to normoalbuminuria compared to placebo or no treatment (RR, 3.06; 95% CI, 1.76 to 5.35 and RR, 1.42; 95% CI, 1.05 to 1.93, respectively). The seven trials that compared ACE inhibitors to ARBs did not report the outcome of ESRD or doubling of serum creatinine. Progression from micro- to macroalbuminuria and from micro- to normoalbuminuria were evaluated each in one trial and showed a nonsignificant difference in the risk between ACE inhibitors and ARBs. ACE inhibitors were associated with a significant increase in the risk of cough but not hyperkalemia, headache or impotence when compared to placebo or no treatment. ARBs were associated with a significant increase in the risk of hyperkalemia but not cough or headache compared to placebo or no treatment. Secondary: Not reported
Other Studies				
Papademetriou et al[87] (SCOPE) Candesartan 16 mg QD	DB, MC, PC, PG, RCT Patients 70 to 89	N=1,518 3.7 years	Primary: First major coronary event including cardiovascular	Primary: There was no difference in the first major cardiovascular event between patients (with isolated systolic hypertension) who were treated with candesartan vs placebo (RR, 0.89; 95% CI, 0.65 to 1.21; *P*>0.20).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo in addition to conventional therapy (diuretics, ACE inhibitors, β-blockers, CCBs)	years of age with isolated systolic HTN (SBP >160 mm Hg and DBP <90 mm Hg) and MMSE scores ≥24		death, nonfatal MI or nonfatal stroke Secondary: Cardiovascular death, nonfatal and fatal stroke and MI	Secondary: A total of 20 fatal/nonfatal strokes occurred in the candesartan group and 35 in the control group (RR, 0.58; 95% CI, 0.33 to 1.00) for a RR reduction of 42% (*P*=0.050 unadjusted and *P*=0.049 adjusted for baseline risk). There were no marked or statistically significant differences between the treatment groups in other cardiovascular end points or all-cause mortality.
Fliser et al[88] (EUTOPIA) Olmesartan 20 mg QD and after 6 weeks, pravastatin 20 mg QD daily was added vs placebo and after 6 weeks, pravastatin 20 mg QD was added	DB, PC, PG, RCT Patients 18 years of age and older with HTN, atherosclerotic disease, type 2 diabetes mellitus and/or LDL-C between 3.89 to 6.48 mmol/L	N=199 12 weeks	Primary: Evaluate anti-inflammatory effects of olmesartan using a panel of inflammation markers: high-sensitivity C-reactive protein, high-sensitivity tumor necrosis factor-α, interleukin-6 Secondary: Not reported	Primary: After six weeks of therapy, olmesartan treatment significantly reduced serum levels of C-reactive protein (-15.1%; *P*<0.05), tumor necrosis factor-α (-8.9%; *P*<0.02), interleukin-6 (-14.0%; *P*<0.05) and monocyte chemotactic protein-1 (-6.5%; *P*<0.01), whereas placebo treatment had no major effect on inflammation markers. After 12 weeks of therapy, C-reactive protein (-21.1%; *P*<0.02), tumor necrosis factor-α (-13.6%; *P*<0.01) and interleukin-6 (-8.0%; *P*<0.01) decreased further with olmesartan and pravastatin cotherapy, but treatment with pravastatin alone did not significantly alter inflammation markers. In contrast, addition of pravastatin led to a significant (*P*<0.001) reduction in LDL-C in the olmesartan and placebo groups (-15.1 and -12.1%, respectively). Secondary: Not reported

*Not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily
Study abbreviations: AC=active comparator, CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, RRR=relative risk reduction
Miscellaneous abbreviations: ACE=angiotensin-converting enzyme, ABPM=ambulatory blood pressure monitoring, AF=atrial fibrillation, ARB=angiotensin II receptor antagonist, β-blockers=β-adrenergic blocking agents, BP=blood pressure, CCBs=calcium channel blocking agents, CHD=coronary heart disease, CHF=congestive heart failure, DBP=diastolic blood pressure, ESRD=end-stage renal disease, GFR=glomerular filtration rate, HCTZ=hydrochlorothiazide, HTN=hypertension, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, LVH=left ventricular hypertrophy, MAP=mean arterial pressure, MI=myocardial infarction, MMSE=Mini Mental State Examination, NYHA=New York Heart Association, SeSPB=seated systolic blood pressure, SBP=systolic blood pressure, SR=sustained release, UAER=urinary albumin excretion rate, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Azilsartan	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Candesartan	No dosage adjustment required in the elderly. Approved for use in children one to <17 years of age for the treatment of hypertension. Safety and efficacy in children have not been established for the treatment of heart failure.	No dosage adjustment required.	A lower starting dose may be considered in patients with moderate hepatic impairment.	C (first trimester) D (second and third trimester)	Unknown
Eprosartan	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Irbesartan	No dosage adjustment required in the elderly. Approved for use in children six years of age and older.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown
Losartan	No dosage adjustment required in the elderly. Approved for use in children six years of age and older.	No dosage adjustment required.	A lower starting dose may be considered in patients with a history of hepatic impairment.	C (first trimester) D (second and third trimester)	Unknown
Olmesartan	No dosage adjustment required in the elderly.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester)	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Approved for use in children six years of age and older.			D (second and third trimester)	
Telmisartan	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Initiate therapy at a low dose and titrate slowly.	C (first trimester) D (second and third trimester)	Unknown
Valsartan	No dosage adjustment required in the elderly. Approved for use in children six years of age and older.	No dosage adjustment required.	No dosage adjustment required.	C (first trimester) D (second and third trimester)	Unknown

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
Cardiovascular								
Abnormal ECG	-	-	<1	-	-	-	>0.3	-
Angina	-	a	<1	<1	<1	-	>0.3	-
Arrhythmia	-	-	-	<1	<1	-	-	-
Atrial fibrillation	-	-	<1	-	<1	-	a	-
Atrioventricular block (second degree)	-	-	-	-	<1	-	-	-
Bradycardia	-	-	<1	-	<1	-	a	-
Cardiac murmur	-	-	-	<1	-	-	-	-
Cardio-respiratory arrest	-	-	-	<1	-	-	-	-
Chest pain	-	>1	≥1	≥1	1 to 12	>0.5	≥1	a
Congestive heart failure	-	-	-	-	-	-	a	-
Extrasystoles	-	-	<1	-	-	-	-	-
Heart failure	-	-	-	<1	-	-	-	-
Hypertension	-	-	-	<1	-	-	≥1	-
Hypertensive crisis	-	-	-	<1	-	-	-	-
Hypotension	0.4	-	<1	0.4 to 5.4	4 to 7	-	a	1.4 to 7.0
Myocardial infarction	-	a	-	<1	<1	-	a	-
Orthostatic effects	-	-	-	-	<1	-	-	-
Palpitations	-	>0.5	<1	-	<1	-	>0.3	>0.2

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
Tachycardia	-	>0.5	<1	≥1	<1	>0.5	>0.3	-
Ventricular fibrillation	-	-	-	-	<1	-	-	-
Ventricular tachycardia	-	-	-	-	<1	-	-	-
Central Nervous System								
Anxiety	-	>0.5	<1	≥1	<1	-	>0.3	>0.2
Asthenia	≥0.3	>0.5	<1	-	1 to 14	a	a	>0.2
Ataxia	-	-	<1	-	<1	-	-	-
Cerebrovascular accident	-	-	-	<1	<1	-	-	-
Cerebrovascular disorder	-	-	-	-	-	-	>0.3	-
Confusion	-	-	-	-	<1	-	-	-
Depression	-	>0.5	1	<1	<1	-	>0.3	-
Dizziness	≥0.3	4	≥1	10.2	3	-	≥1	2 to 17
Dream abnormalities	-	-	-	-	<1	-	-	-
Dysgeusia	-	-	-	-	a	-	-	-
Emotional disturbance	-	-	-	<1	-	-	-	-
Fatigue	≥0.3	>1	2	4	1 to 14	-	≥1	2 to 3
Headache	-	>1	≥1	≥1	≥1	>1	≥1	>1
Hypesthesia	-	-	-	-	5	-	-	-
Hypoesthesia	-	-	-	-	-	-	>0.3	-
Insomnia	-	-	<1	-	≥1	-	>0.3	>0.2
Memory impairment	-	-	-	-	<1	-	-	-
Migraine	-	-	<1	-	<1	-	>0.3	-
Nervousness	-	-	<1	-	<1	-	>0.3	-
Neuritis	-	-	<1	-	-	-	-	-
Numbness	-	-	-	<1	-	-	-	-
Panic disorder	-	-	-	-	<1	-	-	-
Paresthesia	-	>0.5	<1	<1	<1	-	>0.3	>0.2
Peripheral neuropathy	-	-	-	-	<1	-	-	-
Sleep disturbance	-	-	-	<1	<1	-	-	-
Somnolence	-	>0.5	<1	<1	<1	-	>0.3	>0.2
Syncope	-	-	-	a	<1	-	a	a
Transient ischemic attack	-	-	-	<1	-	-	-	-
Tremor	-	-	-	<1	<1	-	-	-
Vertigo	-	>0.5	<1	a	<1	>0.5	>0.3	>0.2
Weakness	-	-	-	-	-	-	a	-
Dermatological								
Alopecia	-	-	-	-	<1	a	-	a
Cellulitis	-	-	-	-	7	-	-	-
Ecchymosis	-	-	-	<1	<1	-	-	-
Eczema	-	-	<1	-	-	-	>0.3	-
Erythema	-	-	-	<1	<1	-	a	-

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
Erythroderma	-	-	-	-	a	-	-	-
Dermatitis	-	-	-	<1	-	-	>0.3	-
Drug eruption	-	-	-	-	-	-	a	-
Dry skin	-	-	-	-	<1	-	-	-
Flushing	-	-	-	<1	<1	-	>0.3	-
Furunculosis	-	-	<1	-	-	-	-	-
Photosensitivity	-	-	-	-	<1	-	-	-
Pruritis	-	a	<1	<1	<1	a	>0.3	>0.2
Rash	-	>0.5	<1	≥1	<1	>0.5	>0.3	>0.2
Skin ulcer	-	-	-	-	-	-	3	-
Urticaria	-	a	-	<1	<1	a	a	-
Gastrointestinal								
Abdominal distension	-	-	-	<1	-	-	-	-
Abdominal pain	-	>1	2	≥1	≥1	>0.5	≥1	2
Anorexia	-	-	<1	-	<1	-	-	a
Constipation	-	-	<1	<1	<1	-	>0.3	>0.2
Dental pain	-	-	-	-	<1	-	-	-
Diarrhea	2	>1	≥1	3	1 to 15	>1	3	5
Dry mouth	-	-	<1	-	<1	-	>0.3	>0.2
Dyspepsia/ heartburn	-	>0.5	≥1	2	1 to 4	>0.5	≥1	>0.2
Esophagitis	-	-	<1	-	-	-	-	-
Flatulence	-	-	<1	<1	<1	-	>0.3	>0.2
Gastritis	-	-	<1	-	<1 to 5	-	>0.3	-
Gastroenteritis	-	>0.5	<1	<1	-	>0.5	>0.3	-
Gastroesophageal reflux	-	-	-	-	-	-	>0.3	-
Gingivitis	-	-	<1	-	-	-	-	-
Hemorrhoids	-	-	-	-	-	-	>0.3	-
Nausea/vomiting	≥0.3	>1	<1	≥1	≥1	>0.5	≥1	>1
Oral lesion	-	-	-	<1	-	-	-	-
Periodontitis	-	-	<1	-	-	-	-	-
Taste perversion	-	-	-	-	<1	-	-	-
Toothache	-	-	<1	-	-	-	>0.3	-
Laboratory Test Abnormalities								
Albuminuria	-	>1	<1	-	-	-	-	-
Agranulocytosis	-	a	-	-	-	-	-	-
BUN increased	-	a	1.3	<0.7	a	-	-	-
Elevated creatine phosphokinase	-	>0.5	<1	-	-	>1	a	-
Eosinophilia	-	-	-	-	-	-	a	-
Glycosuria	-	-	<1	-	-	-	-	-
Hematocrit decreased	0.4	a	-	-	a	a	-	-
Hematuria	-	>0.5	<1	-	-	>1	-	-
Hemoglobin decreased	0.2	a	0.1	0.2	a	a	0.8	-
Hyper-	-	-	<1	-	-	>0.5	>0.3	-

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
cholesterolemia								
Hyperglycemia	-	>0.5	<1	-	14	>1	-	-
Hyperkalemia	-	a	<1	a	7	a	a	2
Hyper-triglyceridemia	-	>0.5	1	-	-	>1	-	-
Hyperuricemia	-	>0.5	-	-	-	>0.5	a	-
Hypoglycemia	-	-	-	-	-	-	a *	-
Hypokalemia	-	-	<1	-	-	-	-	-
Hyponatremia	-	a	<1	-	a	-	-	-
Leukopenia	-	a	a	-	-	-	-	-
Liver enzymes increased	-	-	<1	a	a	a	a .	a
Neutropenia	-	a	-	0.3	-	-	-	-
Platelet count abnormalities	<0.1	-	a	-	a	-	a	a
Red blood cell count decreased	0.3	-	-	-	-	-	-	-
Serum creatinine increased	a	a	0.6	<0.7	a	a	0.4	0.6
White blood cell count abnormalities	<0.1	-	0.3	-	-	-	-	-
Musculoskeletal								
Arthralgia	-	>1	2	-	<1	>0.5	>0.3	3
Arthritis	-	-	<1	<1	<1	>0.5	>0.3	-
Arthrosis	-	-	<1	-	-	-	-	-
Bursitis	-	-	-	<1	-	-	-	-
Fibromyalgia	-	-	-	-	<1	-	-	-
Joint stiffness	-	-	-	<1	<1	-	-	-
Joint swelling	-	-	-	-	<1	-	-	-
Leg cramps	-	-	<1	-	-	-	>0.3	-
Muscle contractions, involuntary	-	-	-	-	-	-	>0.3	-
Muscle cramps	-	-	-	<1	1	-	a	>0.2
Muscle weakness	-	-	-	<1	<1	-	-	-
Musculoskeletal chest pain	-	-	-	<1	-	-	-	-
Myalgia	-	>0.5	≥1	<1	≥1	>0.5	≥1	>0.2
Pain (includes back and leg)	-	3	<1	≥1	1 to 12	>1	3	3
Skeletal pain	-	-	<1	-	-	-	-	-
Tendinitis	-	-	<1	-	-	-	a	-
Trauma	-	-	-	-	4	-	-	-
Respiratory								
Asthma	-	-	<1	-	-	-	>0.3	-
Bronchitis	-	>1	≥1	-	<1 to 10	>1	>0.3	-
Congestion	-	-	-	<1	-	-	-	-
Cough	≥0.3	>1	4	2.8	11	0.9	≥1	0.6 to

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
								2.6
Dyspnea	-	>0.5	-	<1	<1	-	>0.3	>0.2
Epistaxis	-	>0.5	<1	<1	<1	-	>0.3	-
Influenza/ influenza-like symptoms	-	-	<1	≥1	10	>1	≥1	-
Nasal congestion	-	-	-	-	2	-	-	-
Pharyngitis	-	2	4	≥1	≥1	>1	1	>1
Pulmonary congestion	-	-	-	<1	-	-	-	-
Respiratory congestion	-	-	-	-	<1	-	-	-
Rhinitis	-	2	4	≥1	<1	>1	>0.3	>1
Sinus disorder	-	-	-	≥1	≥1	-	-	-
Sinusitis	-	>1	≥1	-	1 to 6	>1	3	>1
Tracheobronchitis	-	-	-	<1	-	-	-	-
Upper respiratory tract infection	-	6	8	-	8	-	7	>1
Wheezing	-	-	-	<1	-	-	-	-
Miscellaneous								
Abscess	-	-	-	-	-	-	>0.3	-
Abnormal urination	-	-	-	<1	-	-	-	-
Abnormal vision	-	-	<1	<1	<1	-	>0.3	a
Acute renal failure	-	-	-	-	-	a	a	-
Alcohol intolerance	-	-	<1	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-	a	-
Angioedema	-	a	a	a	a	a	a	a
Angioneurotic edema	-	-	-	-	-	-	a	-
Anemia	-	-	<1	-	<1 to 14	-	a	-
Cataract	-	-	-	-	7	-	-	-
Chills	-	-	<1	-	-	-	-	-
Conjunctivitis	-	-	<1	<1	<1	-	>0.3	-
Cystitis	-	-	<1	-	-	-	>0.3	-
Diabetes	-	-	-	-	-	-	>0.3	-
Diabetic neuropathy	-	-	-	-	4	-	-	-
Diabetic vascular disease	-	-	-	-	10	-	-	-
Ear abnormality	-	-	-	<1	-	-	-	-
Ear infection	-	-	-	<1	-	-	-	-
Ear pain	-	-	-	<1	-	-	>0.3	-
Edema	-	-	≥1	≥1	≥1	-	a	>1
Eye disturbance	-	-	-	<1	<1	-	-	-
Eyelid abnormality	-	-	-	<1	-	-	-	-
Facial edema	-	-	-	<1	-	-	-	-
Fever	-	>0.5	<1	<1	<1 to 4	-	>0.3	-
Gout	-	-	<1	<1	<1	-	>0.3	-
Hearing	-	-	-	<1	-	-	-	-

Adverse Event	Azil-sartan	Cande-sartan	Epro-sartan	Irbe-sartan	Lo-sartan	Olme-sartan	Telmi-sartan	Val-sartan
abnormality								
Hemolysis	-	-	-	-	a	-	-	-
Hepatic dysfunction	-	-	-	-	-	-	a	-
Hepatitis	-	a	-	a	a	-	-	a
Herpes simplex	-	-	<1	-	-	-	-	-
Hot flushes	-	-	<1	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	a	>0.2
Hypertension	-	-	-	a	-	-	-	-
Infection	-	-	-	-	5	-	>0.3	-
Infection, fungal	-	-	-	-	-	-	>0.3	-
Injury	-	-	2	-	-	-	-	-
Intermittent claudication	-	-	-	-	-	-	7	-
Jaundice	-	-	-	a	-	-	-	-
Libido decreased	-	-	-	-	<1	-	-	-
Malaise	-	-	<1	-	a	-	>0.3	-
Micturition frequency	-	-	<1	-	<1	-	>0.3	-
Nocturia	-	-	-	-	<1	-	-	-
Otitis externa	-	-	<1	-	-	-	-	-
Otitis media	-	-	<1	-	-	-	>0.3	-
Peripheral edema	-	>1	<1	-	-	>0.5	≥1	-
Peripheral ischemia	-	-	<1	-	-	-	-	-
Polyuria	-	-	<1	-	-	-	-	-
Prostate disorder	-	-	-	<1	-	-	-	-
Purpura	-	-	<1	-	-	-	-	-
Renal calculus	-	-	<1	-	-	-	-	-
Renal failure	-	a	-	-	-	-	-	-
Renal impairment	-	a	-	-	-	-	-	a
Rhabdomyolysis	-	a	a	a	a	a	a	a
Rigors	-	-	<1	-	-	-	-	-
Sexual dysfunction	-	-	-	<1	<1	-	>0.3	>0.2
Sweating	-	>0.5	-	-	<1	-	>0.3	-
Tinnitus	-	-	<1	-	<1	-	>0.3	-
Upper extremity edema	-	-	-	<1	-	-	-	-
Urinary incontinence	-	-	<1	-	-	-	-	-
Urinary tract infection	-	-	1	≥1	<1 to 16	-	≥1	-
Vasculitis	-	-	-	-	a	-	-	a
Viral infection	-	-	2	-	-	-	-	3
Weight gain	-	-	-	-	4	-	-	-
Xerophthalmia	-	-	<1	-	-	-	-	-

*In diabetic patients
BUN=blood urea nitrogen, ECG=electrocardiogram
- Event not reported.
a Percent not specified.

