OPTUMRx®

Silver State Scripts Board Meeting

MARCH 25, 2021

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Agenda

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting:	February 16, 2021
Date of Meeting:	Thursday, March 25, 2021 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), Silver State Scripts Board.
Place of Meeting:	**Microsoft Teams** OR https://teams.microsoft.com/l/meetup-join/19%3ameeting_OTI4NjJmYzYtNWNmYS00YmUyLTk1NTUtMTg1ZmRiZTk4YzE2%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%2242971ee7-a94c-4957-b200-48069e3c9add%22%7d Out of deference to Declaration of Emergency Directive 006 from the State of Nevada Executive Department signed by Governor Sisolak on March 22, 2020 & Emergency Directive 003 signed March 20, 2020, a physical location will not be open to the public for attendance at this time. Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email Tanya Benitez at tbenitez@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.*
Meeting Audio Information:	Phone: (952) 222-7450 Event: 106 959 100#

[Please place your phone on mute unless providing public comment.]

Closed Executive Session – 1:00 PM

Open Session/Public Meeting – will begin upon completion of the Closed Executive Session

AGENDA

1. Call to Order and Roll Call

2. Public Comment on Any Matter on the Agenda (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (rxinfo@dhcfp.nv.gov). There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. This guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations.*)

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from January 21, 2021.

b. Status Update by the DHCFP.

c. Presentation and discussion of updated Silver State Scripts Board bylaws.

4. Proposed New Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

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

a. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers - Antidiabetic Agents - Inulin (vials, Pens and Inhaled).

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.

iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/combo and Dopamine Antagonists.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

6. Established Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Genitourinary Agents - Bladder Antispasmodics.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

7. OptumRx Reports: New Drugs to Market and New Line Extensions

8. Closing Discussion

a. Public comments on any subject. (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (rxinfo@dhcfp.nv.gov). There*

may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).)

b. Date and location of the next meeting.

i. Discussion of the time of the next meeting.

c. Adjournment.

PLEASE NOTE: **Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to three minutes and written comments are encouraged if possible.**

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov as well as Carson City, Las Vegas, and Reno central offices for the Division of Health Care Financing and Policy. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). At this time, in deference to Emergency Directive 006 dated March 22, 2020 and related directives which have discouraged certain in-person activities, notice has not been posted at other physical locations.

If you require a physical copy of supporting material for the public meeting, please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). Supporting material will also be posted online as referenced above.

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

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at tbenitez@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 3: The requirements contained in NRS 241.020 (4) (a) that public notice agendas be posted at physical locations within the State of Nevada are suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 4: Public bodies must still comply with requirements in NRS 241.020 (4)(b) and NRS 241.020 (4)(c) that public notice agendas be posted to Nevada's notice website and the public body's website, if it maintains one along with providing a copy to any person who has requested one via U.S. mail or electronic mail.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 5: The requirement contained in NRS 241.020 (3)(c) that physical locations be available for the public to receive supporting material for public meetings is suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

Summary of Silver State Scripts Board

Silver State Scripts Board

By statute (NRS 422.4025), the State of Nevada requires the DHCFP to develop and maintain a Preferred Drug List (PDL) to be used for the Medicaid program and CHIP, and each public or nonprofit health benefit plan that elects to use the PDL. The Silver State Scripts Board (formerly known as the Pharmacy & Therapeutics or P&T Committee) was established to identify prescription drugs to be included on the PDL.

A governing body of a county, school district, municipal corporation, political subdivision, public corporation or other local government agency of the State of Nevada that provides coverage of prescription drugs pursuant to NRS 287.010 or any issuer of a policy health insurance purchased pursuant to NRS 287.010 may use the PDL developed by DHHS as its PDL.

The PDL is not a restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The Silver State Scripts Board consists of members who are Director-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada as either an actively practicing physician or an actively practicing pharmacist.

Meetings are held quarterly and are open to the public. Anyone wishing to address the Silver State Scripts Board may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each Board member and an electronic copy to the DHCFP Coordinator for official record.

For pharmacists and physicians wishing to serve on the Silver State Scripts Board, please email your contact information, NPI and current CV/Resume to rxinfo@dhcfp.nv.gov

Current Board Members:

Mark Decerbo, PharmD (Chairman)

Kate Ward, PharmD (Vice Chairman)

Joseph Adashek, MD

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2021

Date	Time	South Nevada Location	North Nevada Location
March 25, 2021	1:00 PM	Microsoft Teams	None
June 24, 2021	1:00 PM	TBD	None
September 23, 2021	1:00 PM	TBD	None
December 9, 2021	1:00 PM	TBD	None

Web References

Preferred Drug List:

https://www.medicaid.nv.gov/providers/rx/PDL.aspx

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Silver State Scripts Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/PandT_Bylaws.pdf

The Division of Health Care Financing and Policy Public Notices:

http://dhcfp.nv.gov/Public/AdminSupport/PublicNotices/

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."