Contraindications/Precautions

Angiotensin receptor blockers (ARBs) are contraindicated in patients with a known hypersensitivity to any component of the individual agents.[1-10]

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women during the second and third trimester. When pregnancy is detected, ARBs should be discontinued as soon as possible.[1-10]

Drugs that act directly on the renin-angiotensin system have been associated with fetal and neonatal injury when used during the second and third trimesters, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, possibly resulting from decreased renal function in the fetus. Oligohydramnios has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Rarely, no alternative to an ARB may be found. In these cases, the mother should be informed of the potential risk and serial ultrasound examinations should be performed. If oligohydramnios is observed, the ARB should be discontinued unless considered life saving for the mother. Oligohydramnios may not be detected until after the fetus has sustained irreversible injury.[1-10]

Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported though their association to exposure to drugs is unclear. Infants with a history of in utero exposure to ARBs should be closely monitored for hypotension, oliguria and hyperkalemia.[1-10]

Symptomatic hypotension may occur after initiation of an ARB in patients with an activated renin-angiotensin system, such as those who are volume- and/or salt-depleted (i.e., patients on high doses of diuretics). Volume and salt depletion should be corrected before administration of an ARB. If an excessive fall in blood pressure occurs, the patients should be placed in the supine position and given an intravenous infusion of normal saline if necessary. A transient hypotensive response does not contraindicate further treatment once blood pressure has been stabilized.[1-10]

Changes in renal function may be anticipated in patients being treated with medications which inhibit the renin-angiotensin system. Patients whose renal function may depend on the renin-angiotensin system (i.e., patients with severe congestive heart failure, renal artery stenosis or volume depletion), treatment with ARBs may be associated with oliguria or progressive azotemia, acute renal failure and death.[1-10]

Children under one year of age should not receive candesartan. Drugs that act directly on the renin-angiotensin system can have effects on the development of immature kidneys.[3]

Administer candesartan with caution in patients with heart failure. Some reduction in blood pressure is common. In patients with symptomatic hypotension, temporary dose reduction of candesartan and/or volume repletion may be indicated. Monitoring of blood pressure is recommended during dose escalation and periodically thereafter.[3]

In heart failure patients treated with candesartan, increased in serum creatinine may occur. Dose reduction or discontinuation and volume repletion may be required.[3]

In heart failure patients treated with candesartan, hyperkalemia may occur. Monitoring of serum potassium is recommended during dose escalation and periodically thereafter. [3]

Hypotension may occur during major surgery and anesthesia in patients on candesartan. Very rarely, hypotension may be severe and require intravenous fluids and/or vasopressors. [3]

Based on pharmacokinetic data, a lower starting dose of candesartan and losartan should be considered in patients with moderate hepatic impairment.[3,6]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for the Angiotensin II Receptor Antagonists Single Entity Agents[2-9]

WARNING
When pregnancy is detected, the angiotensin II receptor antagonist should be discontinued as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Drug Interactions

Table 7. Drug Interactions[1-10]

Drug(s)	Interaction	Mechanism
Angiotensin II receptor blockers	Lithium	Angiotensin II receptor blockers may decrease lithium renal excretion by enhancing its reabsorption. Lithium levels may increase, resulting in an increase in pharmacologic and toxic effects of lithium. Monitor patients for lithium toxicity and adjust dose as needed.
Angiotensin II receptor blockers	Potassium sparing diuretics (amiloride, spironolactone, triamterene)	Angiotensin II receptor blockers and potassium sparing diuretics may increase serum potassium levels, leading to additive or synergistic effects. Regularly monitor serum potassium concentrations and renal function in patients receiving these agents concurrently. Consider estimating creatinine clearance in elderly patients and high-risk patients.
Angiotensin II receptor blockers	Nonsteroidal anti-inflammatory agents	Concurrent use of angiotensin II receptor blockers and nonsteroidal anti-inflammatory agents may result in decreased antihypertensive effects and an increased risk of renal impairment.

Dosage and Administration

Table 8. Dosing and Administration[1-10]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Azilsartan	Hypertension: Tablet: 80 mg QD*	Safety and efficacy in children have not been established.	Tablet: 40 mg 80 mg
Candesartan	Heart failure (NYHA class II to IV)†: Tablet: initial, 4 mg QD; target, 32 mg QD Hypertension: Tablet: initial, 16 mg QD when used as monotherapy in patients who are not volume-depleted; maintenance, 8 to 32 mg/day in 1 to 2 divided doses	Hypertension (children 1 to <6 years of age): Tablet: initial, 0.20 mg/kg QD; maintenance, 0.05 to 0.4 mg/kg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and <50 kg): Tablet: initial, 4 to 8 mg QD; maintenance, 4 to 16 mg in 1 to 2 divided doses Hypertension (children 6 to <17 years of age and >50 kg):	Tablet: 4 mg 8 mg 16 mg 32 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Tablet: initial, 8 to 16 mg QD; maintenance, 4 to 32 mg in 1 to -2 divided doses	
Eprosartan	Hypertension: Tablet: initial, 600 mg QD when used as monotherapy in patients who are not volume-depleted; maintenance, 400 to 800 mg/day in 1 to 2 divided doses	Safety and efficacy in children have not been established.	Tablet: 400 mg 600 mg
Irbesartan	Diabetic nephropathy in patients with Type 2 Diabetes and hypertension‡: Tablet: target, 300 mg QD in patients who are not volume-depleted Hypertension: Tablet: initial, 150 mg QD; maximum, 300 mg QD	Hypertension (children 6 to 12 years of age): Tablet: initial, 75 mg QD; maximum, 150 mg QD Hypertension (children 13 years of age and older): Tablet: initial, 150 mg QD; maximum, 300 mg QD	Tablet: 75 mg 150 mg 300 mg
Losartan	Diabetic nephropathy in patients with Type 2 Diabetes and hypertension‡: Tablet: initial, 50 mg QD; maintenance, dose should be increased to 100 mg QD based on blood pressure response Hypertension: Tablet: initial, 50 mg QD in patients who are not volume-depleted; maintenance, 25 to 100 mg/day in 1 to 2 divided doses Reduction in the risk of stroke in patients with hypertension and left ventricular hypertrophy§: Tablet: initial, 50 mg QD; maintenance, HCTZ 12.5 mg QD should be added and/or the losartan dose increased to 100 mg QD followed by an increase in HCTZ 25 mg QD based on blood pressure response	Hypertension(children 6 years of age and older): Tablet: initial, 0.7 mg/kg QD (up to 50 mg total) administered as a tablet or suspension‖	Tablet: 25 mg 50 mg 100 mg
Olmesartan	Hypertension: Tablet: initial, 20 mg QD when used as monotherapy in patients who are not volume depleted; maximum, 40 mg QD	Hypertension (children 6 to 16 years of age and 20 to <35 kg): Tablet: initial, 10 mg QD; maximum, 20 mg QD Hypertension (children 6 to 16 years of age and ≥35 kg): Tablet: initial, 20 mg QD; maximum, 40 mg QD	Tablet: 5 mg 20 mg 40 mg
Telmisartan	Cardiovascular risk reduction in patients unable to take angiotensin converting	Safety and efficacy in children have not been	Tablet: 20 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	enzyme inhibitors¶: Tablet: initial, 80 mg QD Hypertension: Tablet: initial, 40 mg QD; maximum, 80 mg QD	established.	40 mg 80 mg
Valsartan	Heart failure (NYHA class II to IV)#: Tablet: initial, 40 mg BID; maintenance, uptitration to 80 to 160 mg BID should be done to the highest dose as tolerated; maximum, 320 mg in divided doses Hypertension: Tablet: initial, 80 to 160 mg QD when used as monotherapy in patients who are not volume depleted; maintenance, 80 to 320 mg QD Post-myocardial infarction**: Tablet: initial, 20 mg BID; target, 160 mg BID	Hypertension(children 6 to 16 years of age): Tablet: initial, 1.3 mg/kg QD (up to 40 mg total); maximum, 2.7 mg/kg (or in excess of 160 mg) QD††	Tablet: 40 mg 80 mg 160 mg 320 mg

BID=twice daily, HCTZ=hydrochlorothiazide, NYHA=New York Hear Association, QD=once daily
*Consider a starting dose of 40 mg QD in patients on high doses of diuretics.
†To reduce the risk of cardiovascular death and heart failure hospitalization in patients with left ventricular systolic dysfunction. Candesartan has an added effect on these outcomes when used with an angiotensin converting enzyme inhibitor.
‡Reduces the rate of progression to nephropathy in patients with elevated serum creatinine and proteinuria (>300 mg/day).
§There is evidence that this benefit does not apply to African American patients.
‖ Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied.
¶ Reduction of risk of myocardial infarction, stroke or cardiovascular death in patients 55 years of age and older at high risk of developing major cardiovascular events. Use of telmisartan with an angiotensin converting enzyme inhibitor is not recommended. Consider using an angiotensin converting enzyme inhibitor first.
#Reduction in heart failure hospitalizations. There is no evidence that valsartan provides added benefit when used with adequate doses of an angiotensin converting enzyme inhibitor.
**In clinically stable patients with left ventricular failure or dysfunction following myocardial infarction, to reduce the risk of cardiovascular mortality.
††Exposure to valsartan with a compounded suspension is 1.6 times greater than with the tablet.

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that guidelines addressing the treatment of hypertension and stable angina are presented globally, addressing the role of various medication classes in the treatment of these diseases. Due to the complexity of treatment regimens for unstable angina, acute coronary syndromes, myocardial infarction and heart failure, the associated guideline summaries focus on the role of the angiotensin II receptor blockers in disease management.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable**	· Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. · Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. · Patients with hypertension and established coronary artery disease should be treated with blood pressure medication(s) as tolerated, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or β-adrenergic blocking agents (β-blockers) with the addition of

Clinical Guideline	Recommendation
Angina (2007)[18]	other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. · Long-acting calcium-channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. · Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. · ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) of ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. · ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. · Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction and have a LVEF of ≤40%. · ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. · Aldosterone blockade is recommended in patients post-myocardial infarction without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. · It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. · Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Management of Stable Angina Pectoris (2006)**[89]	Therapy to improve prognosis · Aspirin 75 mg once-daily is recommended in all patients without contraindications. · Statin therapy is recommended for all patients with coronary disease. · ACE inhibitor therapy is recommended for patients with indications for ACE inhibition including hypertension, heart failure, left ventricular dysfunction and history of myocardial infarction with left ventricular dysfunction and diabetes. · β-blocker therapy is recommended in patients with history of myocardial infarction or heart failure. · Class IIa evidence includes ACE inhibition in patients with angina and proven coronary disease, clopidogrel in patients with stable angina who are not candidates for aspirin and high dose statin therapy in high risk patients with proven coronary disease. · Class IIb evidence includes fibrates in patients with low high density lipoprotein cholesterol and high triglycerides who have diabetes or metabolic syndrome. · Calcium channel blockers may be recommended in patients with angina who cannot tolerate β-blockers and who have had a myocardial

Clinical Guideline	Recommendation
	infarction and who do not have heart failure. Therapy to improve symptoms and/or reduce ischemia · Short-acting nitroglycerin therapy is recommended for acute symptom relief and situational prophylaxis. · Test the effects of a β-1 blocker and titrate to full dose; consider the need for 24-hour protection against ischemia. · If β-blockers are not effective or not tolerated, attempt monotherapy with a calcium channel blocker, long-acting nitrate or nicorandil*. · If the effects of β-blocker therapy are insufficient, add a dihydropyridine calcium channel blocker. · Class IIa evidence includes a sinus node inhibitor in the case of β-blocker intolerance, or a long-acting nitrate or nicorandil* in place of a calcium channel blocker in the case of insufficient response to calcium channel blocker monotherapy or combination therapy with a calcium channel blocker and β-blocker. · Class IIb evidence includes the use of metabolic agents where available as add-on therapy or in place of conventional therapy when conventional therapy is not tolerated. Treatment of syndrome X · Therapy with nitrates, β-blockers and calcium channel blockers alone or in combination is recommended. · Statin therapy is recommended in patients with hyperlipidemia. · ACE inhibitors are recommended in patients with hypertension. · Class IIa evidence includes a trial of other anti-anginal agents such as nicorandil and metabolic agents. Treatment of vasospastic angina · Treatment with calcium channel blockers is recommended in patients whose coronary arteriogram is normal or shows only non-obstructive lesions.
American College of Cardiology/American Heart Association: **2011 Focused Update Incorporated into the American College of Cardiology/American Heart Association 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (2011)**[19]	· An ACE inhibitor is recommended in the first 24 hours in patients with or without pulmonary congestion or LVEF ≤40%, in the absence of hypotension or known contraindications. · An ARB is recommended in patients intolerant to ACE inhibitors and who have either clinical or radiological signs of heart failure or LVEF ≤40%. · ACE inhibitors should be initiated and continued indefinitely in patients with heart failure, left ventricular dysfunction, diabetes or hypertension, unless contraindicated. · ARBs should be prescribed at discharge to patients who are intolerant of an ACE inhibitor and have signs of heart failure and LVEF<40%. · ACE inhibitors are reasonable for all patients, even without left ventricular dysfunction, hypertension or diabetes mellitus, unless contraindicated. · Long-term aldosterone receptor blockade should be prescribed for patients without significant renal dysfunction (creatinine clearance >30 mL per min) or hyperkalemia (≤5 mEq per liter) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF<40%., and have either symptomatic HF or diabetes mellitus. · ACE inhibitors are reasonable for patients with heart failure and LVEF

Clinical Guideline	Recommendation
	>40%. · Combination ACE inhibitor and ARB therapy may be considered in patients with persistent symptomatic heart failure and LVEF <40% despite conventional therapy including an ACE inhibitor or ARB alone.
European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation (2011)**[20]	· ACE inhibitors and ARBs are well established in secondary prevention, especially in patients with reduced LV function. · ACE inhibitors are recommended in all patients with LVEF ≤40% and in patients with heart failure, diabetes, chronic kidney disease and hypertension, unless otherwise contraindicated. · ACE inhibitors should be considered for all other patients to prevent the recurrence of ischemia. · ARBs are recommended for patients who are intolerant to ACE inhibitors, with preference given to agents and doses of proven efficacy. · The combination of an ACE inhibitor and an ARB is generally not recommended.
American College of Cardiology/American Heart Association: **2009 Focused Updates: Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (Updating the 2004 Guidelines and 2007 Focused Update) and the Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and the 2007 Focused Update)**[90]	· This guideline does not contain updated recommendations regarding the use of ACE inhibitors or ARBs. · The 2007 Focused Update remains current with regard to the use of ACE inhibitors and ARBs and is summarized below.
American College of Cardiology/American Heart Association: **2007 Focused Update of the American College of Cardiology/American Heart Association 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (2007)**[21]	Secondary prevention · Patients with comorbid hypertension should be treated initially with β-blockers and/or ACE inhibitors with the addition of other medications as needed to achieve a blood pressure goal of <140/90 mm Hg (or <130/80 mm Hg in patients with diabetes or chronic kidney disease). · ACE inhibitors are recommended in all patients with a LVEF ≤40% and those with hypertension, diabetes or chronic kidney disease, unless contraindicated. · ACE inhibitors are reasonable in patients with normal left ventricular function and well-controlled cardiovascular risk factors. · ARBs are recommended in patients who are intolerant to ACE inhibitors and have heart failure or who have a LVEF of ≤40%. · ARBs should be considered in all patients intolerant to ACE inhibitor therapy. · Combination therapy with ARBs and ACE inhibitors may be considered in patients with systolic dysfunction heart failure.
European Society of Cardiology:	Prophylactic therapies in the acute phase · ACE inhibitors should be given to patients with an impaired ejection

Clinical Guideline	Recommendation
Management of Acute Myocardial Infarction in Patients Presenting with Persistent ST-Segment Elevation (2008)[22]	fraction of ≤40% or those who have experienced heart failure in the early phase. · ACE inhibitors should be started in the first 24 hours, unless contraindicated. · There are differing opinions on giving ACE inhibitors to all patients or only those at high risk. · Patients who do not tolerate ACE inhibitors should be treated with an ARB. Secondary prevention · Trials have established that ACE inhibitors reduce mortality after ST-segment elevation myocardial infarction (STEMI) in patients with reduces residual left ventricular function. · There is a strong case to administer ACE inhibitors to patients who have experienced heart failure in the acute phase, even if no features of this persist, in those who have a LVEF of ≤40% or wall motion index of ≥1.2. · There is a case for administering ACE inhibitors to all patients with STEMI from admission in the absence of contraindications. · Arguments against administering ACE inhibitors to all patients is the increased incidence of hypotension and renal failure and the small benefit to those at low risk, though some trials show reduction in mortality and stroke in patients with stable cardiovascular disease and without left ventricular dysfunction. · Trials support the use of valsartan as an alternative agent in patients who cannot tolerate ACE inhibitors and have clinical signs of heart failure and/or a LVEF of ≤40%.
National Institute for Health and Clinical Excellence: **Post-Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[23]	· All patients should be offered an ACE inhibitor early after presenting with an acute myocardial infarction. · Assessment of left ventricular function is recommended in all patients post-myocardial infarction. · All patients with preserved left ventricular function or with left ventricular systolic dysfunction should continue treatment with an ACE inhibitor indefinitely, whether or not they have symptoms of heart failure. · Routine use of ARBs after a myocardial infarction is not recommended. · ARBs may be considered alternatives in patients who are intolerant to ACE inhibitor therapy. · Combined treatment with an ACE inhibitor and an ARB is not routinely recommended. · In patients with a proven myocardial infarction in the past and with heart failure and left ventricular systolic failure, treatment should be in line with recommendations for chronic heart failure. · In patients with a proven myocardial infarction in the past and with asymptomatic left ventricular systolic dysfunction and in those without heart failure and preserved left ventricular function, ACE inhibitors are recommended (ARBs may be given to patients who are intolerant to ACE inhibitors).
American College of Cardiology/American Heart Association: **Guideline Update for the Diagnosis and Management of**	Patients at risk for developing heart failure (Stage A) · Systolic and diastolic hypertension should be controlled according to contemporary guidelines. Diuretics, ACE inhibitors and β-blockers have been shown to prevent heart failure. The ARBs, losartan and irbesartan have been shown to reduce the incidence of heart failure in patients with type 2 diabetes mellitus and nephropathy.

Clinical Guideline	Recommendation
Chronic Heart Failure in the Adult (2005)[24] and Diagnosis and Management of Heart Failure in Adults (2009 Focused Update)[25]	· Lipid disorders should be treated according to contemporary guidelines. · ACE inhibitors and ARBs have been shown to decrease the incidence of end-organ disease and clinical events in diabetic patients. ACE inhibitors and ARBs have been shown to decrease the development of renal disease in diabetic patients, and long-term treatment with ramipril has been shown to decrease the likelihood of cardiovascular death, myocardial infarction and heart failure. ARBs have been shown to reduce the incidence of first hospitalization for heart failure and have beneficial effects on renal function in diabetic patients with left ventricular dysfunction or hypertension. · ACE inhibitors and ARBs may be useful in the prevention of heart failure in patients with atherosclerotic disease, diabetes and hypertension with other cardiovascular risk factors. <u>Patients with cardiac structural abnormalities or remodeling who have not developed heart failure symptoms (Stage B)</u> · β-blockers and ACE inhibitors should be used in all patients with a recent or past history of myocardial infarction. · β-blockers and ACE inhibitors should be used in patients who have reduced LVEF and do not have a history of myocardial infarction or heart failure. · ARBs are recommended for patients with reduced LVEF and a history of a myocardial infarction if they are intolerant to ACE inhibitors. · ACE inhibitors and ARBs may be beneficial in patients with hypertension and left ventricular hypertrophy. <u>Patients with current or prior symptoms of heart failure (Stage C)</u> · ACE inhibitors are recommended in all patients with current or past symptoms of heart failure and reduced LVEF, unless contraindicated. · ARBs are recommended in all patients intolerant to ACE inhibitors with current or past symptoms of heart failure and reduced LVEF. · ARBs are reasonable alternatives to ACE inhibitors as first-line therapy in patients with mild-to-moderate heart failure and reduced LVEF. · The addition of an ARB is reasonable in patients who are symptomatic despite conventional treatment. · The routine use of a combination of an ACE inhibitor, ARB and aldosterone antagonist is not recommended. <u>Patients with heart failure and normal LVEF</u> · β-blockers, ARBs, ACE inhibitors and calcium channel blocker may be useful in patients with heart failure and controlled hypertension to improve symptoms.
Heart Failure Society of America: **2010 Comprehensive Heart Failure Practice Guideline (2010)[27]**	<u>Patients at risk for development of heart failure</u> · ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with coronary artery disease, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. <u>Patients with asymptomatic heart failure and reduced LVEF</u> · ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%).

Clinical Guideline	Recommendation
	· ARBs may be used in patients who are intolerant to ACE inhibitors. · Routine use of a combination of ACE inhibitors and ARBs is not recommended. Patients with left ventricular systolic dysfunction · ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. · ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. · The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. · The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a myocardial infarction and have left ventricular dysfunction is not recommended. · The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. · Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction. Patients with heart failure and preserved LVEF · ACE inhibitors or ARBs should be considered in this patient population. · ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. Patients with heart failure and ischemic heart disease · ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a myocardial infarction. · ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-myocardial infarction with reduced LVEF or heart failure. Managing patients with heart failure and hypertension · Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. · Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. · Patients with symptomatic left ventricular dysfunction and left ventricular dilation and reduced ejection fraction should receive various doses of ACE inhibitors, ARBs, β-blockers, aldosterone antagonists and

Clinical Guideline	Recommendation
	isosorbide dinitrate/hydralazine at target doses. If blood pressure remains elevated (>130/80 mm Hg), the addition of a non-cardiac-depressing calcium channel blocker (amlodipine) may be considered. Managing heart failure in the elderly, women and African Americans · Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. · ACE inhibitor and β-blocker therapy are recommended in all women with heart failure and left ventricular systolic dysfunction. · ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors.
European Society of Cardiology: **Guidelines for the Diagnosis and Treatment of Chronic Heart Failure (2008)**[26]	· ACE inhibitors should be used in all patients with symptomatic heart failure and LVEF ≤40%, unless contraindicated. In hospitalized patients, treatment with and ACE inhibitor should be initiated before discharge. · ARBs are recommended in patients with heart failure and LVEF ≤40% who remain symptomatic despite optimal treatment with an ACE inhibitor and β-blocker, unless also taking an aldosterone antagonist. · ARBs are recommended in patients who are intolerant to ACE inhibitor therapy. · ACE inhibitors or ARBs are recommended in patients with hypertension and left ventricular dysfunction. · ACE inhibitors and ARBs are considered first-line agents in patients with hypertension and preserved ejection fraction. · ACE inhibitors and ARBs can be useful in patients with diabetes to decrease the risk of end-organ damage and cardiovascular complications and subsequently, the risk of heart failure. · In patients with diabetes and heart failure, ACE inhibitors and ARBs confer benefit at least comparable to that demonstrated in non-diabetic patients with heart failure. · ACE inhibitors/ARBs should be initiated before hospital discharge in patients presenting with acute heart failure.
National Heart, Lung, and Blood Institute: **The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (2004)**[15]	· Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with another class (ACE inhibitors, ARBs, β-blockers, calcium channel blockers) demonstrated to be beneficial in randomized controlled outcome trials. · Certain high-risk conditions are compelling reasons for initiating therapy with a drug from another class including β-blockers, ACE inhibitors, ARBs or calcium channel blockers. This recommendation is based on the results of several large trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial that showed diuretics to be more effective than other antihypertensive agents in preventing cardiovascular complications. · Most patients will need more than one antihypertensive medication to achieve blood pressure goals. Most patients with stage 2 hypertension will require initial therapy with medications from two drug classes. · When a single drug in adequate doses fails to achieve the blood pressure goal, then a second agent from a different class should be added to the treatment regimen. Initial treatment with two antihypertensive agents should be considered for patients with a baseline blood pressure of more than 20/10 mm Hg above goal.

Clinical Guideline	Recommendation
	However, caution should be used with patients who are at increased risk of orthostatic hypotension. One of the agents should be a thiazide diuretic. · High-risk conditions with compelling indications for individual drug classes are as follows: heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), post-myocardial infarction (β-blockers, ACE inhibitors and aldosterone antagonists), high coronary disease risk (diuretics, ACE inhibitors, β-blockers and calcium channel blockers), diabetes (diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers), chronic kidney disease (ACE inhibitors and ARBs) and recurrent stroke prevention (diuretics and ACE inhibitors). · The drug of choice in patients with hypertension and stable angina is a β-blocker. Long-acting calcium channel blockers may also be used. · For asymptomatic patients with ventricular dysfunction, ACE inhibitors and β-blockers are recommended. For patients with symptomatic ventricular dysfunction or end-stage heart disease, ACE inhibitors, ARBs, β-blockers and aldosterone antagonists are recommended. · Thiazide diuretics, ACE inhibitors, ARBs, β-blockers and calcium channel blockers are beneficial in reducing cardiovascular disease and stroke in patients with diabetes. ACE inhibitors and ARBs have been shown to favorably affect the progression of diabetic nephropathy and reduce albuminuria, and ARBs have been shown to reduce the progression to microalbuminuria. · Patients with chronic kidney disease often require treatment with three or more antihypertensive agents to achieve a blood pressure goal of <130/80 mm Hg. ACE inhibitors and ARBs have been shown to be beneficial in patients with diabetic and nondiabetic kidney disease. As renal disease advances, increasing doses of loop diuretics are often required, along with other medications. · African American patients have shown decreased responses to monotherapy with ACE inhibitors, ARBs and β-blockers compared to calcium channel blockers and diuretics. The incidence of ACE-inhibitor-induced angioedema is two to four times higher in African Americans. · Calcium channel blockers may be useful in Raynaud's syndrome and certain arrhythmias. · ACE inhibitors and ARBs should not be given to women who are pregnant or may become pregnant.
World Health Organization/ International Society of Hypertension: **2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)**[17]	· When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. · Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-myocardial infarction (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).
European Society of Hypertension/ European Society of Cardiology:	· In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage.

Clinical Guideline	Recommendation

2007 Guidelines for the Management of Hypertension (2007)[91], **Reappraisal of Guidelines on Hypertension Management (2009)**[16]	· In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended.
	· There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous myocardial infarction (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics).
	· Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents.
	· Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk.
	· Fixed combination medications can favor compliance and simplify regimens.
	· When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated.
	  · Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker.
	  · Avoid β-blocker/diuretic combination unless required for other reasons.
	  · If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses.
	  · A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances.
	· Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker.
	· Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored.

Clinical Guideline	Recommendation
	· Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. · Antihypertensive treatment should always be initiated in diabetic patients when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. · The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. · In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
National Institute for Health and Clinical Excellence/British Hypertension Society: **Hypertension: Clinical Management of Primary Hypertension in Adults: (2011)**[92]	· Initial therapy in patients <55 years of age should be an ACE inhibitor or an ARB if the patient is intolerant to ACE inhibitors. · Do not combine an ACE inhibitor with an ARB to treat hypertension. · Initial therapy in patients ≥55 years of age should be a calcium channel blocker or for black people of African or Caribbean family origin of any age. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. · If diuretic treatment is to be initiated or changed, offer a thiazide-like diuretic, such as chlorthalidone (12.5 to 25.0 mg daily) or indapamide (1.5 mg modified-release daily or 2.5 mg once) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide. · Beta-blockers are not a preferred initial therapy for hypertension. However, beta-blockers may be considered in younger people, particularly those with an intolerance or contraindication to ACE inhibitors and ARBs, women of child-bearing potential those with an increased sympathetic drive. · If a second medication is required treatment with a calcium channel blocker in combination with an ACE inhibitor or an ARB should be added. If a calcium channel blocker is not suitable, or if there is evidence of heart failure or a high risk of heart failure, a thiazide-like diuretic is recommended. · If three medications are required, a combination of calcium channel blocker, ACE inhibitor and diuretic should be used. If blood pressure remains uncontrolled, consider adding a fourth medication or consult a specialist. · If clinic blood pressure remains higher than 140/90 mmHg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic as resistant hypertension, and consider adding a fourth antihypertensive drug and/or seeking expert advice. · For resistant hypertension, consider further diuretic therapy with low dose spironolactone (25 mg daily) if the blood potassium level is less than 4.5 mmol/L. Consider a higher-dose thiazide-like diuretic if the blood potassium level is greater than 4.5 mmol/L.
American Diabetes	General Recommendations

Clinical Guideline	Recommendation

Association: **Standards of Medical Care in Diabetes—2011**[28]	· If ACE inhibitors, ARBs or diuretics are used, kidney function and serum potassium levels should be closely monitored.
	· ACE inhibitors and ARBs are contraindicated during pregnancy.
	
	Hypertension
	· Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB. If one class is not tolerated, the other should be substituted. If additional medications are needed to achieve blood pressure goals, a thiazide diuretic may be added if estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2 or a loop diuretic for patients whose estimated glomerular filtration rate is <30 mL/min/1.73 m^2.
	
	Coronary Heart Disease
	· In patients with known cardiovascular disease, ACE inhibitor, aspirin and statin therapy (if not contraindicated) should be used to reduce the risk of cardiovascular events.
	
	Diabetic Nephropathy
	· In the treatment of the nonpregnant patient with micro- or macroalbuminuria, either ACE inhibitors or ARBs should be used.
	· While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
	  · In patients with type 1 diabetes, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy.
	  · In patients with type 2 diabetes, hypertension and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria.
	  · In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency (serum creatinine >1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy.
	· If one class is not tolerated, the other should be substituted.

*Not available in the United States.

Conclusions

The angiotensin II receptor blockers (ARBs) are Food and Drug Administration (FDA)-approved for the treatment of hypertension, heart failure, to reduce the risk of cardiovascular death and heart failure hospitalization in patients with heart failure, to treat diabetic nephropathy with elevated serum creatinine and proteinuria in patients with type 2 diabetes and hypertension, to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, cardiovascular risk reduction in patients unable to take angiotensin converting enzyme (ACE) inhibitors and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.[1-10] To date, the FDA has approved eight ARBs for the indications listed above, including azilsartan (Edarbi®), candesartan (Atacand®), eprosartan (Teveten®), irbesartan (Avapro®), losartan (Cozaar®), olmesartan (Benicar®), telmisartan (Micardis®) and valsartan (Diovan®). All of the ARBs are approved for the treatment of hypertension. Losartan is the only ARB that is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy. Telmisartan is the only agent in the class that is approved for cardiovascular risk reduction in patients unable to take ACE inhibitors, and valsartan is the only ARB approved to reduce the risk of cardiovascular mortality in clinically stable

patients with left ventricular failure or dysfunction following myocardial infarction.[6,8,9] All of the agents in this class are dosed once daily and only losartan and eprosartan are available generically.[1-10]

Treatment guidelines for hypertension indicate that many patients will require more than one antihypertensive agent to achieve goal blood pressure and that patients with stage/grade 2 hypertension may require initial therapy with medications from two different drug classes.[15,16] ARBs are recommended in hypertensive patients with certain compelling indications including heart failure, left ventricular hypertrophy, chronic kidney disease and diabetes.[15-17] Treatment guidelines for the management of stable angina indicate that ARBs are recommended in patients with hypertension and those who have an indication for an ACE inhibitor but are intolerant to them, who have heart failure or who have had a myocardial infarction and have a left ventricular ejection fraction of ≤40%. ARBs may be considered in combination with and ACE inhibitor for heart failure due to left ventricular systolic dysfunction.[18]

Treatment guidelines for the management of unstable angina/non-ST elevation myocardial infarction recommends the use of ARBs who are intolerant to ACE inhibitors and who have had a myocardial infarction or have clinical or radiological signs of heart failure or a left ventricular ejection fraction of ≤40%.[19,20] Current treatment guidelines for the management of ST-elevation myocardial infarction recommend ARBs in patients who are intolerant to ACE inhibitors and have heart failure or who have a left ventricular ejection fraction of ≤40%.[21,22] The National Institute for Health and Clinical Excellence recommends the use of ARBs be reserved for patients post-myocardial infarction who are intolerant to ACE inhibitor therapy. Routine use of ARBs after a myocardial infarction is not recommended.[23]

Treatment guidelines for the management of heart failure recommend ARBs, specifically losartan and irbesartan, in patients with type 2 diabetes mellitus and nephropathy who are at risk for the development of heart failure. ARBs are recommended in patients intolerant to ACE inhibitors who have cardiac structural abnormalities or remodeling who have not developed heart failure symptoms, especially in patients with reduced left ventricular ejection fraction and a history of myocardial infarction. In patients with current or prior symptoms of heart failure, ARBs are recommended in patients who are intolerant to ACE inhibitors and who have reduced ventricular ejection fraction. ARBs may also be a reasonable alternative to ACE inhibitors as first-line therapy in these patients.[24-26] Individual ARBs may be considered as initial therapy instead of an ACE inhibitor in patients with heart failure who have had a myocardial infarction and in patients with chronic heart failure and systolic dysfunction.[27]

Treatment guidelines for the management of hypertension in patients with diabetes recommend a regimen including either an ACE inhibitor or an ARB. If one class is not tolerated the other should be tried. ACE inhibitors and ARBs are recommended in patients with micro- or macroalbuminuria. In patients with type 2 diabetes, hypertension and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria and renal insufficiency, ARBs have been shown to delay the progression of nephropathy.[28]

Clinical trials have demonstrated the safety and efficacy of the ARBs in the treatment of hypertension, diabetic nephropathy, heart failure, post-myocardial infarction, reducing cardiovascular risk and reducing the risk of stroke in patients with left ventricular hypertrophy.[30-88] Head-to-head studies of agents in the class have failed to consistently demonstrate the “superiority” of one ARB over another.[29-32,39,40,43,46,48] Comparisons between the ARBs and ACE inhibitors have generally demonstrated comparable efficacy between classes in the treatment of hypertension, heart failure, post-myocardial infarction, reducing cardiovascular risk and diabetic nephropathy.[35,42,44,50,57-59,61,62,66,67,73]

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Therapeutic Class Overview
Topical Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review encompasses the topical immunomodulators agents used in atopic dermatitis (eczema). The two medications included in this therapeutic class are Elidel® (pimecrolimus) and Protopic® (tacrolimus).[1,2] The mechanism of action of these medications are not known, however, it has been demonstrated that both agents inhibit the phosphatase activity of calcineurin. Inhibition of calcineurin inhibits the transcription of cytokines involved in T-cell activation. Hence, these agents are referred to as calcineurin inhibitors. In addition, both agents have been shown to prevent the release of inflammatory cytokines and mediators from mast cells stimulated by antigen/immunoglobulin E.

  Both agents are Food and Drug Administration (FDA) approved as second-line therapy for the short-term and non-continuous chronic treatment of atopic dermatitis in non immunocompromised adults and children. Pimecrolimus 1% cream is approved for mild-moderate atopic dermatitis for patients two years of age and older while tacrolimus is approved for treatment of moderate to severe atopic dermatitis.[1,2]

  Topical corticosteroids are considered to be the standard of care for the treatment for atopic dermatitis.[3-9] Topical corticosteroids from low-potency to high-potency are utilized one or more times daily for the treatment of acute flare of atopic dermatitis as well as for intermittent use to prevent relapse. Topical immunomodulators should be used on actively affected areas as a steroid-sparing agent. Additionally, concurrent use of a topical corticosteroid with a topical immunomodulator may be recommended in certain patients.[3]

  Concerns regarding the long-term safety of these agents have been addressed in the treatment guidelines and position papers published by medical associations. On January 19, 2006, the FDA approved updated labeling for the topical immunomodulators, pimecrolimus and tacrolimus.[10,11]This updated labeling was a result of cancer-related adverse events with the use of these medications, however position statements from several professional organizations have noted the lack of conclusive evidence linking an increase incidence of malignancies to the topical calcineurin inhibitors.[12-14]

Table 1. Current Medications Available in the Therapeutic Class[1,2,15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Pimecrolimus (Elidel®)	Second-line therapy for short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in nonimmunocompromised patients two years of age and older who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable	Cream: 1%	-
Tacrolimus (Protopic®*)	Second-line therapy for the short-term and noncontinuous chronic treatment of moderate to severe atopic dermatitis in nonimmunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable	Ointment: 0.03% 0.1%	a

Evidence-based Medicine

- Limited head-to-head studies and meta-analyses comparing the efficacy of the calcineurin inhibitors have been conducted, with results favoring efficacy of tacrolimus over pimecrolimus and similar adverse effects between the groups were similar.[16-20]
- When compared to medium and high potency corticosteroids tacrolimus was found to be equivalent while pimecrolimus was found to be less effective compared to potent corticosteroids.[21-27]
- A meta-analysis that evaluated the use of immunomodulators pediatric atopic dermatitis concluded that pimecrolimus and tacrolimus were significantly more effective than placebo vehicle and there is generally no difference between pimecrolimus and tacrolimus.[28]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[3-9]
    - Topical immunomodulators are to be used as second line therapy following failure or contraindication to topical corticosteroids.
    - Topical immunomodulators due not cause atrophy of the skin like prolonged topical corticosteroids use and may be used on body parts where atrophy is a concern or where a potent-very-high potent topical corticosteroid is not appropriate.
    - Concurrent use of a topical corticosteroid with a topical immunomodulator may be recommended in certain patients.
- Other Key Facts:
    - There are no generic agents in the class.
    - Pimecrolimus is approved for mild-moderate atopic dermatitis for patients two years of age and older.[1]
    - Tacrolimus is approved in children and adults with moderate-severe atopic dermatitis.[2]

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Therapeutic Class Overview
Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

Therapeutic Class

- **Overview/Summary:** This review encompasses the ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) bromfenac sodium (Bromday®, Prolensa®), diclofenac sodium, flurbiprofen sodium (Ocufen®), ketorolac tromethamine (Acular®, Acular LS®, Acuvail®) and nepafenac (Ilevro®, Nevanac®).[1-11] These agents are indicated for use prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, and the reduction of pain and discomfort following cataract and refractive surgery. Although not Food and Drug Administration (FDA)-approved, ophthalmic NSAIDs are also used for the prevention and treatment of cystoid macular edema following cataract surgery.[12,13] Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.[1-10] Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[14-16]

  The American Academy of Ophthalmology and the American Optometric Association both recommend using ophthalmic NSAIDs for preventing and treating cystoid macular edema following cataract surgery. Neither organization recommends one ophthalmic NSAID over another.[17,18] The American Academy of Ophthalmology also recommends the use of NSAIDs in before and after several refractive surgeries.[19] Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21] The most common adverse events associated with ophthalmic NSAIDs include conjunctival hyperemia, burning and stinging.[15] Corneal ulceration and full-thickness corneal melts associated with the use of these agents is a serious complication. Ophthalmic NSAIDs were first reported to cause corneal melting in 1999. The majority of cases were related to the generic ophthalmic diclofenac sodium solution manufactured by Falcon Laboratories, and ultimately this product was removed from the market. There have been reports of corneal melts and keratitis associated with the use of other ophthalmic NSAIDs; however, available evidence does not alter the favorable benefit-risk ratio of the appropriate use of ophthalmic NSAIDs.[15]

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bromfenac sodium ophthalmic* (Prolensa®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic solution: 0.09% (1.7 mL, 2.5 mL, 5 mL) 0.07% (1.6 mL, 3 mL)	a
Diclofenac sodium ophthalmic	Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery; treatment of postoperative inflammation in patients undergone cataract extraction	Ophthalmic solution: 0.1% (2.5 mL, 5 mL)	a
Flurbiprofen sodium ophthalmic (Ocufen®*)	Inhibition of intraoperative miosis	Ophthalmic solution: 0.03% (2.5 mL)	a
Ketorolac tromethamine ophthalmic (Acular®*†, Acular LS®*†, Acuvail®)	Reduction of ocular pain and burning/stinging following corneal refractive surgery (0.4%); temporary relief of ocular itching due to seasonal allergic conjunctivitis (0.5%); treatment of pain and inflammation associated with cataract surgery (0.45%); treatment of postoperative inflammation in patients who have undergone cataract extraction (0.5%)	Ophthalmic solution: 0.4% (5 mL) 0.45% (0.4 mL single-use vials in package of 30) 0.5% (3 mL, 5 mL, 10 mL)	a

Nepafenac ophthalmic (Ilevro®, Nevanac®)	Treatment of pain and inflammation associated with cataract surgery	Ophthalmic suspension: 0.1% (3 mL) 0.3% (1.7 mL, 3 mL)	-

*Generic available in one dosage form or strength.
† Ketorolac tromethamine 0.5 and 0.4% ophthalmic solutions are available generically.