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 non-preferred 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

OPTUMRx®

Current Preferred Drug List

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® SAVELLA® *¥ (Fibromyalgia only)	* PA required *¥No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® GRALISE® LIDOCAINE PATCH * LIDODERM® * LYRICA® CR HORIZANT® QUTENZA®
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 BUTRANS® NUCYNTA® ER	PA required for Fentanyl Patch General PA Form: https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUPRENORPHINE PATCH DOLOPHINE® DURAGESIC® PATCHES QL EXALGO® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
EMBEDA® MORPHABOND® XTAMPZA ER®		ARYMO® ER HYSINGLA ER® OXYCONTIN® QL
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM DICLOFENAC TAB DR		CAMBIA ® POWDER

Preferred Products	PA Criteria	Non-Preferred Products
FLURBIPROFEN TAB IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB QL ¥ MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB	¥ PA Required	DICLOFENAC SODIUM TAB ER DICLOFENAC W/ MISOPROSTOL TAB DUEXIS TAB ETODOLAC CAP ETODOLAC TAB ETODOLAC ER TAB INDOMETHACIN CAP ER KETOPROFEN CAP MEFENAM CAP MELOXICAM SUSP NAPRELAN TAB CR NAPROXEN TAB CR NAPROXEN TAB ER OXAPROZIN TAB SPRIX® SPR TIVORBEX CAP VIMOVO TAB ZIPSOR CAP ZORVOLEX CAP
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE OTC LEVOCETIRIZINE NEW 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® CETIRIZINE D OTC NEW CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBRAMYCIN NEBULIZER		TOBI PODHALER®
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® LEDIPASVIR/ SOFOSBUVIR MAVYRET® SOFOSBUVIR/ VELPATASVIR	PA required: (see below) 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	DAKLINZA® OLYSIO® SOVALDI® TECHNIVIE® VIEKIRA® PAK VOSEVI® ZEPATIER®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMCICLOVIR VALCYCLOVIR		FAMVIR®
Influenza Agents		
AMANTADINE OSELTAMIVIR CAP/SUSP RIMANTADINE RELENZA®		RAPIVAB TAMIFLU® XOFLUZA®
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 / SUSP CEFPODOXIME TABS and SUSP	PA Required	CEDAX® CAPS and SUSP CEFDITOREN CEFIXIME CAPS/SUSP NEW OMNICEF® SPECTRACEF® SUPRAX® VANTIN®

Preferred Products	PA Criteria	Non-Preferred Products
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	PA Required	FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
LEVOFLOXACIN MOXIFLOXACIN	PA Required	AVELOX® LEVAQUIN®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® * SYMJEPI®
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® AVSOLA® NEW CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® STELARA® NEW	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ILARIS® ENTYVIO® NEW ILUMYA® NEW REMICADE® RINVOQ® SKYRIZI® TREMFYA

Preferred Products	PA Criteria	Non-Preferred Products
TALTZ® NEW XELJANZ®		
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® OCREVUS® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent* *PA required*	GLATOPA® GLATIRAMER LEMTRADA® PLEGRIDY®
Oral		
AUBAGIO® GILENYA® TECFIDERA®	PA required	BAFIERTAM® NEW DIMETHYL FUMARATE NEW MAVENCLAD® MAYZENT® VUMERITY® ZEPOSIA® NEW
Specific Symptomatic Treatment		
DALFAMPRIDINEQL	PA required	AMPYRA® QL
Cardiovascular Agents		
Antihypertensive Agents		
Angiotensin II Receptor Antagonists		
LOSARTAN LOSARTAN HCTZ VALSARTAN VALSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® DIOVAN® DIOVAN HCTZ® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)		
BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ	£ PREFERRED FOR AGES 10 AND UNDER	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK®

Preferred Products	PA Criteria	Non-Preferred Products
ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	ǂ NONPREFERRED FOR OVER 10 YEARS OLD	MOEXIPRIL PERINDOPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ		KAPSPARGO® SOTYLIZE®
BYSTOLIC®* CARVEDILOL LABETALOL	*Restricted to ICD-10 codes J40-J48	
METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE AMLODIPINE/BENAZEPRIL NEW AMLODIPINE/VALSARTAN NEW AMLODIPINE/VALSARTAN /HCT NEW CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL FELODIPINE ER NICARDIPINE NIFEDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		EXFORGE® NEW EXFORGE HCT® NEW ISRADIPINE NEW KATERZIA® LOTREL® NEW MATZIM TAB LA NISOLDIPINE ER NEW NORVASC® NYMALIZE® SOLN NEW

Preferred Products	PA Criteria	Non-Preferred Products
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
BOSENTAN NEW ORENITRAM® REVATIO ® NEW TADALAFIL		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN LETAIRIS® OPSUMIT® SILDENAFIL NEW TRACLEER® NEW UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
EZETIMIBE NEW		ZETIA® NEW
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN NEW SIMVASTATIN VYTORIN® NEW		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® CRESTOR® QL NEW EZALLOR® EZETIMIBE-SIMVASTATIN FLUVASTATIN FLUVASTATIN XL LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO®