Evidence-based Medicine

- The ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be safe and effective in inhibiting intraoperative miosis, reducing postoperative inflammation and pain associated with cataract surgery, relieving pain and photophobia following corneal refractive surgery and relieving seasonal allergic conjunctivitis symptoms in placebo-controlled trials.[22-49,56-64] Although not Food and Drug Administration (FDA)-approved, there is evidence to support the use of ophthalmic NSAIDs for preventing or treating cystoid macular edema and for reducing pain associated with various other refractive surgeries.[51-54]
- The results of head-to-head trials comparing ophthalmic NSAIDs have not consistently demonstrated any one agent to be more efficacious than another for a given indication.[31,32,34,35,48,49,51,52,57,58,61]
- With regard to safety, not one agent was consistently reported to be better tolerated than another across trials, although there is some evidence that the preservative-free products may be associated with less ocular irritation.[45]
- Corneal complications have been reported to occur with all of the agents in the class and the risk does not appear to be higher with one agent vs another.
- Consensus guidelines established by the American Academy of Ophthalmology and the American Optometric Association recommend the use of topical NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. Available evidence suggests that ophthalmic NSAIDs either alone or in combination with ophthalmic corticosteroids are more effective than ophthalmic corticosteroids alone. The ophthalmic NSAIDs are not associated with an increase in intraocular pressure, which may occur with the use of corticosteroids. [17,18]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for preventing and treating cystoid macular edema due to cataract surgery is recommended.[17,18]
  - For refractive surgery, specifically surface ablation techniques and laser in situ keratomileusis, the use of ophthalmic NSAIDs is recommended. Judicious NSAID application should be done after surface ablation to reduce pain and inflammation and to delay corneal epithelialization NSAID application should be done before laser in situ keratomileusis to ameliorate postop pain. No NSAID is recommended over another.[19]
  - Both organizations note that ophthalmic NSAIDs are effective in treating the signs and symptoms of allergic conjunctivitis.[20,21]
- Other Key Facts:
  - Several formulations are available in generic formulations:
    - Bromfenac 0.09% (twice daily).
    - Diclofenac sodium.
    - Flurbiprofen sodium.
    - ketorolac tromethamine 0.5 and 0.4%.
  - Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are formulated as preservative-free.[4,6]
  - Nepafenac 0.3% and two formulations of bromfenac sodium (Bromday®, Prolensa®) are approved for once daily dosing.[1,2,10]
  - Ketorolac Tromethamine 0.4% is the only ophthalmic NSAID used as needed.[8]

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Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-17]

  Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[18-35] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[26,27,30] Given the paucity of clinical experience and long-term safety data, the 2013 European League against Rheumatism guidelines recommend that tofacitinib should primarily be used when biological treatment has failed.[18] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[36]

  The FDA has recently granted Humira® (adalimumab) orphan drug designation for the treatment of moderate to severe hidradenitis suppurativa (Hurley Stage II and Hurley Stage III disease), a chronic inflammatory skin disease which affects fewer than 200,000 patients in the United States.[2] Hidradenitis suppurativa is characterized by inflamed, painful lesions typically located around the armpits and groin, on the buttocks and under the breasts.[37] Other treatment options for people with hidradenitis suppurativa include surgery to remove skin affected by the disease and antibiotics to treat infections that may occur. Current clinical guidelines and systematic reviews and clinical literature currently guide the treatment of hidradenitis suppurativa. Generally, topical or oral antibiotics, intralesional steroids, retinoids, zinc, anti-androgens or laser surgery are recommended for mild (stage I disease). Stage II disease should generally be treated similar to Stage I with the addition of rifampin plus clindamycin, dapsone and prednisone. Stage III disease is treated with similar measures as Stages I and II, however the use of anti-inflammatory agents is recommended, with anti-TNF biologics adalimumab and infliximab having the most positive data.[38-42]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥six years)	Prefilled syringe: 125 mg/mL Single use vial: 250 mg	-
Adalimumab	Rheumatoid arthritis (adults only); polyarticular	Prefilled pen:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Humira®)	juvenile idiopathic arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (age ≥six years); ulcerative colitis (adults only); plaque psoriasis (adults only)	40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL	
Anakinra (Kineret®)	rheumatoid arthritis (adults); cryopyrin-associated periodic syndromes – neonatal-onset multisystem inflammatory disease (no age restriction)	Prefilled syringe: 100 mg/0.67 mL	-
Canakinumab (Ilaris®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥ four years); juvenile idiopathic arthritis (age ≥ two years)	Vial: 180 mg (150 mg/mL)	-
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥2 years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL, 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial*: 50 mg/4 mL	-
Infliximab	Crohn's disease (age ≥6 years); ulcerative colitis	Single use vial:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Remicade®)	(age ≥6 years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only), plaque psoriasis (adults only)	100 mg	
Rilonacept (Arcalyst®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years)	Vial: 220 mg (80 mg/mL)	-
Secukinumab (Cosentyx®)	Plaque Psoriasis (adults only)	Prefilled pen, syringe: 150 mg/mL Vial: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ 2 years) ; systemic juvenile idiopathic arthritis (age ≥ 2 years); rheumatoid arthritis (adults only);	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®)	Rheumatoid arthritis (adults only)	Tablet: 5 mg	-
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Single use vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[49-144]
- The safety and efficacy of Humira in the treatment of hidradenitis suppurativa was established in two clinical trials PIONEER I and PIONEER II. Both were 36-week, multicenter, randomized, double-blind clinical trials with a total of 633 adult patients with moderate to severe (Hurley Stage II and III) hidradenitis suppurativa who had an inadequate response to a trial of oral antibiotics, total abscess and inflammatory nodule count of ≥3 and lesions present in ≥2 body areas. At 12 weeks, therapy was evaluated and effectiveness was defined as improvement in abscesses and inflammatory nodules at 12 weeks using the Hidradenitis Suppurativa Clinical Response (HiSCR). In PIONEER I and PIONEER II, adalimumab achieved a statically significant improvement using the HiSCR measure when compared to placebo (P=0.003 and P<0.001, respectively).[47,48]

- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[77]
- The safety and efficacy of secukinumab was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,84-86]
- To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results. In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[126] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[127,128] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[129] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.
- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.[143]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[18-35]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[26,27,30] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary. In general, no one agent is preferred over another; however, given the paucity of clinical experience and long-term safety data, the use of tofacitinib for rheumatoid arthritis is recommended primarily after biological treatment has failed.[18]

- Other Key Facts:
    - None of the immunomodulators included in this review are available generically.
    - Dosing frequency and route of administration vary between products.
        - Tofacitinib is formulated as an oral tablet dosed twice daily.
        - Abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab (vial), and vedolizumab
            - Each is infused over 30 minutes, with the exception of infliximab which is infused over two hours.
        - Anakinra is administered subcutaneously, but requires more frequent (daily) administration.
    - Intravenous formulation of golimumab and subcutaneous formulation of tocilizumab are only indicated in the treatment of rheumatoid arthritis.

- Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

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Therapeutic Class Overview
Alzheimer's Agents

Therapeutic Class

- **Overview/Summary:** Alzheimer's disease is a progressive neurodegenerative disorder in older adults that affects cognition, behavior and activities of daily living.[1] It is the most common form of dementia and the average life expectancy from the onset of symptoms to death is approximately 8 to 10 years.[1-3] Diagnostic features include memory impairment and one or more of the following: aphasia, apraxia, agnosia, and/or disturbance in executive functioning.[1]

  The pathophysiologic mechanisms are not entirely understood; however, the disease is characterized by the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in various regions of the brain. Inflammation and free radical processes lead to neuron dysfunction and death. It is thought that memory loss is partially the result of a deficiency of cholinergic neurotransmission.[2-3] Glutamate, an excitatory neurotransmitter, may also play a role in the pathophysiology of Alzheimer's disease. Glutamate activates N-methyl-D-aspartate (NMDA) receptors and is involved in learning and memory. However, excessive amounts of glutamate in the brain may lead to excitotoxicity and cell death.[3]

  There are five agents approved for the treatment of Alzheimer's disease, including cholinesterase inhibitors (donepezil, galantamine and rivastigmine), an NMDA receptor antagonist (memantine) and a combination product (memantine extended release [ER]/donepezil).[4-13] Although none of the agents delay the progression of neurodegeneration, they do delay the progression of symptoms. The cholinesterase inhibitors enhance cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by acetylcholinesterase. Memantine blocks NMDA receptors and inhibits their overstimulation by glutamate. Currently, donepezil (tablets, orally-disintegrating tablets), galantamine (tablets, oral solution, ER capsules), rivastigmine (capsules, patch) and memantine (tablets) are available in a generic formulation.

Table 1. Medications Included Within the Therapeutic Class Review[4-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Products			
Donepezil (Aricept®*, Aricept ODT®)	Mild-to-moderate dementia of the Alzheimer's type Moderate-to-severe dementia of the Alzheimer's type	Orally disintegrating tablet: 5 mg 10 mg Tablet: 5 mg 10 mg 23 mg	a
Galantamine (Razadyne®*, Razadyne ER®*)	Mild-to-moderate dementia of the Alzheimer's type	Extended release capsule: 8 mg 16 mg 24 mg Solution: 4 mg/mL Tablet: 4 mg 8 mg 12 mg	a
Rivastigmine (Exelon®*,	Mild-to-moderate dementia of the Alzheimer's type (capsule and	Capsule: 1.5 mg	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Exelon Patch®*)	solution) Mild, moderate, and severe dementia of the Alzheimer's type (transdermal patch) Mild-to-moderate dementia associated with Parkinson's disease	3 mg 4.5 mg 6 mg Solution: 2 mg/mL Transdermal patch: 4.6 mg/24 hours 9.5 mg/24 hours 13.3 mg/24 hours	
Memantine (Namenda®*, Namenda XR®, Namenda Titration Pack®, Namenda XR Titration Pack®)	Moderate-to-severe dementia of the Alzheimer's type	Extended release capsule: 7 mg 14 mg 21 mg 28 mg Solution: 10 mg/5 mL Tablet: 5 mg 10 mg	-
Combination Products			
Memantine ER/donepezil (Namzaric®)	Moderate to severe dementia of the Alzheimer's type for patients stabilized on memantine and donepezil	Capsule: 14 mg/10 mg 28 mg/10 mg	-

ER=extended-release
*Generic is available in at least one dosage form or strength.

Evidence-based Medicine

- Clinical trials have demonstrated the safety and efficacy of the Alzheimer's agents.[15-103]
- Overall there is limited head to head data available comparing the efficacy of the different agents used to treat Alzheimer's disease. Several different outcomes have been assessed using more than forty different instruments, including cognition, global function, behavior and quality of life. There is inconsistent evidence from well-designed trials that donepezil, galantamine, rivastigmine and memantine positively affect cognition and global function, although the improvements are modest. These findings are less consistent for other outcomes, including behavior and quality of life. In most cases, the duration of well-designed clinical trials were less than one year. There are very few studies that directly compare their various agents. Most of the trials have compared active treatment to placebo or no treatment. The published studies also differ with regards to design, patient population and treatment duration, which make it difficult to directly compare the results.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[104-109]
  - Supports use of the cholinesterase inhibitors as first-line agents for mild-moderate Alzheimer's disease.
  - Memantine is effective in the treatment of moderate-to-severe Alzheimer's disease.
  - Memantine may be added to a cholinesterase inhibitor.

- Evidence does not show clinically meaningful advantages to administering higher doses of donepezil; however, higher doses of rivastigmine patch may be associated with greater benefit.[107]

· Other Key Facts:
  - Currently donepezil, galantamine and rivastigmine are available generically.
  - Rivastigmine is uniquely indicated for symptoms of dementia in Parkinson's disease patients.

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Therapeutic Class Overview
Oral Atypical (Second-Generation) Antipsychotics

Therapeutic Class Overview/Summary:
This overview will focus on the atypical antipsychotics, which are also known as second-generation antipsychotics (SGAs).[1-14] While several atypical antipsychotics are formulated as long-acting injections, these formulations will not be covered in this review. Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[15] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[16]

In addition to blocking D_2 receptors in the mesolimbic pathway, FGAs also block D_2 receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways.[16] D_2 blockade in these other pathways is thought to be responsible for the hyperprolactinemia and extrapyramidal symptoms (EPS) associated with this class.[17] FGAs may be characterized according to their affinity for the D_2 receptor. Low potency antipsychotics, such as chlorpromazine and thioridazine, are more sedating and associated with a higher incidence of anticholinergic side effects. Fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine are high potency antipsychotics that are less sedating but associated with a higher incidence of EPS. The medium potency antipsychotics (loxapine, molindone, and perphenazine) possess a moderate risk of EPS and anticholinergic side effects.[18] With the exception of pimozide, all FGAs are indicated for use in the treatment of schizophrenia. FGAs are effective in the treatment of positive symptoms of schizophrenia, which include agitation, aggression, delusions, and hallucinations. Negative symptoms of schizophrenia which include avolition, anhedonia, alogia, affective flattening, and social withdrawal, do not respond as well to this antipsychotic class.[17] Pimozide is indicated only for the suppression of motor and phonic tics in patients with Tourette's disorder.

The term "atypical antipsychotic" was introduced in 1989 when clozapine was approved for use by the Food and Drug Administration (FDA). Originally, this term referred to an antipsychotic with a low risk of EPS.[18] As a class, SGAs or atypical antipsychotics are more selective in targeting the mesolimbic D_2 pathway. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than D_2 receptors.[16,18] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[16,18] Atypical antipsychotics have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[16] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. The SGAs are aripiprazole, asenapine, brexpiprazole clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone.

Although in some respects the SGAs are safer and better tolerated than the FGAs, they are still associated with a number of serious risks and side effects. For this reason, the FDA has required various warnings to be inserted in the manufacturers' product information for these agents. All bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes. [1-14] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[1-14] Aripiprazole, brexpiprazole, lurasidone and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[1,3,8,11,12] All SGAs carry a black box warning noting that they are associated with an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Most of the deaths that prompted the addition of the warning were due to cardiac-related events (e.g., heart failure or sudden death) or infection.[21] Of note, this last black box warning is directed at using antipsychotics in a manner that is not FDA-approved.

Due to the potential side-effect risks associated with these medications, any off-label use deserves close attention. Data published in peer-reviewed journals and in national and international guidelines support the use of SGAs as a treatment option for certain off-label uses. In many of these scenarios, SGAs are reserved for patients who are refractory to other first-line treatment modalities, including both pharmacotherapy and psychotherapy, and used in adjunction to mainstream therapies, as part of a multimodal approach.

Over the past 20 years, antipsychotic use in children and adolescents has grown. In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002. According to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[22] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders. Off-label indications with limited available evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA-approved for the management of children and adolescents with autism (aged 5 to 16 and 6 to 17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, asenapine, olanzapine, quetiapine and risperidone are FDA-approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[1-14]

Concerns have also been raised about the risks of combination therapy with the antipsychotics, which can multiply the risks of dangerous adverse events. The practice of polypharmacy is not supported by well-designed clinical trials published in the peer-reviewed literature. However, national and international consensus guidelines consider this approach in patients with treatment-refractory illness.

Table 1. Current Medications Available in Therapeutic Class[1-14]

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify®*, Abilify Discmelt®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults; irritability associated with autistic disorder in children and adolescents aged six to 17 years	Injection: 7.5 mg/mL Orally disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg	a

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Asenapine (Saphris®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults or adolescents (10 to 17 years of age); adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; acute and maintenance treatment of schizophrenia in adults	Sublingual tablet: 5 mg 10 mg	-
Brexpiprazole (Rexulti®)	Adjunctive treatment to antidepressants for major depressive disorder in adults; treatment of schizophrenia in adults	Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	-
Clozapine (Fazaclo ODT®*, Clozaril®*, Versacloz®)	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults; treatment-resistant schizophrenia in adults	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg Suspension: 50 mg/mL	a
Iloperidone (Fanapt®)	Treatment of schizophrenia in adults	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Lurasidone (Latuda®)	Treatment of schizophrenia in adults, treatment of depressive episodes associated with bipolar disorder in adults	Tablet: 20 mg 40 mg 80 mg 60 mg 120 mg	-
Olanzapine (Zyprexa®*, Zyprexa IM®*, Zyprexa Zydis®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed	Injection: 10 mg vials Orally disintegrating tablet: 5 mg	a

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	episodes associated with bipolar I disorder; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; treatment of agitation associated with bipolar I mania in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; adjunctive treatment to antidepressants for major depressive disorder in adults	10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg	
Paliperidone (Invega®*)	Acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 12 to 17; treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Suspension for IM injection: 39 mg 78 mg 117 mg 156 mg 234 mg	a
Quetiapine (Seroquel®*, Seroquel XR®)	Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10 to 17 years; treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg	a
Risperidone (Risperdal®*, Risperdal M-Tab®*)	Adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; short-term treatment of acute manic or mixed	Orally disintegrating tablet: 0.25 0.5 mg	a

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	episodes associated with bipolar I disorder in adults and in children and adolescents aged 10 to 17 years; short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; irritability associated with autistic disorder in children and adolescents aged five to 16 years	1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	
Ziprasidone (Geodon®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; treatment of acute manic or mixed episodes associated with bipolar disorder; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adults	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL	a

*Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of second generation antipsychotics (SGAs) compared to first generation antipsychotics (FGAs) in patients with chronic schizophrenia.[43-45] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation.
    - Due to relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The role of the SGAs has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine extended-release and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder).
- Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[46-58,68-72] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. Aripiprazole tended to exhibit lower efficacy than the other agents.[46-58,68-72]
- A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[68] The next best treatment options, in order of decreased efficacy, were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo.
- In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[77]

- The efficacy and safety of brexpiprazole in the treatment of schizophrenia was demonstrated by two pivotal multicenter, randomized, double-blind, placebo controlled six week trials, VECTOR and BEACON.[27,28] Positive and Negative Syndrome Scale (PANSS) scores were significantly improved with brexpiprazole when compared to placebo. Treatment differences were -8.72 (P<0.0001), -7.64 (P=0.0006) and -6.47 (P=0.0022) for brexpiprazole 2 mg, 4 mg, and 4 mg respectively.[27,28]
- The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from six weeks to one year[29-32]. The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[59-63]
    - In a direct-comparison study, asenapine was less effective than olanzapine in terms of changes from baseline in PANSS and Clinical Global Impression-Severity of Illness (CGI-S) scores.[32] Study discontinuation due to inadequate efficacy was noted in 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[32] In another study, clinically significant weight gain was noted in 17% of patients receiving risperidone and 9% of patients in the asenapine group.[29]
    - In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in Young Mania Rating Scale (YMRS) scores at week-52 of therapy.[63]
    - A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[68]
- Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia.
    - Three six-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[34]
    - One four-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo. [33]
- Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two six-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[39-42]
    - Lurasidone and ziprasidone were comparable in terms of reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] In addition, both drugs were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[40,41] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality.
    - Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (*P*=0.046).[41]
- Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[214]
- Data from the Food and Drug Administration Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[243]
- Risperidone is associated with the greatest risk of prolactin elevation-related adverse events. [46-58,68-72,260]

- Risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[222] Quetiapine is associated with the least risk of extrapyramidal adverse events.[222]
- The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[226]
- The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[78, 189]
    - Indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of selective serotonin reuptake inhibitors for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[89] Refer to Appendices IIa and IIb for additional details.
- The AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[95,96] For details, refer to Appendices IIIa and IIIB.
    - Indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome.
    - No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons.
    - The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain.
    - Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data).
    - Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo.
- According to a systematic review by Safer et al, weight gain secondary to atypical antipsychotics is greater in children and adolescents than in adults.[257]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Antipsychotics are a mainstay in therapy for schizophrenia.[306-308]
    - Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[293-296]
    - The American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[297]
    - For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[291,292] Second-line treatment options include serotonin norepinephrine reuptake inhibitors (SNRIs) or switching to alternative selective serotonin reuptake inhibitors (SSRIs). Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists.
    - In major depressive disorder, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[300-302] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy.
    - In obsessive compulsive disorder, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[303] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of post-traumatic stress disorder (PTSD).[304,305]
    - Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD.

- The European Society for the Study of Tourette Syndrome guideline recommends risperidone as a first-line agent for the treatment of tics.[319] Aripiprazole has a role in treatment-refractory patients.
- The American Academy of Child and Adolescent Psychiatry (AACAP) guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[314]
- Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[321]
- In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[319] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication.
- Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients.[319]
- There is almost no data to support the use of atypical antipsychotics in pre-school aged children.[319] The guideline recommends a marked amount of caution before using these agents in pre-schoolers.
- Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.[319]

Table 2. Evidence for the Use of Atypical Antipsychotics in Pediatrics (2011 AACAP guideline)[308]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasi-done	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourette's/tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies
+++ One randomized controlled study
++ Uncontrolled study
+ Case studies
* FDA approved in children and/or adolescents

· Other Key Facts:

- Paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug.
- The use of clozapine is limited due to a risk of agranulocytosis.
- Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone are available generically.

Appendix I: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[189]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**

Indication	Strength of Evidence	Findings	Conclusions
		superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at six or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder er
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of nine trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone.	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine. e.

Indication	Strength of Evidence	Findings	Conclusions
		The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (two) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 vs 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a three-fold decline in PTSD Scale (CAPS) scores in	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Indication	Strength of Evidence	Findings	Conclusions
		patients treated with quetiapine monotherapy compared to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were efficacious for combat-related PTSD but not PTSD in abused women.	
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared to placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	Olanzapine had **mixed results** in seven trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Schizotypal	**Low**	Risperidone was superior to	Risperidone had **mixed**

Indication	Strength of Evidence	Findings	Conclusions
		placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	**results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for eight to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder.
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low** (quetiapine)	In a pooled analysis of three trials, there was no difference in change in BMI at either one or three months with olanzapine compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.

Indication	Strength of Evidence	Findings	Conclusions
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect vs placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy vs placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be **inefficacious.**
Meth-amphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix II: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[189]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively,	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
	compared to a monthly weight loss of 0.9 lbs for placebo patients.	a large cohort study.	
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
			risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and	No evidence reported	More common in patients taking risperidone, according to the meta-

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
	risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).		analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine vs benzodiazepines. No difference in three trials of olanzapine and three of risperidone vs conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone vs olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine vs risperidone. More patients on haloperidol than risperidone reported sleep	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		problems in one trial.	

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix III: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[96]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs SGA (2 RCTs)	Low	No significant difference
	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD, 218.3; 95% CI, 227.1 to 29.5; I2, 79.6%); CARS (MD, 24.9; 95% CI, 28.5 to 21.4; I2, 64%).
CGI	SGA vs placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD, 21.7; 95% CI, 23.2 to 20.3; I2, 49%).
Medication adherence	SGA vs placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD, 221.0; 95% CI, 231.1 to 210.8; I2, 62%); BPI (MD, 23.8; 95% CI, 26.2 to 21.4; I2, 0%); NCBRF (MD, 26.9; 95% CI, 210.4 to 23.5; I2, 62%).
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD, 21.0; 95% CI, 21.7 to 20.3; I2, 45%); CGI–S (MD, 21.3; 95% CI, 22.2 to 20.5; I2, 78%).
Medication adherence	SGA vs placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.7; 95% CI, 20.8 to 20.5; I2, 36%).
Depression	SGA vs	Low	No significant difference

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	placebo (7 RCTs)		
Manic Symptoms	SGA vs placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR, 2.0; 95% CI, 1.0 to 4.0; I2, 0%).
Suicide-related behavior	SGA vs placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD, 20.8; 95% CI, 21.3 to 20.3; I2, 0%).
	Clozapine vs olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.5; 95% CI, 20.7 to 20.3; I2, 28%).
Positive and negative symptoms	FGA vs SGA (3 RCTs)	Low	No significant difference
	Clozapine vs olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 28.7; 95% CI, 211.8 to 25.6; I2, 38%).
Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs	Low	No significant difference

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	placebo (2 RCTs)		
Suicide-related behaviors	SGA vs placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD, 27.0; 95% CI, 210.3 to 23.6; I2, 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study.

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[96]

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR, 0.25; 95% CI, 0.08 to 0.8)[a] and 95% CI, 271.3 to 27.4).[a] No significant differences were observed for clozapine vs olanzapine, olanzapine vs quetiapine and quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.5; 95% CI, 1.4, 4.4)[a], olanzapine (RR, 2.4; 95% CI, 1.2 to 4.9; I^2, 45%), and quetiapine (RR, 2.4; 95% CI, 1.1 to 5.4; I2, 0%).
	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD, 10.2 mg/dL; 95% CI, 3.1 to 17.2; I^2, 0%) and triglycerides (MD, 17.3 mg/dL; 95% CI, 3.5 to 31.1; I2, 0%).	NA
EPS	Low	No significant difference for clozapine vs olanzapine, clozapine vs risperidone, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	No significant differences for placebo compared to olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR, 4.2; 95% CI, 2.4 to 7.2; I^2, 0%) and risperidone (RR, 2.7; 95% CI, 1.4 to 4.9; I^2, 0%).

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Insulin Resistance	Low	No significant difference for olanzapine vs quetiapine, olanzapine vs risperidone or quetiapine vs risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD, 210.8 ng/dL; 95% CI, 216.7 to 24.8; I^2, 21%). No significant difference for quetiapine vs risperidone.	Significant effect in favor of placebo over risperidone in seven or eight studies (not pooled due to heterogeneity). No significant difference for quetiapine compared to placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR, 0.4; 95% CI, 0.2 to 0.6; I^2, 0%).	Significant effect in favor of aripiprazole over placebo (MD, 24.1 ng/mL; 95% CI, 26.3 to 21.8; I2, 0%). Significant effect in favor of placebo over olanzapine (MD, 11.5 ng/mL; 95% CI, 8.8 to 14.1; I2, 0%).
Sedation	Low	No significant differences for clozapine vs olanzapine, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.7; 95% CI, 1.1 to 6.5; I2, 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR, 2.9; 95% CI, 1.5 to 5.5; I^2, 32%) and ziprasidone (RR, 3.0; 95% CI, 1.7 to 5.2; I^2, 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD, 24.1 kg; 95% CI, 25.5 to 22.7),a quetiapine (MD, 21.6 kg; 95% CI, 23.0 to 20.3)[a] and risperidone (MD, 22.3 kg; 95% CI, 23.9 to 20.7).a No significant difference for clozapine vs olanzapine, clozapine vs risperidone, and quetiapine vs risperidone.	No significant difference for ziprasidone compared to placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR,	Significant effect in favor of placebo over

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
		1.5; 95% CI, 1.1 to 2.0; I^2, 0%) and risperidone over olanzapine (MD, 2.4 kg; 95% CI, 1.5 to 3.3; I^2, 72%).	aripiprazole (MD, 0.8 kg; 95% CI, 0.4 to 1.2; I^2, 13%), olanzapine (MD, 4.6 kg; 95% CI, 3.1 to 6.1; I2, 70%), quetiapine (MD, 1.8 kg; 95% CI, 1.1 to 2.5; I^2, 49%), and risperidone (MD, 1.8 kg; 95% CI, 1.5 to 2.1; I^2, 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

References

Please refer to the full therapeutic class review on atypical antipsychotics for a list of references.

Therapeutic Class Overview
Ophthalmic Antihistamines

Therapeutic Class

- **Overview/Summary:**
  All of the ophthalmic antihistamines listed in Table 1 are Food and Drug Administration (FDA)-approved for the prevention or treatment of the signs and symptoms of allergic conjunctivitis.[1-10] Ketotifen (Alaway®, Zaditor®) is also indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.[6,7] Allergic conjunctivitis is the most common form of ocular allergy. Itching manifests as the primary symptom; however, other common symptoms include ocular burning, chemosis, conjunctival and eyelid edema, hyperemia, photophobia and tearing.[11] Symptoms usually occur in both eyes, yet one eye may be affected more than the other.[11] Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea.[12] None of the ophthalmic antihistamines are FDA-approved for the treatment of vernal conjunctivitis. Following topical administration to the conjunctiva, ophthalmic antihistamines competitively bind histamine receptor sites to reduce itching and vasodilation.[1-10] The ocular antihistamines are relatively selective for the histamine type 1 (H_1-antihistamine) receptor but may also inhibit the degranulation of mast cells, thereby limiting the release of inflammatory mediators such as histamine, eosinophil and neutrophil chemotactic factors.[1-3,5-10] Emedastine (Emadine®) has only H_1-antihistamine activity.[4] Ophthalmic antihistamines have demonstrated a faster onset of action compared to oral antihistamines and ophthalmic mast-cell stabilizers and they are all approved for use in children.[1-11] The most common adverse events associated with these agents are ocular burning, stinging and headache.[1-11] In general, drug interactions are limited due to low systemic bioavailability via the ocular route. The administration schedule for these products ranges from once daily to four times daily, with only alcaftadine (Lastacaft®), olopatadine 0.2% (Pataday®) and olopatadine 0.7% (Pazeo®) are approved for once daily use.[1,9,10] Azelastine (Optivar®), epinastine (Elestat®) and ketotifen are available generically. Ketotifen is also available over-the-counter.

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alcaftadine (Lastacaft®)	Allergic conjunctivitis†	Ophthalmic solution: 0.25% (3 mL)	-
Azelastine (Optivar®*)	Allergic conjunctivitis†	Ophthalmic solution: 0.05% (6 mL)	a
Bepotastine (Bepreve®)	Allergic conjunctivitis†	Ophthalmic solution: 1.5% (5, 10 mL)	-
Emedastine (Emadine®)	Allergic conjunctivitis‡	Ophthalmic solution: 0.05% (5 mL)	-
Epinastine (Elestat®*)	Allergic conjunctivitis§	Ophthalmic solution: 0.05% (5 mL)	a
Ketotifen (Alaway®*, Zaditor®*)	Allergic conjunctivitis§, ocular itching‖	Ophthalmic solution: 0.025% (OTC, RX) (5, 10 mL)	a #
Olopatadine (Pataday®, Patanol®, Pazeo®)	Allergic conjunctivitis (0.2%)† (0.1%)‡, ocular itching (0.7%)	Ophthalmic solution: 0.1% (5 mL) 0.2% (2.5 mL)	-

OTC=over-the-count, RX=prescription
* Available generically in one dosage form or strength.
† For the treatment of ocular itching associated with allergic conjunctivitis.
‡ For the treatment of signs and symptoms of allergic conjunctivitis.
§ For the prevention of ocular itching associated with allergic conjunctivitis.
‖ For the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair and dander.
Product is also available over-the-counter in at least one dosage form or strength.

Evidence-based Medicine

- The ophthalmic antihistamines are significantly more effective compared to placebo for reducing the symptoms of allergic conjunctivitis including ocular itching and conjunctival redness.[14-18]
- The safety and efficacy of olopatadine 0.7% (Pazeo®) was based on clinical trials of ophthalmic olopatadine 0.1% (Patanol®) and 0.2% (Pataday®).[8-10]
- Limited head-to-head trials comparing olopatadine, azelastine and ketotifen have failed to consistently show the "superiority" of one ophthalmic antihistamine over another for the management of allergic conjunctivitis.[19-24]
- A meta-analysis of four trials found that patients were 1.3 times more likely to perceive their treatment response as "good" with ophthalmic antihistamines compared to patients receiving pure ophthalmic mast-cell stabilizers; however, the difference was not statistically significant.[25]
- The ophthalmic antihistamines have consistently demonstrated a greater improvement in allergy symptoms and/or patient comfort scores compared to ophthalmic mast-cell stabilizers and ocular vasoconstrictors; however, many of these trials were conducted using single doses of study medication (conjunctival allergen challenge model) in a small number of patients.[26-36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Ophthalmic formulations of agents from the following classes are useful in treating allergic conjunctivitis: corticosteroids, vasoconstrictor/antihistamine combinations, antihistamines, nonsteroidal anti-inflammatories (NSAIDs), mast-cell stabilizers, antihistamine/mast-cell stabilizers and immunosuppressants.[13]
  - An over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist is recommended for mild allergic conjunctivitis. No preference is given to any one OTC antihistamine/vasoconstrictor or antihistamine.[37]
  - If the condition is frequently recurrent or persistent, use mast-cell stabilizers. No single mast-cell stabilizer is preferred over another.[37]
  - Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. No one antihistamine/mast-cell stabilizer is preferred over another.[37]
  - If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used because of the potential for adverse events with their protracted use (e.g., cataract formation and elevated intraocular pressure).[13,37]
  - Ketorolac, a NSAID, is also Food and Drug Administration-approved for the treatment of allergic conjunctivitis.[13,37]

- Other Key Facts:
  - Alcaftadine and emedastine are classified as pregnancy category B while the other agents in this class have a pregnancy category C rating.
  - Alcaftadine and olopatadine (0.2%, 0.7%) are the only agents within the class that are approved for once daily use.
  - Ophthalmic formulations of azelastine, epinastine and ketotifen are available generically.
  - Ketotifen is also available over-the-counter.

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Therapeutic Class Overview
Short-acting β_2-Agonists

Therapeutic Class

- **Overview/Summary:** Respiratory short acting β_2-agonists (SABAs) are Food and Drug Administration (FDA)-approved indications include asthma, chronic obstructive pulmonary disease, exercise-induced bronchospasm (EIB), and/or and reversible bronchospasm. Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-15] The β_2-agonists can be divided into two categories: short-acting and long-acting. The short-acting respiratory β_2-agonists consist of albuterol (ProAir HFA®, ProAir Respiclick®, Proventil HFA®, Proventil HFA®, Ventolin HFA®), levalbuterol (Xopenex®, Xopenex HFA®), metaproterenol and terbutaline. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-15] As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all albuterol metered dose inhalers (MDIs) containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. These inhalers were replaced by MDIs which use hydrofluoroalkanes (HFAs). There is no difference in the safety or efficacy of the HFA inhalers compared to the CFC inhalers; however, there may small differences in taste and/or feel with the HFA inhalers. The deadline for removal of the pirbuterol (Maxair®) CFC inhaler is December 31, 2013.[16]

Table 1. Current Medications Available in the Therapeutic Class[1-15]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Short-Acting β_2-agonists			
Albuterol (AccuNeb®*, ProAir HFA®, ProAir Respiclick®, Proventil HFA®, Ventolin HFA®, VoSpire ER®*)	Relief of bronchospasm in patients with asthma†,‖, treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†‡§, prevention of exercise-induced bronchospasm†‡	Dry Powder Inhaler: 90 µg Meter dose aerosol inhaler (HFA): 120 µg albuterol sulfate# Solution for nebulization: 0.63 mg 1.25 mg 2.5 mg 0.5% concentrated solution (3 mL unit dose vials) Sustained-release tablet: 4 mg 8 mg Syrup:	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		2 mg/5 mL Tablet: 2 mg 4 mg	
Levalbuterol (Xopenex®*, Xopenex HFA®)	Treatment or prevention of bronchospasm in patients with reversible obstructive airway disease†	Meter dose aerosol inhaler (HFA): 59 µg¶ Solution for nebulization: 0.31 mg 0.63 mg 1.25 mg (3 mL vials)	a
Metaproterenol*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Syrup: 10 mg/5 mL Tablet: 10 mg 20 mg	a
Terbutaline*	Prevention and treatment of asthma and reversible bronchospasm, which may occur in association with bronchitis and emphysema	Injection: 1 mg/mL (2 mL vial) Tablet: 2.5 mg 5 mg	a

*Generic available in at least one dosage form or strength.
†Inhalation solution.
‡Metered-dose inhaler.
§Dry powder inhaler.
‖Oral formulations.
¶Delivering 45 µg levalbuterol base.
#Delivering 108 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy SABAs in providing relief from reversible bronchospasms and EIA.[21-41]
- Safety and efficacy of albuterol dry powder inhaler (ProAir Respiclick®) was evaluated in two 12-week randomized, double-blind, placebo-controlled studies. Forced expiratory volume in one second (FEV_1) was significantly improved with albuterol dry powder inhaler compared with placebo (no P value reported).[7]
- In clinical trials that comparing albuterol to levalbuterol, inconsistent results have been reported and have not consistently demonstrated improved outcomes with levalbuterol compared to albuterol. Moreover, studies have shown no significant differences between the two agents in the peak change in FEV_1 or the number and incidence of adverse events.[21-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[17-20]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis.[17-20]

- Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[17-20]
- The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[17-20]
- The use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[17]

· Other Key Facts:
- Studies have failed to consistently demonstrate significant differences between products.
- Albuterol oral solution, oral tablets, and solution for nebulization, levalbuterol solution for nebulization, metaproterenol oral solution and oral tablets, and terbutaline oral tablets and solution for injection are available generically.
- There are currently branded albuterol hydrofluoroalkanes (HFA) inhalers and one dry-powder inhaler; however, no generic equivalents are available.

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RxOutlook®

Recap: a monthly summary of pharmaceutical pipeline news, events, and trends

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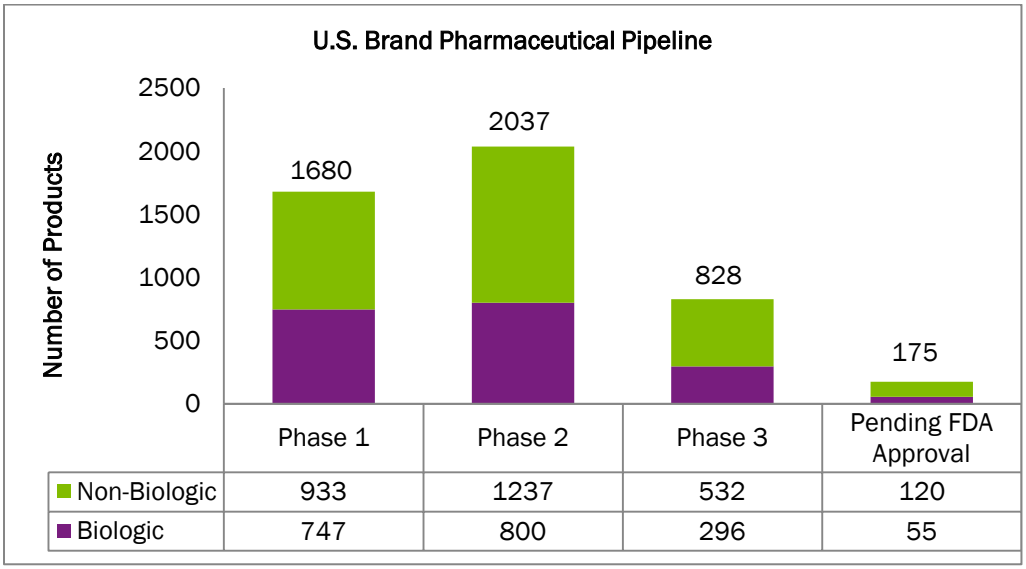
brand pipeline snapshot

- As of September 30, 2015, there are approximately 4,720 products either pending FDA approval or in phase 1, 2, or 3 of clinical development within the United States.