	Preferred Products	PA Criteria	Non-Preferred Products
			MEVACOR® PRAVACHOL® SIMCOR® ZOCOR® ZYPITAMAG®
Niacin Agents			
	NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids			
	OMEGA-3-ACID VASCEPA®		LOVAZA®
Dermatological Agents			
Antipsoriatic Agents			
	DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE DUOBRII® LOTION ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics			
	CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LICART® LIDODERM® QL LIDAMANTLE® ZTLIDO®
Topical Anti-infectives			
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products			
	ACANYA® ACZONE GEL® NEW AZELEX® 20% cream BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM NEW	PA required if over 21 years old	AMZEEQ® FOAM NEW BENZACLIN® NEW BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DAPSONE GEL NEW DUAC CS® ERYTHROMYCIN ONEXTON GEL® NEW SODIUM SULFACETAMIDE/SULFUR

Preferred Products	PA Criteria	Non-Preferred Products
		SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antivirals		
ABREVA® DENAVIR® XERESE® CREAM ZOVIRAX® CREAM NEW ZOVIRAX®, OINTMENT		ACYCLOVIR OINT ACYCLOVIR CREAM NEW
Topical Scabicides		
LINDANE NATROBA® NIX® PERMETHRIN RID® ULESFIA®		EURAX® MALATHION OVIDE® SKLICE® SPINOSAD VANALICE® GEL
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	PIMECROLIMUS TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
DIFFERIN® NEW RETIN-A NEW TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ADAPALENE/BENZOYL PEROXIDE NEW ATRALIN® AVITA® EPIDUO® RETIN-A MICRO®(Pump and Tube) NEW TAZAROTENE NEW TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE CAP CALCIUM ACETATE TAB NEW		AURYXIA ® FOSRENOL®

Preferred Products	PA Criteria	Non-Preferred Products
PHOSLYRA® NEW RENAGEL® RENVELA®		LANTHANUM CARBONATE NEW PHOSLO® SEVELAMER CARBONATE SEVELAMER HCL NEW VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Pregnancy-induced Nausea and Vomiting Treatment		
BONJESTA® NEW OTC Doxylamine 25mg/Pyridoxine 10mg		DICLEGIS® NEW DOXYLAMINE-PYRIDOXINE TAB 10-10
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	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)		
DEXILANT® NEXIUM® POWDER FOR SUSP* OMEPRAZOLE PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM
Functional Gastrointestinal Disorder Drugs		
AMITIZA® LINZESS®	PA required	MOTEGRITY® NEW MOVANTIK® RELISTOR® SYMPROIC® TRULANCE® ZELNORM® NEW
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL®SUPP		BALSALAZIDE® ASACOL HD® NEW

Preferred Products	PA Criteria	Non-Preferred Products
CANASA® COLAZAL® NEW DELZICOL® NEW PENTASA® SULFASALAZINE DR SULFASALAZINE IR		LIALDA ® MESALAMINE (GEN APRISO) NEW MESALAMINE (GEN ASACOL HD) MESALAMINE (GEN DELZICOL) NEW MESALAMINE (GEN LIALDA) MESALAMINE ENEMA SUSP MESALAMINE SUPP NEW
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
ALFUZOSIN NEW DOXAZOSIN TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® SILODOSIN NEW UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER SOLIFENACIN NEW TOVIAZ®		DARIFENACIN NEW DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM VESICARE® NEW

Preferred Products	PA Criteria	Non-Preferred Products
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*
Injectable		
FONDAPARINUX ENOXAPARIN FRAGMIN®		ARIXTRA® INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL RETACRIT®	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL PROCRIT® QL
Platelet Inhibitors		
AGGRENOX® ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE PRASUGREL NEW	* PA required	ANAGRELIDE NEW ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® YOSPRALA® ZONTIVITY®
Hormones and Hormone Modifiers		
Androgens		
ANDRODERM®	PA required PA Form: https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	ANDROGEL® AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL TESTOSTERONE SOL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET®		GLUCOPHAGE®

Preferred Products	PA Criteria	Non-Preferred Products
METFORMIN EXT-REL (Glucophage XR®) METFORMIN EXT-REL (Glucophage XR®) METFORMIN (Glucophage®) METFORMIN ER (GEN GLUMETZA) RIOMET®		GLUCOPHAGE XR® GLUMETZA® METFORMIN (GEN FORTAMET)
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics		
BYDUREON® BYDUREON® PEN BYETTA® OZEMPIC® NEW TRULICITY® VICTOZA®	No PA required if Dx of Type 2 Diabetes transmitted on claim	ADLYXIN® BYDUREON® BCISE RYBELSUS® SOLIQUA® TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® 70/30 HUMULIN® U-500 INSULIN LISPRO INJ 100U/ML LANTUS® LEVEMIR ® NOVOLIN® N NOVOLIN® R NOVOLIN® 70/30 NOVOLOG® TOUJEO SOLO® 300 IU/ML TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMULIN ® N HUMULIN® R HUMALOG® U-200 INSULIN ASPART INSULIN ASPART MIX INSULIN LISPRO MIX NEW LYUMJEV® NEW
Meglitinides		
REPAGLINIDE		NATEGLINIDE (Starlix®) PRANDIN® STARLIX®
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		

	Preferred Products	PA Criteria	Non-Preferred Products
	FARXIGA® GLYXAMBI® NEW INVOKANA® INVOKAMET® JARDIANCE® SYNJARDY® NEW SYNJARDY® XR NEW XIGDUO XR®		INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ TRIJARDY® XR
Sulfonylureas			
	DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® CHLORPROPAMIDE GLYNASE® GLUCOTROL® GLUCOTROL XL® GLYBURIDE/METFORMIN (Glucovance®) GLUCOVANCE® GLIPIZIDE/METFORMIN (Metaglip®) TOLAZAMIDE TOLBUTAMIDE
Thiazolidinediones			
	PIOGLITAZONE		ACTOPLUS MET XR® ACTOPLUS MET® ACTOS® AVANDAMET® AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
Anti-Hypoglycemic Agents NEW			
	GLUCAGON EMERGENCY KIT		BAQSIMI® GVOKE®
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®

Preferred Products	PA Criteria	Non-Preferred Products
		SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions		
DUPIXENT® FASENRA® NEW NUCALA® XOLAIR®	PA Required	CINQAIR®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCRYS® TAB NEW PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCHICINE TAB/CAP NEW FEBUXOSTAT NEW MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE FOSAMAX PLUS D® IBANDRONATE SKELID®
Nasal Calcitonins		
CALCITONIN-SALMON		MIACALCIN®
Restless Leg Syndrome Agents		
PRAMIPEXOLE ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP XL NEW REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL		

Preferred Products	PA Criteria	Non-Preferred Products
METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE TABS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
APTIOM® BANZEL® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® EPITOL® ETHOSUXIMIDE FELBATOL® FYCOMPA® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR® LAMACTAL ODT®	PA required for members under 18 years old	DIACOMIT® OXTELLAR XR® POTIGA® SPRITAM® TOPIRAMATE ER NEW TROKENDI XR® VIGABATRIN NEW XCOPRI® NEW

Preferred Products	PA Criteria	Non-Preferred Products
LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE QUDEXY XR® NEW SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE IR TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines		
CLOBAZAM CLONAZEPAM CLORAZEPATE DIASTAT® NEW DIAZEPAM NAYZILAM® SPRAY* TRANXENE T-TAB® VALIUM® VALTOCO® SPRAY* NEW	PA required for members under 18 years old *PA Required for all ages	DIAZEPAM rectal soln NEW KLONOPIN® ONFI® SYMPAZAN® FILM
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN	PA required for members under 18 years old	

Preferred Products	PA Criteria	Non-Preferred Products
PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
AJOVY® EMGALITY®	PA required for all products	AIMOVIG® NURTEC® ODT UBRELVY®
Serotonin-Receptor Agonists		
RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN ODT ZOMIG® SPRAY	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® FROVA® ELETRIPTAN FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® RELPAX® REYVOW® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN NASAL SPRAY SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® TAB ZOMIG® ZMT
Antiparkinsonian Agents		
Dopamine Precursors		
CARBIDOPA/LEVODOPA CARBIDOPA/LEVODOPA ER CARBIDOPA/LEVODOPA ODT STALEVO®	*Trial of only one agent is required before moving to a non-preferred agent*	CARBIDOPA/LEVODOPA/ENTACAPONE DUOPA™ INBRIJA™ (INH) LODOSYN® TAB RYTARY™

Preferred Products	PA Criteria	Non-Preferred Products
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST BAK Free TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL® ZERVIATE®

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN VIGAMOX® ZYMAXID® NEW		CILOXAN® GATIFLOXACIN NEW LEVOFLOXACIN NEW MOXEZA® NEW MOXIFLOXACIN OFLOXACIN®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DUREZOL® FLAREX® NEW FML® NEW FML FORTE® NEW MAXIDEX® NEW PRED FORTE® NEW		DEXAMETHASONE NEW FLUOROMETHOLONE NEW INVELTYS® NEW LOTEMAX® NEW LOTEPREDNOL NEW OMNIPRED® PREDNISOLONE NEW PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® RESTASIS® MULTIDOSE XIIDRA®

Preferred Products	PA Criteria	Non-Preferred Products
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR CONCERTA® DAYTRANA® DESOXYN® NEW DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB FOCALIN XR® GUANFACINE ER JORNAY PM® NEW METADATE CD® METHYLIN® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL RITALIN LA® STRATTERA® VYVANSE®	PA required for entire class Children's Form: https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf Adult Form: https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® ADHANSIA® XR ADZENYS® AMPHETAMINE ER SUSP AMPHETAMINE SALT COMBO XR APTENSIO XR® ATOMOXETINE CLONIDINE HCL ER COTEMPLA XR®-ODT DEXEDRINE® DEXTROAMPHETAMINE SOLUTION DYANAVEL® NEW EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW MYDAYIS® PROCENTRA® NEW QUILLICHEW® NEW QUILLIVANT® XR SUSP NEW RELEXXII® RITALIN® ZENZEDI®