	Phase 1	Phase 2	Phase 3	Pending FDA Approval
Non-Biologic	933	1237	532	120
Biologic	747	800	296	55

Biologic = blood products, allergenics, recombinant peptides or proteins, monoclonal antibodies, vaccines, and cell or gene therapies (includes both specialty and non-specialty potentially designated products)

select pipeline & trend headlines

Brand Pipeline-Related

- BPL Announces Enrollment of the First Subject in a Phase 3 Clinical Trial to Evaluate a New Subcutaneous Immunoglobulin Product for Patients with Primary Immunodeficiency
- Valeant and AstraZeneca to Partner on Brodalumab
- Gilead's Investigational Fixed-Dose Combination of Emtricitabine/Tenofovir Alafenamide (F/TAF) Meets Primary 48-Week Objective in Phase 3 Study
- Amgen and UCB Announce Positive Top-Line Results From Open-Label Phase 3 Study Of Romosozumab Compared With Teriparatide
- Inovio Pharmaceuticals Announces First Patient Dosed With Universal HIV Vaccine
- Biogen Enrolls First Patient in Global Phase 3 Study of Investigational Treatment Aducanumab (BIIB-037) for Early Alzheimer's Disease
- AcelRx Pharmaceuticals' ARX-04 Meets all Endpoints in Pivotal Phase 3 Study for Moderate-to-Severe Acute Pain

- Tetraphase Announces Top-Line Results From IGNITE2 Phase 3 Clinical Trial of Eravacycline in cUTI
- Pharmaceutical Research & Manufacturers of America (PhRMA): Medicines in Development for Cancer - More than 800 Medicines and Vaccines in Clinical Testing for Cancer Offer New Hope to Patients
- Theravance Biopharma Presents Positive Clinical Data on Fixed-Dose Combination (FDC) of Axelopran (TD-1211) and Oxycodone at PAINWeek 2015
- Theravance Biopharma and Mylan Initiate Phase 3 Program for Revefenacin (TD-4208) for Treatment of Chronic Obstructive Pulmonary Disease (COPD)
- Laguna Pharmaceuticals Initiates Phase 3 Study of Vanoxerine in Atrial Fibrillation and Atrial Flutter
- Sanofi Reports Positive Top-Line Results in Second Pivotal LixiLan (insulin glargine 100 Units/mL/lixisenatide) Phase 3 Study
- FORUM Pharmaceuticals Inc. Updates Encenicline Phase 3 Clinical Trial Programs in Alzheimer's Disease and Cognitive Impairment in Schizophrenia – Places drug on clinical hold
- Intra-Cellular Therapies Announces Positive Top-Line Results From the First Phase 3 Trial of ITI-007 in Patients With Schizophrenia and Confirms the Unique Pharmacology of ITI-007 in a Separate Positron Emission Tomography Study
- Merck's Omarigliptin, an Investigational Once-Weekly DPP-4 Inhibitor, Achieved Similar A1C Reductions to JANUVIA® (sitagliptin) in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Monotherapy
- Aerie Pharmaceuticals Reports Positive RHOPRESSA™ Phase 3 Efficacy Results
- Merck Provides Diabetes Portfolio Update and Underscores Comprehensive, Long-Term Commitment to Patients with Diabetes
- Thomson Reuters Life Sciences Connect: Good Prospects for Ixazomib, First Oral Proteasome Inhibitor in Multiple Myeloma
- Gilead Announces SVR12 Rates from Four Phase 3 Studies Evaluating a Once-Daily, Fixed-Dose Combination of Sofosbuvir (SOF) and Velpatasvir (VEL) (GS-5816) for the Treatment of All Six Hepatitis C Genotypes
- Pfizer Announces Positive Top-Line Results from Two Phase 3 Trials of Oral XELJANZ® (Tofacitinib) in Adults with Moderate-to-Severe Ulcerative Colitis
- Pivotal Phase 3 Studies of Bezlotoxumab, Merck's Investigational Antitoxin to Prevent Clostridium Difficile Infection Recurrence, Met Primary Endpoint
- KemPharm Expands Its Abuse-Deterrent Opioid Pipeline With New Acetaminophen-Free, Immediate Release Hydrocodone And Immediate Release Oxycodone Prodrug Product Candidates
- Genentech's Ocrelizumab First Investigational Medicine to Show Efficacy in People with Primary Progressive Multiple Sclerosis in Large Phase 3 Study
- Novartis drug AFINITOR® significantly improves progression-free survival in advanced nonfunctional gastrointestinal and lung NET
- Baricitinib Superior to Methotrexate in Reducing Signs and Symptoms in Pivotal Phase 3 Study in Patients with Rheumatoid Arthritis
- Lilly and Sanofi Reach Settlement Agreement in U.S. Insulin Glargine Litigation

Generic/Biosimilar Pipeline-Related

- Mylan Confirms the U.S. Patent and Trademark Office Institutes Inter Partes Review Proceeding against Third COPAXONE® 40 mg/mL Dosing Patent on All Claims
- Horizon Pharma plc Announces the U.S. Patent and Trademark Office Issuance of an Additional Notice of Allowance With Claims Covering PENNSAID (Diclofenac Sodium Topical Solution) 2%
- Allergan Announces Agreement with Amneal Related to NAMENDA XR® Patent Litigation
- Depomed Files New Patent Infringement Lawsuit Against NUCYNTA® ER ANDA Filer
- FirstWord: BioMarin settles patent challenge, allowing Dr. Reddy's to launch generic version of phenylketonuria treatment KUVAN (may require free registration to access)
- Appeals Court Affirms Shire's VYVANSE® (lisdexamfetamine dimesylate) Patents Are Valid Until 2023
- Noven Announces Favorable Decisions in the Inter Partes Reviews Challenging Novartis' EXELON® Patch Patents
- United Therapeutics Announces Settlement of Patent Litigation with Sandoz Inc. Regarding REMODULIN® (treprostinil) Injection
- Amgen And Allergan Announce Positive Top-line Results From Phase 3 Study of Biosimilar Candidate ABP 215

Trend-Related

- Mercer: Good News, Bad News: The High Cost of Specialty Drugs
- National Bureau of Economic Research (NBER): Health Care Spending - Historical Trends and New Directions
- Associated Press: Half of US Adults have diabetes or pre-diabetes, study says
- Altarum Health: September 2015 Health Sector Economic Indicators℠ Briefs
- FiercePharma: Payer hardball cuts price growth, with biggest hits in diabetes, COPD and hep C
- American Association for Cancer Research (AACR): AACR Cancer Progress Report 2015
- EP Vantage: After Turing, the industry's biggest price gougers (may require free registration to access)

Other News

- GlaxoSmithKline and Theravance announce results from the SUMMIT COPD CV Survival Study
- JARDIANCE® (empagliflozin) is the only diabetes medication to show a significant reduction in both cardiovascular risk and cardiovascular death in a dedicated outcome trial
- ANI Pharmaceuticals to Acquire Two NDAs (corticotropin gel and corticotropin-zinc hydroxide) from Merck for $75 Million

upcoming FDA approvals

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
TARCEVA (erlotinib) Astellas	Antineoplastics & Adjunctive Therapies	Oral	New Indication	Pediatric Ependymoma	2015-Sep to 2015-Oct 31
(pegfilgrastim biosimilar) ApoBiologix / Apotex; Intas	Hematological Agents	Subcutaneous	Biosimilar	Neutropenia	2015-Sep to 2015-Oct 16
(necitumumab) Eli Lilly	Antineoplastics & Adjunctive Therapies	Intravenous	New Molecular Entity	In Combintion with Gemcitabine and Cisplatin for the First-Line Treatment of Locally-Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)FT	2015-Sep to 2015-Dec
GRASTOFIL (filgrastim biosimilar) ApoBiologix / Apotex; Intas	Hematological Agents	Intravenous; Subcutaneous	Biosimilar	Neutropenia	2015-Sep 30 to 2015-Oct 30
FLUCELVAX (influenza virus vaccine) Novartis	Vaccines	Intramuscular	New Indication	Influenza Virus Infection Prevention in Patients >/= 4 Years of Age	2015-Sep/Oct
RETACRIT (epoetin alfa biosimilar) Hospira	Hematological Agents	Intravenous; Subcutaneous	Biosimilar	Anemia Secondary to Chronic Kidney Disease (CKD)	2015-Oct
ENSTILAR (calcipotriene / betamethasone dipropionate aerosol foam) Leo	Dermatologicals	External	New Formulation	An Aerosol Foam (0.005%/0.064%) Formulation for the Treatment of Plaque Psoriasis	2015-Oct
(hydrocodone bitartrate extended-release) Cephalon / Teva	Analgesics & Anesthetics	Oral	New Formulation	Twice-Daily, Single-Entity, Extended-Release, Abuse-Deterrent Formulation for Chronic Pain TreatmentFT	2015-Oct
(oxycodone HCl / naltrexone HCl extended-release) Pfizer	Analgesics & Anesthetics	Oral	New Formulation; New Combination	Extended-Release, Abuse-Resistant Formulation for Moderate to Severe Chronic Pain	2015-Oct
XELJANZ (tofacitinib citrate) Pfizer	Analgesics & Anesthetics	Oral	New Indication	Moderate to Severe Chronic Plaque Psoriasis	2015-Oct
(meloxicam solumatrix) iCeutica	Analgesics & Anesthetics	Oral	New Formulation	A Low Dose Nonsteroidal Antiinflammatory Drug (NSAID) for the Management of Osteoarthritis Pain	2015-Oct to 2015-Nov

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
SAXADAPA (saxagliptin / dapagliflozin) AstraZeneca	Endocrine & Metabolic Drugs	Oral	New Combination	Type 2 Diabetes Mellitus (T2DM)	2015-Oct to 2015-Dec
KEYTRUDA (pembrolizumab) Merck	Antineoplastics & Adjunctive Therapies	Intravenous	New Indication	Advanced Non-Small Cell Lung Cancer (NSCLC) in Patients Whose Disease has Progressed on or after Platinum Chemotherapy and an FDA-Approved Therapy for Epidermal Growth Factor Receptor (EGFR) Mutation or Anaplastic Lymphoma Kinase (ALK) Genomic Tumor Aberrations, if Present[AA, BT, PR]	2015-Oct 2
LETAIRIS (ambrisentan) Gilead Sciences	Cardiovascular Agents	Oral	New Indication	First-Line Combination Therapy with Tadalafil in Patients with Pulmonary Arterial Hypertension (PAH)[OD]	2015-Oct 5
XTAMPZA ER (oxycodone ER) Collegium	Analgesics & Anesthetics	Oral	New Formulation	Extended-Release, Abuse-Deterrent Formulation for Treatment of Moderate to Severe Chronic Pain[FT]	2015-Oct 12
DYNAVEL XR (amphetamine extended-release) Tris	ADHD / Antinarcolepsy / Antiobesity / Anorexic Agents	Oral	New Formulation	Extended-Release Oral Suspension Formulation for Once Daily Administration for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)	2015-Mid Oct
(patiromer calcium) Relypsa	Gastrointestinal Agents	Oral	New Molecular Entity	Treatment of Hyperkalemia in Chronic Kidney Disease (CKD) Patients	2015-Oct 21
EVOMELA (melphalan hydrochloride (intravenous/Captisol)) Ligand; Spectrum	Antineoplastics & Adjunctive Therapies	Intravenous	New Formulation	A Propylene Glycol-Free, One-Vial Formulation for Use as a High-Dose Conditioning Treatment Prior to Hematopoietic Progenitor (Stem) Cell Transplantation in Patients with Multiple Myeloma; Palliative Treatment of Patients with Multiple Myeloma for whom Oral Therapy is not Appropriate[OD]	2015-Oct 23
(irinotecan, nano-liposomal) Merrimack; Baxalta	Antineoplastics & Adjunctive Therapies	Intravenous	New Formulation	An Encapsulated Nanoliposomal Formulation for the Treatment of Patients with Metastatic Adenocarcinoma of the Pancreas who have been Previously Treated with Gemcitabine-Based Therapy[FT, OD, PR]	2015-Oct 23
BELBUCA (buprenorphine (buccal, BEMA)) BioDelivery Sciences; Endo	Analgesics & Anesthetics	Oral	New Formulation	BioErodible MucoAdhesive (BEMA) Transmucosal Formulation for Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment and for which Alternative Treatment Options are Inadequate	2015-Oct 23
(lifitegrast) Shire	Ophthalmic Agents	Intraocular	New Molecular Entity	Treatment for the Signs and Symptoms of Dry Eye Disease in Adults[PR]	2015-Oct 25
COAGADEX (human coagulation factor X) Bio Products Laboratory	Hematological Agents	Intravenous	Biologic	Hereditary Factor X Deficiency[OD]	2015-Oct 27
ONCOVEX (talimogene laherparepvec) Biovex; Amgen	Antineoplastics & Adjunctive Therapies	Intratumoral	New Molecular Entity	Treatment of Patients with Regionally or Distantly Metastatic Melanoma	2015-Oct 27
YERVOY (ipilimumab) Bristol Myers Squibb; Medarex	Antineoplastics & Adjunctive Therapies	Intravenous	New Indication	Adjuvant Treatment of Patients with Stage 3 Melanoma Who are at High Risk of Recurrence Following Complete Surgical Resection[FT, OD]	2015-Oct 28
STRENSIQ (asfotase alfa) Alexion	Endocrine & Metabolic Drugs	Subcutaneous	New Molecular Entity	Infantile- and Juvenile-Onset Hypophosphatasia (HPP)[BT, FT, OD]	2015-Q4

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
REMSIMA; INFLECTRA (infliximab biosimilar) Celltrion; Hospira	Analgesics & Anesthetics	Intravenous	Biosimilar	Rheumatoid Arthritis (RA); Crohn's Disease (CD); Ulcerative Colitis (UC); Ankylosing Spondylitis (AS); Psoriasis; Psoriatic Arthritis (PsA) (seeking all REMICADE indications)	2015-Q4
RIZAPORT (rizatriptan) RedHill; IntelGenx	Analgesics & Anesthetics	Sublingual	New Formulation	Oral Thin-Film Formulation for Treatment of Acute Migraines	2015-Q4
NOCDURNA (desmopressin acetate) Ferring	Genitourinary Products	Sublingual	New Formulation; New Indication	Treatment of Nocturia Due to Nocturnal Polyuria in Adults Who Awaken Two or More Times Each Night to Void	2015-Q4
BIOTHRAX (anthrax vaccine adsorbed) Emergent BioSolutions	Vaccines	Intramuscular	New Indication	To be Used in Combination with Antibiotics for Post-Exposure Prophylaxis (PEP) of Anthrax Disease in People with Suspected or Confirmed Exposure to Anthrax Spores[OD]	2015-Q4
AVRIDI (oxycodone hydrochloride immediate-release) Purdue	Analgesics & Anesthetics	Oral	New Formulation	Immediate-Release, Abuse-Deterrent Formulation for the Management of Acute and Chronic Moderate to Severe Pain where the Use of an Opioid Analgesic is Appropriate	2015-Q4
REXTORO (testosterone undecanoate) Clarus Therapeutics	Endocrine & Metabolic Drugs	Oral	New Formulation	Testosterone Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone: Primary Hypogonadism (Congenital or Acquired) and Hypogonadotropic Hypogonadism (Congenital or Acquired)	2015-Q4
YONDELIS (trabectedin) Janssen	Antineoplastics & Adjunctive Therapies	Intravenous	New Molecular Entity	Treatment of Patients with Advanced Soft Tissue Sarcoma (STS), including Liposarcoma and Leiomyosarcoma Subtypes, who have Received Prior Chemotherapy Including an Anthracycline[OD, PR]	2015-Q4
FERAHEME (ferumoxytol) AMAG	Hematological Agents	Intravenous	New Indication	Treatment of Iron Deficiency Anemia (IDA) in Adult Patients who have Failed or Could not Tolerate Oral Iron Treatment	2015-Q4
ONGLYZA (saxagliptin) AstraZeneca; Bristol Myers Squibb	Endocrine & Metabolic Drugs	Oral	Label Expansion	Label Expansion (Cardiovascular Outcomes) Based on SAVOR-TIMI 53 Study	2015-Q4
PREVNAR 13 (pneumococcal polysaccharide conjugate vaccine [13-valent, adsorbed]) Pfizer	Vaccines	Intramuscular	New Indication	Use of PREVNAR 13 to include Adults 18 to 49 Years of Age for the Prevention of Invasive Disease Caused by 13 *S. pneumoniae* Strains	2015-Q4
(naloxone) AntiOp; Indivior	Antidotes	Nasal	New Formulation	Prefilled Nasal Spray Device for the Treatment of Opioid Overdose	2015-Q4
ANTHIM (obiltoxaximab) Elusys Therapeutics	Antiinfective Agents	Intravenous; Intramuscular	New Molecular Entity	Prophylaxis and Treatment of Inhalational Anthrax[FT, OD]	2015-Q4 to 2016-Mar 20

AA=Accelerated Approval Pathway; BT=Breakthrough Therapy; FT=Fast-Track; PR=Priority Review; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

upcoming patent expirations/generic and biosimilar launches

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Availability	Anticipated Launch Type	Comments
ADVICOR (niacin/lovastatin) AbbVie	Hyperlipidemia	$42 million	H2 2015	Exclusive	Per a settlement agreement, Teva may launch generic ADVICOR any time after September 20, 2013. It is unknown when or if Teva will launch its generic. Other generics are not expected to launch until March 2018.
ANDRODERM (testosterone) Allergan	Replacement Therapy in Males with Deficiency of Endogenous Testosterone	$84 million	H2 2015	Unknown	None
ASACOL (mesalamine) Allergan	Ulcerative Colitis	$577 million	H2 2015	Exclusive with Authorized Generic	Generic availability applies to ASACOL 400 mg tablets. Brand name ASACOL 400 mg tablet has been discontinued; Allergan has released DELZICOL 400 mg that contains the same amount of mesalamine in a delayed-release capsule. Zydus will have an opportunity to launch generic ASACOL HD 800 mg in November 2015.
CIPRO HC (ciprofloxacin hydrochloride / hydrocortisone) Alcon	Acute Otitis Externa	$39 million	H2 2015	Unknown	None
EMEND (aprepitant) Merck	Chemo-Associated Nausea & Vomiting; Prevention of Post-Op Nausea & Vomiting	$280 million	H2 2015	Exclusive	Generic availability applies to the oral formulation only. Sandoz received FDA approval for generic EMEND capsules on September 24, 2012. Patents will likely protect EMEND injection from generic competition until March 4, 2019 pending patent litigation.
EPIPEN (epinephrine) Mylan	Anaphylactic Reactions	$856 million	H2 2015	Exclusive	There are several auto-injectable epinephrine products on the market; however, they are not A-rated to EPIPEN. They cannot be substituted for EPIPEN. Per a settlement agreement, Teva may launch its generic EPIPEn as of June 22, 2015, subject to FDA approval.
EPOGEN (epoetin alfa) Amgen	Anemia Associated with Cancer, Kidney Disease, and Zidovudine Treatment in Patients with Human Immunodeficiency Virus; Decrease Allogeneic Transfusions in Certain Surgeries	$2.4 billion	H2 2015	Biosimilar	In December 2014, Hospira announced its biosimilar submission for RETACRIT; reference products are EPOGEN and PROCRIT.
FACTIVE (gemifloxacin mesylate) Merus Labs; Vansen	Chronic Bronchitis; Community-Acquired Pneumonia	$6.3 million	H2 2015	Exclusive	Orchid received FDA approval of generic FACTIVE on June 15, 2015.
FUZEON (enfuvirtide) Roche/Genentech	Human Immunodeficiency Virus (HIV) Infection	$15 million	H2 2015	Unknown	None
NASONEX (mometasone furoate) Schering/Merck	Seasonal & Perennial Allergic Rhinitis; Nasal Polyps	$1.2 billion	H2 2015	Exclusive	An “at risk” launch is possible at any time if the FDA grants effective approval to Apotex’s generic NASONEX product.
OXYTROL (oxybutynin transdermal patch) Allergan	Overactive Bladder	$15 million	H2 2015	Exclusive	Teva received FDA approval of generic OXYTROL on March 4, 2014. Allergan reached a settlement agreement with Teva permitting launch of generic OXYTROL on April 26, 2015. An OTC product, OXYTROL for WOMEN, became available in September 2013 for the treatment of overactive bladder in women.