Preferred Products	PA Criteria	Non-Preferred Products
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® (Discontinued) CYMBALTA® DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX® 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® PAROXETINE ER PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE	 PA required for Ages under 18 years old PA Forms: https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® ABILIFY MYCITE ® CAPLYTA® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL® SECUADO®

Preferred Products	PA Criteria	Non-Preferred Products
SAPHRIS® VRAYLAR® ZIPRASIDONE		SEROQUEL® SEROQUEL XR® ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable		
ABILIFY® MAINTENA ARISTADA® ARISTADA® INITIO INVEGA® SUSTENNA INVEGA® TRINZA* RISPERDAL® CONSTA PERSERIS® ZYPREXA® RELPREVV	*****PA Required	
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
ARMODAFINIL * NUVIGIL® * PROVIGIL® * WAKIX® **	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	MODAFINIL* SUNOSI®** XYREM® **
Respiratory Agents		
Nasal Antihistamines		
AZELASTINE DYMISTA® OLOPATADINE		ASTEPRO® PATANASE®
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER

Preferred Products	PA Criteria	Non-Preferred Products
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR® DISKUS NEW ADVAIR HFA® ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX® BEVESPI® BREO ELLIPTA® NEW BUDESONIDE NEBS* DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL INCRUSE ELLIPTA ® NEW PULMICORT FLEXHALER® QVAR® QVAR® REDIHALER™ NEW SEREVENT DISKUS® QL SPIRIVA® HANDIHALER SPIRIVA RESPIMAT® NEW STIOLTO RESPIMAT® STRIVERDI RESPIMAT®		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® BROVANA® BUDESONIDE / FORMOTEROL NEW DUAKLIR® PRESSAIR NEW FLUTICASONE PROPIONATE/SALMETEROL POW NEW LONHALA MAGNAIR® PERFOROMIST NEBULIZER® SEEBRI NEOHALER® TRELEGY ELLIPTA® UTIBRON NEOHALER ® WIXELA® YUPELRI® NEW

	Preferred Products	PA Criteria	Non-Preferred Products
	SYMBICORT® TUDORZA®		
Short-Acting/Rescue Therapy			
	ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL PROAIR® HFA NEW VENTOLIN HFA® NEW XOPENEX® HFA* QL XOPENEX® Solution* QL NEW		ALBUTEROL AER HFA LEVALBUTEROL* HFA LEVALBUTEROL* NEBS NEW PROAIR RESPICLICK® PROVENTIL® HFA NEW
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
	BUPRENORPHINE / NALOXONE TAB NEW BUPRENORPHINE SUB TAB SUBLOCADE® SUBOXONE® VIVITROL®		BUNAVAIL® BUPRENORPHINE / NALOXONE FILM ZUBSOLV®

Meeting Minutes

Proposed New Classes

OPTUMRx

Therapeutic Class Overview

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

INTRODUCTION

- Cardiovascular disease (CVD) is the leading cause of death worldwide and accounted for 859,125 deaths in the United States (U.S.) in 2017. Key cardiovascular (CV) risk factors include smoking, physical inactivity, obesity, hypercholesterolemia, poor nutrition, hypertension, and diabetes mellitus *(American Heart Association [AHA] 2020)*.
- Serum cholesterol is known to be related to atherosclerotic CVD (ASCVD), with low-density lipoprotein cholesterol (LDL-C) being the dominant form of atherogenic cholesterol. LDL-C is a primary cause of atherosclerosis, but other major contributing risk factors include cigarette smoking, hypertension, dysglycemia, and other lipoprotein abnormalities *(Grundy et al 2019).*
- Almost 40% of American adults have total cholesterol serum levels of ≥ 200 mg/dL, and nearly 30% have elevated levels of LDL-C (≥ 130 mg/dL) *(AHA 2020)*.
- Familial hypercholesterolemia (FH) is a common and serious genetic condition resulting in severely elevated cholesterol concentrations and increased risk of premature coronary heart disease (CHD) (*Goldberg et al 2011*). Patients can have homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH is estimated to occur in 1 in 200 to 250 adults in the U.S.; HoFH is much rarer with an estimated prevalence of 1:300,000 to 1:400,000, but homozygous patients are more adversely affected by the condition *(Rosenson and Durrington 2019).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that leads to the degradation of hepatocyte LDL-C receptors (LDLR), which results in increased LDL-C levels; by inhibiting PCSK9, LDLR recycling is preserved, and LDL-C levels are subsequently reduced *(Navarese et al 2015*). The PCSK9 inhibitors are administered subcutaneously (SC) every 2 weeks or once monthly.
- Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) *(Grundy et al 2019)*, American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) *(Handelsman et al 2020)*, and the National Lipid Association (NLA) *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy for hypercholesterolemia or CVD, with ezetimibe and the PCSK9 inhibitors being potential adjunctive agents for patients not achieving adequate LDL-C lowering; however, there is no consensus on goal LDL-C levels.
- Medispan class: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Praluent (alirocumab)	-
Repatha (evolocumab)	-

(Drugs@FDA 2020, Purple Book: Database of Licensed Biological Products 2020)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Praluent (alirocumab)	Repatha (evolocumab)
To reduce the risk of myocardial infarction (MI), stroke, and unstable angina (UA) requiring hospitalization in adults with established CVD	✔	
As an adjunct to diet, alone or in combination with other lipid lowering therapies (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C	✔	✔
As an adjunct to diet and other lipid lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C		✔
To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD		✔

(Prescribing information: Praluent 2020, Repatha 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of alirocumab was evaluated in the ODYSSEY program, which consisted of ten Phase 3, multi-center (MC), double-blind (DB), randomized controlled trials (RCTs) *(Praluent Food and Drug Administration [FDA] Briefing Information).*
  - Patients with HeFH and/or high or very high CV risk were enrolled in 9 of the 10 trials. Eight trials evaluated alirocumab in patients receiving background statin therapy (typically at maximally-tolerated doses), whereas 2 trials evaluated alirocumab as monotherapy, including in statin-intolerant patients (ie, ODYSSEY ALTERNATIVE). Ezetimibe was the comparator in the 5 active-controlled (AC) trials, whereas the other 5 trials were placebo-controlled (PC) *(Praluent FDA Briefing Information).*
- The efficacy of evolocumab was evaluated in the PROFICIO program, which consisted of eight Phase 3, MC, DB, RCTs *(Repatha FDA Briefing Information*).
  - In most of the trials, patients with HeFH, HoFH, or primary hyperlipidemia were randomized to receive evolocumab or placebo, and received background statin therapy in both treatment arms, ranging from moderate-intensity statin therapy (eg, atorvastatin 10 mg) to high-intensity statin therapy (eg, atorvastatin 80 mg). In 2 trials, evolocumab was compared to ezetimibe as monotherapy, including in statin-intolerant patients (ie, GAUSS-2 and -3) *(Repatha FDA Briefing Information).*

Familial hypercholesterolemia (FH)

- ODYSSEY FH I-II and HIGH FH compared the efficacy of alirocumab with placebo in patients with HeFH for a 24-week duration. In FH I-II, patients were initiated on alirocumab 75 mg SC every 2 weeks (Q2W) with an up-titration dosing strategy, whereas patients in HIGH FH were initiated on alirocumab 150 mg SC Q2W with no up-titration (*Kastelein et al 2015*).
  - ODYSSEY FH I-II were 2 identical, PC, RCTs evaluating alirocumab in 735 patients with HeFH and LDL-C > 70 mg/dL with a history of CVD or LDL-C > 100 mg/dL without history of CVD. Patients had a mean baseline LDL-C level of 140 mg/dL while receiving statin therapy; 85% of patients received high-intensity statin therapy, and 60% received ezetimibe. After 24 weeks of treatment, alirocumab reduced LDL-C by 58% and 51% in FH I and FH II, respectively, compared to placebo ($p < 0.0001$) *(Kastelein et al 2015*).
  - ODYSSEY HIGH FH evaluated alirocumab in 107 patients with HeFH and LDL-C > 160 mg/dL. Patients had a mean baseline LDL-C of approximately 200 mg/dL while receiving statin therapy; about 70% of patients were receiving high-intensity statins (eg, atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily). Compared to placebo, alirocumab reduced LDL-C by 39% at 24 weeks ($p < 0.0001$) *(Ginsberg et al 2016*).
- ODYSSEY ESCAPE was a DB, PC, RCT that randomized patients with HeFH who were undergoing lipoprotein apheresis to alirocumab 150 mg SC Q2W (n = 41) or placebo (n = 21) for 18 weeks. Patients were treated in combination with their usual apheresis schedule for 6 weeks. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53.7% in alirocumab-treated patients vs 1.6% in placebo-treated patients; subsequently, apheresis was discontinued in 63.4% of alirocumab-treated patients, and the rate was at least halved in 92.7% *(Moriarty et al 2016).*
- In RUTHERFORD-2, patients with HeFH were randomized to receive evolocumab 140 mg SC Q2W (n = 111), evolocumab 420 mg SC every 4 weeks (Q4W) (n = 110), or placebo (n = 110) for 12 weeks. Patients had a mean baseline LDL-C level of 155 mg/dL while receiving statin therapy; 87% of patients were receiving high-intensity statin therapy, and 62% of patients were receiving ezetimibe. Compared to placebo, evolocumab 140 mg SC Q2W lowered LDL-C by 59% and evolocumab 420 mg SC Q4W by 61% at 12 weeks ($p < 0.0001$) *(Raal et al 2015a).*
  The TESLA Part B trial randomized 50 patients with HoFH on stable lipid-lowering therapy (LLT) to evolocumab 420 mg SC Q4W (n = 33) or placebo (n = 17) for 12 weeks. Patients in the evolocumab group had a mean baseline LDL-C of 356 mg/dL; those in the placebo group had a mean baseline LDL-C of 336 mg/dL. Treatment with evolocumab reduced LDL-C by 23.1%, whereas patients treated with placebo had an increase in LDL-C by 7.9% (treatment difference, -30.9%; $p < 0.0001$); however, the mean on-treatment LDL-C remained significantly elevated at 271 mg/dL *(Raal et al 2015b).*