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Availability	Anticipated Launch Type	Comments
PREMPHASE (conjugated estrogens / medroxyprogesterone acetate) Pfizer	Hormone Replacement Therapy	$6 million	H2 2015	Unknown	None
PREMPRO (conjugated estrogens / medroxyprogesterone acetate) Pfizer	Hormone Replacement Therapy	$221 million	H2 2015	Unknown	None
PROCRIT (epoetin alfa) Janssen	Anemia Associated with Cancer, Kidney Disease, and Zidovudine Treatment in Patients with Human Immunodeficiency Virus; Decrease Allogeneic Transfusions in Certain Surgeries	$1 billion	H2 2015	Biosimilar	In December 2014, Hospira announced its biosimilar submission for RETACRIT; reference products are EPOGEN and PROCRIT.
PROVENTIL HFA (albuterol sufate) Schering/Merck	Asthma; Exercised-Induced Bronchospasm	$155 million	H2 2015	Exclusive	None
RENAGEL (sevelamer hydrochloride) Genzyme/Sanofi	Hyperphosphatemia Associated with Chronic Kidney Disease	$199 million	H2 2015	Unknown	Under a settlement agreement, Endo has permission to launch its generic RENAGEL as of March 16, 2014. Impax, Lupin, Sandoz, and InvaGen have permission to launch their generic RENAGEL on September 16, 2014.
TRAVATAN Z (travoprost) Alcon	Glaucoma; Ocular Hypertension	$447 million	H2 2015	Exclusive	Alcon reached settlement agreements with Par, Actavis, and Wockhardt; terms have not been disclosed.
VIRACEPT (nelfinavir mesylate) ViiV Healthcare	Human Immunodeficiency Virus Infection	$51 million	H2 2015	Unknown	None
WELCHOL (colesevelam hydrochloride) Daiichi Sankyo	Primary Hyperlipidemia; Type 2 Diabetes Mellitus	$574 million	H2 2015	Exclusive	Generic availability applies to oral tablets and granules for suspension. Oral tablets may launch as exclusive. Settlement agreement allows launch of generic WELCHOL beginning on March 2, 2015.
AVODART (dutasteride) GlaxoSmithKline	Benign Prostatic Hypertrophy	$580 million	October 2015	Competitive	Barr and Banner received FDA approval for generic AVODART on December 21, 2010 and May 30, 2013, respectively.
FROVA (frovatriptan succinate) Endo Pharmaceuticals	Migraine Headache	$68 million	October 2015	Competitive	Mylan received FDA approval for generic FROVA on August 28, 2014. Per a settlement agreement, Mylan may launch its generic FROVA on October 10, 2015.
JALYN (dutasteride/tamsulosin hydrochloride) GlaxoSmithKline	Benign Prostatic Hypertrophy	$41 million	October 2015	Exclusive	Anchen/Par received FDA approval of generic JALYN on February 26, 2014.
NEULASTA (pegfilgrastim) Amgen	Prophylaxis of Neutropenia in Cancer Patients	$3.7 billion	October 2015	Biosimilar	Apotex's biosimilar biologics license application (BLA) for pegfilgrastim (reference product, NEULASTA) was accepted by the FDA on December 17, 2014.

recent FDA product filings/acceptances

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
EMPLICITI (elotuzumab) AbbVie; Bristol Myers Squibb	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Multiple Myeloma as Combination Therapy in Patients Who Have Received One or More Prior Therapies[BT, OD]	2016-Feb 18 to 2016-Mar 17 (priority review)
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Previously Treated Patients with Non-Squamous (NSQ) Non-Small Cell Lung Cancer (NSCLC)[BT]	2016-Jan 2 (priority review)
ZETIA (ezetimibe) Merck	New Indication	Cardiovascular Agents	Oral	Reduction of Cardiovascular Events (based on the IMPROVE-IT trial)	2016-Feb (standard review)
VYTORIN (ezetimibe / simvastatin) Merck	New Indication	Cardiovascular Agents	Oral	Reduction of Cardiovascular Events (based on the IMPROVE-IT trial)	2016-Feb (standard review)
NUPLAZID (pimavanserin) Acadia	New Molecular Entity	CNS Drugs	Oral	Parkinson's Disease (PD) Psychosis[BT]	2016-May 3 (if priority review request granted) or 2016-Sep 3 (if standard review)
(osimertinib); AZD-9291 AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Metastatic Epidermal Growth Factor Receptor (EGFR) T790M Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) where the Disease Progresses During Treatment with an FDA-Approved EGFR Tyrosine Kinase Inhibitor (TKI)	2016-Feb 19 to 2016-Mar 21 (priority review)
RELISTOR (methylnaltrexone bromide) Valeant; Progenics	New Formulation	Gastrointestinal Agents	Oral	Oral Tablet Formulation for the Treatment of Opioid-Induced Constipation (OIC) in Adult Patients with Chronic Non-Cancer Pain	2016-Apr 19 (standard review)
(alectinib) Genentech/Roche	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Treatment of People with ALK-Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) who have Progressed on or are Intolerant to XALKORI (crizotinib)[BT, OD]	2016-Mar 4 (priority review)
(ixazomib citrate) Takeda	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Relapsed and/or Refractory Multiple Myeloma[OD]	2016-Mar 14 (priority review)
ABILIFY (aripiprazole) Otsuka; Proteus	Drug/Device Combination	CNS Drugs	Oral	Tablet Imbedded with an Ingestible Sensor to Measure Actual Medication-Taking Patterns and Physiologic Response (which is Communicated to the Patient - and with the consent of the Patient - to the Patient's Physician and/or Caregiver) for the Treatment of Schizophrenia, Bipolar Disorder, and Adjunctive Therapy of Major Depressive Disorder (MDD)	2016-Apr 25 to 2016-May 25 (standard review)
PROAIR RESPICLICK (albuterol sulfate) Teva	New Indication	Respiratory Agents	Inhalation	Treatment or Prevention of Bronchospasm in Patients 4 to 11 Years of Age with Reversible Obstructive Airway Disease and for the Prevention of Exercise-Induced Bronchospasm (EIB)	2016-Apr (standard review)
XURIDEN (uridine triacetate) BTG; Wellstat	New Indication	Antidotes	Oral	Treatment for Patients at Risk of Serious Toxicity Following an Overdose of the Chemotherapy Agent 5-Fluorouracil (5-FU) and Patients Exhibiting Symptoms of Serious Toxicity within 96 Hours of 5-FU Administration[OD]	2016-Mar (priority review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
AGGRASTAT (tirofiban hydrochloride) Medicure	New Indication	Hematological Agents	Intravenous	Treatment of Patients Presenting with ST Segment Elevation Myocardial Infarction (STEMI)	2016-Jul (standard review)
VIBATIV (telavancin) Theravance	Label Expansion	Antiinfective Agents	Intravenous	Label Expansion Supporting Use Against Concurrent Bacteremia in Cases of Complicated Skin and Skin Structure Infections (cSSSI) or Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP)	2016-Q2 (standard review)
REPATHA (evolocumab) Amgen	New Strength	Cardiovascular Agents	Subcutaneous	Seeking Approval of a Single-Dosing Option for the Monthly Administration Allowing the 420 mg Monthly Dose to be Administered as a Single Injection as an Adjunct to Diet and Maximally Tolerated Statins in Patients with Heterozygous Familial Hypercholesterolemia (HeFH) or Clinical Atherosclerotic Cardiovascular Disease (ASCVD), who Require Additional Lowering of LDL-C; and as an Adjunct to Diet and Other LDL-Lowering Therapies for Patients with Homozygous Familial Hypercholesterolemia (HoFH), who Require Additional Lowering of LDL-C	2016-Jul 11 (standard review)
ORFADIN (nitisinone) Swedish Orphan Biovitrum [Sobi]	New Formulation	Endocrine & Metabolic Drugs	Oral	Oral Suspension Formulation for the Treatment of Hereditary Tyrosinemia Type 1 (HT-1)	2016-Q2 (standard review)
FYCOMPA (perampanel) Eisai	New Formulation	Neuromuscular Drugs	Oral	A 0.5 mg/mL Oral Suspension Formulation for Adjunctive Therapy in the Treatment of Partial-Onset Seizures (POS) with or without Secondarily Generalized Seizures and Primary Generalized Tonic-Clonic (PGTC) Seizures in Patients with Epilepsy 12 Years of Age and Older	2016-Apr 30 (standard review)
IMBRUVICA (ibrutinib) Pharmacyclics/AbbVie; Janssen Biotech	Label Expansion	Antineoplastics & Adjunctive Therapies	Oral	Treatment-Naive Chronic Lymphocytic Leukemia (CLL) Patients Aged 65 Years or Older (based on the phase 3 RESONATE-2 trial)[OD]	2016-Jul 14 (if standard review)
XEGLYZE (abametapir) Hatchtech; Promius / Dr. Reddy's	New Molecular Entity	Dermatologicals	External	Head Lice	2016-Sep 14 (standard review)
FANAPT (iloperidone) Vanda	New Indication	CNS Drugs	Oral	Maintenance Treatment of Schizophrenia in Adults	2016-May 27 (standard review)
GAMMAGARD (immune globulin) Baxalta	New Formulation	Passive Immunizing Agents	Subcutaneous	20% Formulation for Primary Immunodeficiencies (PI)	2016-Jul 15 (standard review)
ZTLIDO (lidocaine patch 1.8%) Scilex	New Formulation	Analgesics & Anesthetics	Transdermal	Treatment of Postherpetic Neuralgia (PHN)	2016-Jul (standard review)
SOMAKIT-TATE (Gallium (68Ga) edotreotide) Advanced Accelerator Applications	New Formulation	Diagnostic Products	Injection	Diagnose and Manage Somatostatin Receptor-Positive Neuroendocrine Tumor (NET) patients Using Positron Emission Tomography (PET)[OD]	2016-Mar 1 (priority review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
RESPIMUNE (immune globulin); RI-002 ADMA Biologics	New Formulation	Passive Immunizing Agents	Intravenous	Plasma-Derived, Polyclonal Antibody-Containing Intravenous Formulation for Primary Immunodeficiency Disease (PIDD)	2016-Jul 31 (standard review)
SUSTOL (granisetron) Heron Therapeutics	New Formulation	Gastrointestinal Agents	Subcutaneous	Extended-Release Formulation (Therapeutic Drug Levels Maintained for 5 Days with a Single Subcutaneous Injection) for Prevention of Acute- and Delayed-Onset Chemotherapy-Induced Nausea & Vomiting (CINV) in Patients Receiving Moderately Emetogenic Chemotherapy (MEC) Agents or Highly Emetogenic Chemotherapy (HEC)	2016-Jan 17 (standard review)
KYPROLIS (carfilzomib) Onyx/Amgen	Label Expansion	Antineoplastics & Adjunctive Therapies	Intravenous	Label Expansion Based on the ENDEAVOR Study for Use In Combination with Dexamethasone for Treatment of Patients with Relapsed Multiple Myeloma who have Received at Least One Prior Therapy	2016-Jan 22 (priority review)
VESNEO (latanoprostene bunod ophthalmic solution 0.024%) Bausch & Lomb/Valeant; Nicox	New Molecular Entity	Ophthalmic Agents	Intraocular	A Nitric Oxide Donating Prostaglandin Receptor Agonist for the Treatment of Glaucoma and Ocular Hypertension	2016-Jul 21 (standard review)
NARCAN (naloxone) Lightlake Therapeutics; Adapt	New Formulation	Antidotes	Intranasal	Nasal Spray Formulation for Opioid Overdose[FT]	2016-Jan 27 (priority review)
ARZERRA (ofatumumab) Genmab; Novartis	Label Expansion	Antineoplastics & Adjunctive Therapies	Intravenous	Maintenance Treatment of Patients with Relapsed Chronic Lymphocytic Leukemia	2016-Jan 21 (priority review)
HALAVEN (eribulin mesylate) Eisai	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Patients with Inoperable Soft Tissue Sarcoma (STS) who have Received Prior Chemotherapy for Advanced or Metastatic Disease[OD]	2016-Jan 30 (priority review)
DEXTENZA (dexamethasone sustained-release) Ocular Therapeutix	New Formulation	Ophthalmic Agents	Intracanalicular	Treatment of Ocular Pain Following Ophthalmic Surgery	2016-Jul 28 (standard review)
ONTINUA ER (arbaclofen) Osmotica	New Formulation; New Indication	Misc. Psychotherapeutic & Neurological Agents	Oral	Alleviation of Spasticity Associated with Multiple Sclerosis (MS)	2016-Jul 28 (standard review)
LYXUMIA (lixisenatide) Sanofi; Zealand	New Molecular Entity	Endocrine & Metabolic Drugs	Subcutaneous	Type 2 Diabetes Mellitus (T2DM)	2016-Jul (standard review)
(rociletinib) Clovis; Celgene	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Treatment of Patients with Mutant Epidermal Growth Factor Receptor (EGFR) Non-Small Cell Lung Cancer (NSCLC) Who Have Been Previously Treated with an EGFR-Targeted Therapy and Have the EGFR T790M Mutation as Detected by an FDA Approved Test[BT, OD]	2016-Mar 30 (priority review)
DEFITELIO (defibrotide) Jazz	New Molecular Entity	Hematological Agents	Intravenous	Treatment of Patients with Hepatic Veno-Occlusive Disease (VOD), Also Known as Sinusoidal Obstruction Syndrome (SOS), with Evidence of Multi-Organ Dysfunction (MOD) Following Hematopoietic Stem-Cell Transplantation (HSCT)[FT, OD]	2016-Mar 31 (priority review)

BT=Breakthrough Therapy; FT=Fast-Track; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

products receiving FDA complete response letters (CRL) or refuse-to-file (RTF) letters

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Comments
None Noted					

FDA/CDC advisory committee (AdCom) meeting announcements / outcomes

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
AVRIDI (oxycodone hydrochloride immediate-release) Purdue	Analgesics & Anesthetics	Oral	Immediate-Release, Abuse-Deterrent Formulation for the Management of Acute and Chronic Moderate to Severe Pain where the Use of an Opioid Analgesic is Appropriate	09/10/2015	Biospace reported that the FDA's Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 23 to 1 against the approval of AVRIDI. The drug is to be taken every 4 to 6 hours on an empty stomach. Any food would decrease the drug's effects, which, the panel indicated, would cause patients to take more of the drug, leading to potentially dangerous dosages.
XTAMPZA ER (oxycodone extended-release) Collegium	Analgesics & Anesthetics	Oral	Extended-Release, Abuse-Deterrent Formulation for the Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment and for which Alternative Treatment Options are Inadequate	09/11/2015	The FDA's Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Committee voted 23 to 0 to recommend approval of Collegium's NDA for XTAMPZA ER.
FLUAD (Agrippal S1 + MF-59 influenza vaccine) NVS Influenza Vaccines; CSL Limited	Vaccines	Intramuscular	Active Immunization of Adults Aged 65 and Older Against Influenza Disease Caused by Influenza Virus Subtypes A and B Contained in the Vaccine	09/15/2015	The FDA's Vaccines and Related Biological Products Advisory Committee voted to recommend licensure of a candidate vaccine to help protect against seasonal influenza in those aged 65 years and older via accelerated approval. It contains the World Health Organization (WHO) recommended antigens and the Novartis proprietary adjuvant MF59® designed to help elicit an immune response to vaccine antigens.
Fluoroquinolones Various	Antiinfective Agents	Various	Treatment of Acute Bacterial Sinusitis, Acute Bacterial Exacerbation of Chronic Bronchitis in Patients who have Chronic Obstructive Pulmonary Disease, and Uncomplicated Urinary Tract Infections	11/05/2015	The FDA's Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee) and the Drug Safety and Risk Management Advisory Committee will discuss the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions.
BRIDION (sugammadex sodium injection) Merck	Neuromuscular Drugs	Intravenous	Reversal of Moderate or Deep Neuromuscular Blockade Induced by Rocuronium or Vecuronium	11/06/2015	The FDA's Anesthetic and Analgesic Drug Products Advisory Committee will discuss new drug application 022225, sugammadex sodium injection, submitted by Organon USA

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
					Inc., a subsidiary of Merck & Co., Inc., for the proposed indication of reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium.
Various (influenza vaccine) Various	Vaccines	Intradermal; Inhalation	Prevention of Influenza	11/13/2015	The FDA's Vaccines and Related Biological Products Advisory Committee will meet in open session to discuss considerations for evaluation of the safety and effectiveness of vaccines administered to pregnant women to protect the infant.
(Mycobacterium phlei cell wall nucleic acid complex); MCNA Telesta Therapeutics	Antineoplastics & Adjunctive Therapies	Intravesical	Treatment of Non-Muscle Invasive Bladder Cancer at High Risk of Recurrence or Progression in Adult Patients who Failed Prior Bacillus Calmette-Guérin (BCG) Immunotherapy, e.g., in Patients who are BCG-Refractory or BCG-Relapsing	11/18/2015	The FDA's Cellular, Tissue, and Gene Therapies Advisory Committee and the Oncologic Drugs Advisory Committee will meet to discuss the safety and efficacy of Biologics License Application 125593, Mycobacterium phlei Cell wall-Nucleic Acid complex (MCNA), submitted by Telesta Therapeutics, Inc.
(gepirone hydrochloride extended-release) Fabre-Kramer	CNS Drugs	Oral	Major Depressive Disorder (MDD)	12/01/2015	The FDA's Psychopharmacologic Drugs Advisory Committee will discuss the efficacy and safety data for new drug application 21164, gepirone hydrochloride extended-release tablets, submitted by Fabre-Kramer Pharmaceuticals, Inc., for the proposed indication of major depressive disorder.
CINQUIL (reslizumab) Teva	Respiratory Agents	Intravenous	Reduce Exacerbations, Relieve Symptoms, and Improve Lung Function in Adults and Adolescents 12 Years of Age and Above, with Asthma and Elevated Blood Eosinophils, who are Inadequately Controlled on Inhaled Corticosteroids	12/09/2015	The FDA's Pulmonary-Allergy Drugs Advisory Committee will discuss biologics license application 761033, reslizumab for injection, submitted by Teva Pharmaceutical Industries, Ltd., for the proposed indication to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents 12 years of age and above, with asthma and elevated blood eosinophils, who are inadequately controlled on inhaled corticosteroids.
VYTORIN (ezetimibe / simvastatin) Merck	Cardiovascular Agents	Oral	Reduction of Cardiovascular Events (based on the IMPROVE-IT trial)	12/14/2015	The FDA has set a tentative meeting for the Endocrinologic and Metabolic Drugs Advisory Committee for the review of the VYTORIN label expansion for December 14, 2015.
ZETIA (ezetimibe) Merck	Cardiovascular Agents	Oral	Reduction of Cardiovascular Events (based on the IMPROVE-IT trial)	12/14/2015	The FDA has set a tentative meeting for the Endocrinologic and Metabolic Drugs Advisory Committee for the review of the ZETIA label expansion for December 14, 2015.

products receiving special FDA review designations or statuses

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(udenafil) Mezzion	New Formulation; New Indication	Cardiovascular Agents	Phase 2	Oral	Orphan Drug	Treatment of Single Ventricle Congenital Heart Disease with Fontan Physiology