- In HAUSER-RCT, pediatric patients (10 to 17 years of age) with HeFH who had received stable LLT for at least 4 weeks before screening were randomly assigned to evolocumab 420 mg (n = 104) or placebo (n = 53) SC once monthly (*Santos et al 2020*). Results revealed a mean percentage change from baseline in LDL-C levels of -44.5% for evolocumab and -6.2% for placebo at week 24 (difference, -38.3%; p < 0.001). Results for all secondary lipid variables were also significantly improved with evolocumab therapy. The incidences of adverse effects (AEs) were similar between groups.
- Evolocumab was also shown to have long-term efficacy and safety in 300 patients with either HoFH or severe HeFH over a median of 4.1 years in the final report from the TAUSSIG trial (*Santos et al 2020*). The most commonly reported AEs with therapy were nasopharyngitis, influenza, upper respiratory tract infection, and headache; improvements in LDL-C were sustained over time.
- Alirocumab has not been evaluated in patients with HoFH.

Patients with hypercholesterolemia not adequately controlled on other LLTs

- ODYSSEY COMBO I and II were 2 similarly designed 24-week, DB, RCTs in high CVD risk patients who were inadequately controlled with maximally-tolerated statin therapy. Patients were included if they had a history of CVD with LDL-C ≥ 70 mg/dL, or LDL-C ≥ 100 mg/dL and CHD risk equivalents. In COMBO I, patients were randomized to alirocumab 75 mg SC Q2W (n = 209) or placebo (n = 107), whereas in COMBO II, patients were randomized to alirocumab 75 mg SC Q2W (n = 479) or ezetimibe 10 mg daily (QD) (n = 241). Both studies employed the up-titration protocol *(Cannon et al 2015, Kereiakes et al 2015).*
  - In COMBO I, 78.2% of patients had a history of CHD, 43.0% had CHD risk equivalents, and 43.0% had type 2 diabetes mellitus (T2DM). All patients but 1 received statin therapy, with 62.7% receiving high-dose statin therapy. From a baseline of 100.3 mg/dL for patients with alirocumab and 104.6 mg/dL for patients with placebo, alirocumab reduced LDL-C by 45.9% compared with placebo (p < 0.0001) *(Kereiakes et al 2015).*
  - In COMBO II, 75.6% of patients had CHD, 31.0% had CHD risk equivalents, and 30.7% had T2DM. All patients but 1 received statin therapy, with 66.7% receiving high-dose statin therapy. From a mean baseline of 109.0 mg/dL for patients with alirocumab and 105.0 mg/dL for patients with ezetimibe, alirocumab reduced LDL-C by 29.8% compared with ezetimibe (p < 0.0001) *(Cannon et al 2015).*
- ODYSSEY OPTIONS I and II were 24-week, DB, RCTs evaluating alirocumab in combination with atorvastatin or rosuvastatin in patients with hypercholesterolemia who were inadequately controlled (very high CV risk and LDL-C ≥ 70 mg/dL or high CV risk and LDL-C ≥ 100 mg/dL). In ODYSSEY OPTIONS I, 355 patients on atorvastatin 20 or 40 mg at baseline were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, (3) double their atorvastatin dose, or (4) switch to rosuvastatin. In ODYSSEY OPTIONS II, 305 patients on rosuvastatin 10 or 20 mg were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, or (3) double their rosuvastatin dose *(Bays et al 2015, Farnier et al 2016, Robinson et al 2014a).*
  - In OPTIONS I, among patients receiving atorvastatin 20 and 40 mg, greater LDL-C reduction was achieved with add-on alirocumab (44.1%, 54.0%), compared with add-on ezetimibe (20.5%, 22.6%), doubling atorvastatin dose (4.8%, 5.0%), or switching to rosuvastatin (21.4%; p < 0.001 for all comparisons) *(Robinson et al 2014a, Bays et al 2015).*
  - In OPTIONS II, in patients receiving rosuvastatin 10 mg, greater LDL-C reduction was achieved with add-on alirocumab (50.3%) compared with add-on ezetimibe (14.4%), or doubling the rosuvastatin dose (16.3%) (p < 0.0001 for all comparisons). In the rosuvastatin 20 mg group, the addition of alirocumab reduced LDL-C by 36.3%, but the comparisons with the ezetimibe and double rosuvastatin groups did not reach statistical significance *(Farnier et al 2016).*
- LAPLACE-2 was a Phase 3 study evaluating evolocumab in combination with various statin regimens. Patients with different LDL-C levels and different background LLT were first randomized to 1 of 5 open-label (OL) statin regimens (atorvastatin 80 mg, rosuvastatin 40 mg, atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) for 4 weeks, and then randomized to evolocumab 140 mg SC Q2W or 420 mg SC Q4W (n = 1117), ezetimibe 10 mg QD (n = 221; patients receiving atorvastatin only), or placebo (n = 558) for 12 weeks. Compared with placebo, evolocumab further reduced LDL-C by at least 60% in all statin groups; compared with ezetimibe, evolocumab further reduced LDL-C by approximately 40% in patients receiving low-dose and high-dose atorvastatin (*Robinson et al 2014b*).
- Alirocumab was evaluated specifically in patients with diabetes in ODYSSEY DM-INSULIN and ODYSSEY DM-DISLIPIDEMIA *(Leiter et al 2017, Ray et al 2018).*