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
((S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate); LOXO-101 Loxo Oncology	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Treatment of Soft Tissue Sarcoma
(N-acetylcysteine and sodium thiosulfate) Edward A. Neuwelt, MD	New Formulation; New Indication	Antidotes	Unknown	Unknown	Orphan Drug	Prevention of Platinum-Induced Toxicities in Pediatric Patients (0 Through 16 Years of Age)
(modified a-cobratoxin); RPI-78M Nutra Pharma	New Molecular Entity	Misc. Psychotherapeutic & Neurological Agents	Phase 2	Injection	Orphan Drug	Treatment of Pediatric Multiple Sclerosis (0 Through 16 Years of Age)
(triamcinolone acetonide); FX-006 Flexion Therapeutics	New Formulation	Analgesics & Anesthetics	Phase 3	Intraarticular	Fast Track	Osteoarthritis (OA) of the Knee
TP-271 Tetraphase	New Molecular Entity	Antiinfective Agents	Discovery	Intravenous	Fast Track; Qualified Infectious Disease Product (QIDP)	Treatment of Community-Acquired Bacterial Pneumonia
ACE-910 Genentech/Roche	New Molecular Entity	Hematological Agents	Phase 1	Subcutaneous	Breakthrough Therapy	Prophylactic Treatment of People who are 12 years or older with Hemophilia A with Factor VIII inhibitors
MERSAREX (icalprim) Motif Bio	New Molecular Entity	Antiinfective Agents	Phase 3	Intravenous	Fast Track	Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Hospital Acquired Bacterial Pneumonia (HABP)
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Pending Approval	Intravenous	Breakthrough Therapy	Treatment of Previously Treated Patients with Non-Squamous (NSQ) Non-Small Cell Lung Cancer (NSCLC)
(daratumumab) Janssen	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Pending Approval	Intravenous	Priority Review	Treatment for Patients with Multiple Myeloma Who Have Received at Least Three Prior Lines of Therapy Including Both a Proteasome Inhibitor (PI) and an Immunomodulatory Agent (IMiD) or Who are Double Refractory to a PI and an IMiD
TRANSLARNA (ataluren) PTC Therapeutics	New Molecular Entity	Neuromuscular Drugs	Phase 2	Oral	Orphan Drug	Treatment of Aniridia
(purified autologous type 1 regulatory T lymphocytes specific for human type II collagen); Col-Treg TxCell SA	New Molecular Entity	Ophthalmic Agents	Discovery	Intravenous	Orphan Drug	Treatment of Chronic Non-Infectious Uveitis
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Treatment of Hepatocellular Carcinoma

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
CHRONOCORT (hydrocortisone modified release capsules) Diurnal Ltd	New Formulation; New Indication	Endocrine & Metabolic Drugs	Discovery	Oral	Orphan Drug	Treatment of Adrenal Insufficiency
DTX-101 Dimension Therapeutics	New Formulation	Hematological Agents	Discovery	Injection	Orphan Drug; Fast Track	Treatment of Hemophilia B
BC-819 BioCancell	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Intravesical	Fast Track	Treatment of Non-Muscle-Invasive Bladder Cancer (NMIBC): for Patients who have Failed Treatment with BCG and for Patients who are Unresponsive or Intolerant to BCG Treatment
(tipelukast); MN-101 MediciNova	New Molecular Entity	Respiratory Agents	Phase 2	Oral	Fast Track	Treatment of Patients with Idiopathic Pulmonary Fibrosis (IPF)
(tremelimumab) AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 3	Intravenous	Fast Track	Malignant Mesothelioma
CAT-1004 Catabasis	New Molecular Entity	Neuromuscular Drugs	Phase 2	Oral	Rare Pediatric Disease	Treatment of Duchenne Muscular Dystrophy (DMD)
(pentetrazol) Balance Therapeutics	New Molecular Entity	CNS Drugs	Discovery	Oral	Orphan Drug	Treatment of Idiopathic Hypersomnia
SALVECIN; AR-301 Aridis	New Molecular Entity	Antiinfective Agents	Phase 2	Intravenous	Fast Track	Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia (HAP and VAP) caused by *Staphylococcus aureus*, Including Multi-Drug Resistant MRSA Strains
(2-(2-chlorobenzylidene) hydrazinecarboximidamide acetate) InFlectis BioScience	New Molecular Entity	Neuromuscular Drugs	Uknown	Unknown	Orphan Drug	Treatment of Charcot-Marie Tooth Disease
(everolimus ointment) Aucta	New Indication	Dermatologicals	Unknown	External	Orphan Drug	Topical Treatment of Tuberous Sclerosis Complex-Related Skin Lesions
(mesencephalic, astrocyte-derived neurotrophic factor); MANF Amarantus BioScience Holdings	New Molecular Entity	Ophthalmic Agents	Discovery	Intraocular	Orphan Drug	Treatment of Retinal Artery Occlusion
(immunoglobulin G degrading enzyme of Streptococcus pyogenes); IdeS Hansa Medical AB	New Molecular Entity	Assorted Classes	Phase 2	Intravenous	Orphan Drug	Prevention of Antibody Mediated Organ Rejection in Solid Organ Transplant Patients
(nimotuzumab) InnoCIMab	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Discovery	Intravenous	Orphan Drug	Treatment of Pancreatic Cancer
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Phase 3	Intravenous	Breakthrough Therapy	Advanced or Metastatic Renal Cell Carcinoma (RCC)
VT-1129 Viamet	New Molecular Entity	Antiinfective Agents	Discovery	Oral	Qualified Infectious Disease Product (QIDP)	Treatment of Cryptococcal Meningitis

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(N-((3S, 4S)-3-((6-(2,6-dichloro-3,5-dimethoxyphenyl)quinazolin-2-yl)amino)tetrahydro-2H-pyran-4-yl) acrylamide); BLU-554 Blueprint Medicines	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Treatment of Hepatocellular Cancer (HCC)
(masitinib mesylate) AB Science	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 3	Oral	Orphan Drug	Treatment of Gastric Cancer Including Cancer of the Gastroesophageal Junction
CF-102 Can-Fite BioPharma	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Fast Track	Second Line Treatment for Hepatocellular Carcinoma (HCC)
U-CORD-CELL (mononuclear enriched fraction of human umbilical cord blood) Saneron CCEL Therapeutics	Biologic	Neuromuscular Drugs	Discovery	Injection	Orphan Drug	Treatment of Amyotrophic Lateral Sclerosis (ALS)
KINERET (anakinra) Swedish Orphan Biovitrum AB	New Indication	Analgesics & Anesthetics	Discovery	Subcutaneous	Orphan Drug	Treatment of Still's Disease Including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease
OPDIVO (nivolumab) Bristol Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Treatment of Small Cell Lung Cancer
TAKSTA (sodium fusidate) Cempra	New Molecular Entity	Antiinfective Agents	Phase 2	Oral	Qualified Infectious Disease Product (QIDP)	Acute Bacterial Skin and Skin Structure Infections (ABSSSI)
ZMAPP (monoclonal antibody consisting of three mouse/human chimeric IgG1 monoclonal antibodies (c2G4, c4G7, and c13C6)) Mapp	Biologic	Antiinfective Agents	Phase 2	Intravenous	Fast Track	Ebola Virus Disease
(medtadoxine extended-Release) Alcobra	New Molecular Entity	CNS Drugs	Phase 2	Oral	Fast Track	Treatment of Fragile X Syndrome
(3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (2R,3R)-2,3-dihydroxybutanedioate; ABT-494 AbbVie	New Molecular Entity	Analgesics & Anesthetics	Phase 2	Oral	Orphan Drug	Treatment of Pediatric (0 Through 16 Years of Age) Juvenile Idiopathic Arthritis (JIA) Categories Excluding Systemic JIA
(marizomib) Triphase	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Intravenous	Orphan Drug	Treatment of Malignant Glioma
(mecasermin, recombinant human insulin-like growth factor-1) Keck Graduate Institute of Applied Life Sciences	New Formulation	Endocrine & Metabolic Drugs	Unknown	Unknown	Orphan Drug	Treatment of Rett Syndrome

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(adeno-associated viral (AAV) vector composed of a bioengineered AAV capsid (AAV-Spark100) and a codon-optimized expression cassette (hFIX39-Padua) encoding a high-specific activity variant of human coagulation factor IX); SPK-FIX Spark Therapeutics	New Formulation	Hematological Agents	Phase 2	Intravenous	Orphan Drug	Treatment of Hemophilia B
(recombinant human monoclonal IgG1 antibody against programmed death ligand-1 (anti-PD-L1); avelumab Merck; Pfizer	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Treatment of Merkel Cell Carcinoma
((S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)-imidazo[1,5-a]pyrazine-1-yl)-N-(pyridine-2-yl)-benzamide); ACP-196 Acerta Pharma BV	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Orphan Drug	Treatment of Mantle Cell Lymphoma
OPREGEN (retinal pigment epithelial cells) BioTime; Cell Cure Neurosciences	Biologic	Ophthalmic Agents	Phase 2	Implant	Fast Track	Dry-Form of Age-Related Macular Degeneration (AMD)
(4-Hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl); Recursion-001 Recursion	New Molecular Entity	Miscellaneous	Discovery	Unknown	Orphan Drug	Treatment of Cerebral Cavernous Malformation
(glyburide); RP-1127 Remedy	New Formulation; New Indication	Neuromuscular Drugs	Phase 2	Intravenous	Orphan Drug	Treatment of Acute Spinal Cord Injury
(guadecitabine) Astex	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 3	Subcutaneous	Orphan Drug	Treatment of Acute Myeloid Leukemia
(aden-associated virus vector serotype 9 expressing human a-L-iduronidase); RGX-121 Regenxbio	Biologic	Endocrine & Metabolic Drugs	Discovery	Injection	Orphan Drug	Treatment of Mucopolysaccharidosis Type I (MSP I)

patent litigations/generic filings

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
PROLENSA (bromfenac) Bausch & Lomb	Watson	Ophthalmic Agents	Intraocular	Treatment of Postoperative Inflammation and Reduction of Ocular Pain in Patients who have Undergone Cataract Surgery	8,129,431; 8,669,290; 8,754,131; 8,871,813; 8,927,606	Patent infringement lawsuit following a Paragraph IV certification as part of Watson's filing of an ANDA to manufacture a generic version of B&L's PROLENSA.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
LETAIRIS (ambrisentan) Gilead Sciences	Sigmapharm	Cardiovascular Agents	Oral	Treatment of Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to Improve Exercise Ability and Delay Clinical Worsening	RE42,462	Patent infringement lawsuit following a Paragraph IV certification as part of Sigmapharm's filing of an ANDA to manufacture a generic version of Gilead's LETAIRIS.
ISTODAX (romidepsin) Celgene	Teva	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Cutaneous T-Cell Lymphoma (CTCL) in Patients who have Received at Least One Prior Systemic Therapy; Treatment of Peripheral T-Cell Lymphoma (PTCL) in Patients who have Received at Least One Prior Therapy	7,608,280; 7,611,724	Patent infringement lawsuit following a Paragraph IV certification as part of Teva's filing of an ANDA to manufacture a generic version of Celgene's ISTODAX.
Alimta (pemetrexed) Eli Lilly	Mylan	Antineoplastics & Adjunctive Therapies	Intravenous	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer; Mesothelioma	7,772,209	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Lilly's ALIMTA.
AXIRON (testosterone metered transdermal solution) Eli Lilly	Lupin	Endocrine & Metabolic Drugs	External	Replacement Therapy in Males for Conditions Associated with a Deficiency or Absence of Endogenous Testosterone: Primary Hypogonadism; Hypogonadotropic Hypogonadism	8,435,944; 8,419,307; 8,177,449; 8,807,861; 8,993,520	Patent infringement lawsuit following a Paragraph IV certification as part of Lupin's filing of an ANDA to manufacture a generic version of Eli Lilly's AXIRON.

other/miscellaneous news

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(brigatinib) Ariad	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Anaplastic Lymphoma Kinase Positive (ALK+) Metastatic Non-Small Cell Lung Cancer (NSCLC) In Patients Who are Resistant to XALKORI (Crizotinib)[BT]	Ariad expects to file the NDA for brigatinib in the third quarter of 2016.
AVYCAZ (ceftazidime / avibactam) Allergan; AstraZeneca	Label Expansion	Antiinfective Agents	Intravenous	Treatment for Adult Hospitalized Patients with Complicated Urinary Tract Infections (cUTI), including Pyelonephritis (based on the RECAPTURE 1 & 2 trials)	Allergan plans to submit data from the RECAPTURE 1 and 2 clinical trials as a sNDA to the FDA by the end of 2015.
KANUMA (sebelipase alfa) Alexion	New Molecular Entity	Endocrine & Metabolic Drugs	Intravenous	Lysosomal Acid Lipase (LAL) Deficiency (Wolman Disease)[BT, FT, OD]	Alexion announced that the FDA has extended the PDUFA date for its priority review of the Company's BLA. The previously disclosed September 8, 2015 PDUFA date has been extended by the standard extension period of three months.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(omadacycline) Paratek	New Molecular Entity	Antiinfective Agents	Oral; Intravenous	Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia	Paratek recently initiated dosing in the first of two planned phase 3 registration studies of omadacycline. The first study focuses on the treatment of moderate to severe acute bacterial skin and skin structure infections (ABSSSI). The second study, expected to be initiated before the end of 2015, will focus on moderate to severe community-acquired bacterial pneumonia (CABP). If both studies are successful, the company anticipates submitting a new drug application in the U.S. in the first half of 2018.
(apomorphine); APL-130277 Cynapsus Therapeutics	New Formulation	Neuromuscular Drugs	Sublingual	A Sublingual Thin Filmstrip for Adjunctive Therapy for the On-Demand Management of OFF Episodes (Predictable Wearing OFF, Morning Akinesia (or Morning OFF), Delayed ON (or dose failure), and Unpredictable OFF) in Patients with Parkinson's Disease (PD)	Cynapsus Therapeutics announced enrollment of the first patient in the CTH-301 clinical trial, a pivotal Phase III study to examine the safety and tolerability of APL-130277 for the acute treatment of OFF episodes in patients with Parkinson's disease (PD). The CTH-301 study, together with the CTH-300 efficacy study, will form the basis for the Company's expected NDA submission near the end of 2016.
(betrixaban) Portola	New Molecular Entity	Hematological Agents	Oral	Prevention of Stroke in Atrial Fibrillation Patients; Prevention of Venous Thromboembolic Events after Surgery; Hospital and Post-Discharge Prevention of Venous Thromboembolism (VTE), or Blood Clots, in Acute Medically Ill Patients	Portola expects to file an NDA for the Factor Xa inhibitor betrixaban in the third quarter of 2016.
(brodalumab) AstraZeneca; Valeant	New Molecular Entity	Analgesics & Anesthetics	Subcutaneous	An Interleukin Receptor 17A Antagonist for Moderate to Severe Plaque Psoriasis	AstraZeneca announced that it has entered into a collaboration agreement with Valeant under which it will grant an exclusive license for Valeant to develop and commercialize brodalumab. Regulatory submission in US for brodalumab in moderate-to-severe psoriasis is planned for the fourth quarter of 2015.
(aripiprazole); ZY-102 Zysis	New Formulation	CNS Drugs	Oral	A Controlled-Release Once Weekly Tablet Formulation for the Treatment of Schizo-phrenia and Bipolar Disorder	Zysis anticipates US approval of ZY-102 in 2018. ZY-102 is a long-acting oral tablet formulation of aripiprazole that will be dosed once weekly with monitored/supervised dosing and is intended to reduce relapse rate associated with schizophrenia and bipolar disorder.
GALAFOLD (migalastat) Amicus Therapeutics	New Molecular Entity	Endocrine & Metabolic Drugs	Oral	Fabry Disease[OD]	Amicus announced that a pre-NDA meeting was held with the FDA to discuss migalastat for the treatment of Fabry disease. Based on FDA feedback at the pre-NDA meeting, reduction in disease substrate (kidney interstitial capillary GL-3) will serve as the primary endpoint, supported by the totality of data from completed clinical studies. Amicus remains on track to submit an NDA in the fourth quarter of 2015 under accelerated approval.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(moxidectin) Medicines Development for Global Health	New Molecular Entity	Antiinfective Agents	Oral	Treatment of Onchocerciasis (River Blindness)[OD]	Medicines Development for Global Health plans to submit an NDA filing for moxidectin at the end of 2016.
RHOPRESSA (netarsudil) Aerie	New Molecular Entity	Ophthalmic Agents	Intraocular	A Once-Daily Triple-Action Ophthalmic Solution for the Treatment of Glaucoma and Ocular Hypertension	Aerie expects to file the RHOPRESSA NDA in mid-2016.
(ertugliflozin); (ertugliflozin / sitagliptin); (ertugliflozin / metformin) Merck; Pfizer	New Molecular Entity	Endocrine & Metabolic Drugs	Oral	Type 2 Diabetes Mellitus (T2DM)	Merck expects to submit applications for regulatory approval of the sodium glucose transporter-2 (SGLT2) inhibitor ertugliflozin and its combination products in the US by the end of 2016.
JANUVIA (sitagliptin) Merck	Label Expansion	Endocrine & Metabolic Drugs	Oral	Add Cardiovascular Safety Data to Label (Based on the Trial Evaluating Cardio-vascular Outcomes with Sitagliptin (TECOS))	Merck announced that the results of the TECOS CV safety trial will be submitted to the FDA later this year.
(insulin glargine biosimilar); MK-1293 Merck; Samsung Bioepis	Biosimilar	Endocrine & Metabolic Drugs	Subcutaneous	Type 1 & Type 2 Diabetes Mellitus (T1DM & T2DM)	Merck announced plans to submit MK-1293 for regulatory approval within the next six months.
(sofosbuvir / velpatasvir) Gilead Sciences	New Combination	Antiinfective Agents	Oral	Treatment of Genotype 1-6 Chronic Hepatitis C Virus (HCV) Infection[BT]	Gilead plans to file a NDA for the once-daily fixed-dose combination to the FDA in Q4 2015.
(bezlotoxumab) Merck	New Molecular Entity	Antiinfective Agents	Intravenous	Prevention of Clostridium difficile (C. difficile) Infection Recurrence	Merck plans to submit the BLA to the FDA in 2015.
(pacritinib) CTI BioPharma	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Treatment of Patients with Intermediate and High-Risk Myelofibrosis with Low Platelet Counts of Less than 50,000 per microliter (<50,000/uL)[FT, OD]	CTI plans to submit a NDA to the FDA in the fourth quarter of 2015 and will request accelerated approval. The NDA will be based primarily on data from the PERSIST-1 Phase 3 trial, as well as data from Phase 1 and 2 studies of pacritinib, and additional information requested by the FDA, including a separate study report and datasets for the specific patient population with low platelet counts of less than 50,000 per microliter (<50,000/uL) for whom there are no approved drugs.
MEDIDUR (fluocinolone acetonide) pSivida	New Formulation; New Indication	Ophthalmic Agents	Implant	Posterior Uveitis	pSivida announced that the Company now plans to file a NDA for MEDIDUR for posterior uveitis based on six-month efficacy data for both phase 3 trials. The FDA has advised pSivida that this data will be acceptable for review by the agency. pSivida previously planned to utilize 12-month efficacy data from the first trial and six-month efficacy data from the second trial. As six-month visits in the first trial will be completed this month, top-line results from the first phase 3 trial are now anticipated to be reported in December 2015. Enrollment in the second phase 3 trial continues and is expected to be completed during the first half of 2016, with an NDA anticipated in the first half of 2017.

BT=Breakthrough Therapy; FT=Fast-Track; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

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Prepared by:
Sherry Andes, PharmD, BCPS, BCPP, BCACP, CGP, PAHM
Sr. Manager, Pipeline & Trend Surveillance; Drug Intelligence
Catamaran

Contributor/Reviewer:
Valerie Taylor, PharmD
Clinical Pharmacist, Pipeline & Trend Surveillance; Drug Intelligence
Catamaran