- ODYSSEY DM-INSULIN was a 24-week, DB, PC, RCT in patients with type 1 diabetes mellitus (T1DM) (n = 71) or T2DM (n = 441) treated with insulin and not controlled on maximally-tolerated statin therapy. Patients were randomized to receive alirocumab 75 mg SC Q2W with an up-titration strategy or placebo. Alirocumab reduced LDL-C from baseline to week 24 by 49% and 47.8% vs placebo in patients with T2DM and T1DM, respectively (both p < 0.0001). Glycated hemoglobin (HbA1c) and fasting blood glucose levels remained stable and treatment-emergent AEs were comparable across the groups *(Leiter et al 2017).*
- ODYSSEY DM-DISLIPIDEMIA was a 24-week, OL, RCT in patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥ 100 mg/dL and triglycerides ≥ 150 mg/dL but < 500 mg/dL) not adequately controlled despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (n = 276) or usual care (n = 137). Alirocumab reduced non-HDL-C by 37.3% vs 4.7% with usual care (p < 0.0001). No clinically meaningful effect was seen on HbA1c or change in number of glucose-lowering agents. The rate of treatment-emergent AEs was similar between the groups *(Ray et al 2018).*

Monotherapy and patients unable to tolerate statin therapy

- ODYSSEY MONO was a 24-week, DB, AC, RCT comparing alirocumab monotherapy with ezetimibe in patients with hypercholesterolemia. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 52) with the option to titrate to 150 mg Q2W, or ezetimibe 10 mg QD (n = 51). At 24 weeks, alirocumab reduced LDL-C from baseline by 47.2% vs 15.6% for ezetimibe (treatment difference, -31.6%; p < 0.0001). Adverse effects were similar between the groups *(Roth and McKenney 2015).*
- MENDEL-2 was a 12-week, DB, AC, PC, RCT comparing evolocumab monotherapy with ezetimibe or placebo in patients with hypercholesterolemia. Patients were randomized to receive evolocumab 140 mg SC Q2W (n = 153) or 420 mg SC Q4W (n = 153), ezetimibe 10 mg QD (n = 154), or placebo (n = 155). Evolocumab reduced LDL-C from baseline by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all comparisons). Treatment-emergent AEs and muscle-related AEs were comparable across the groups *(Koren et al 2014b).*
- ODYSSEY ALTERNATIVE was a 24-week, DB, AC, RCT comparing alirocumab with ezetimibe and atorvastatin in statin-intolerant patients. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 126) with the option to titrate to 150 mg, ezetimibe 10 mg QD (n = 125), or atorvastatin 20 mg QD (n = 63) (validation arm). Alirocumab reduced LDL-C by 45% from baseline vs 14.6% for ezetimibe (treatment difference, -30.4%; p < 0.0001). Alirocumab was better-tolerated than atorvastatin in patients in terms of muscle-related treatment-emergent AEs (32.5% vs 46.0%; p = 0.042) *(Moriarty et al 2015).*
- GAUSS-2 and -3 both compared evolocumab with ezetimibe in statin-intolerant patients *(Nissen et al 2016, Stroes et al 2014)*.
  - GAUSS-2 was a 12-week, DB, PC, AC trial with patients randomized to evolocumab 140 mg SC Q2W + placebo orally QD (n = 103), evolocumab 420 mg SC Q4W + placebo orally daily (n = 102), or ezetimibe 10 mg orally QD + placebo SC Q2W or Q4W (n = 102). Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences vs ezetimibe of 37% and 39% (p < 0.001). Muscle-related treatment-emergent AEs occurred in 12% of evolocumab-treated patients vs 23% of ezetimibe-treated patients *(Stroes et al 2014).*
  - GAUSS-3 was a 24-week, 2-stage RCT in patients with a history of intolerance to 2 or more statins (N = 511). Phase A used a 24-week crossover protocol with atorvastatin or placebo to identify patients experiencing muscle-related AEs only to atorvastatin. In Phase B, patients experiencing intolerance only to atorvastatin were randomized to ezetimibe 10 mg QD (n = 73) or evolocumab 420 mg SC Q4W (n = 145) for 24 weeks. From baseline, evolocumab reduced LDL-C by 52.8% vs 16.7% for ezetimibe (treatment difference, -36.1%; p < 0.001). Muscle-related AEs were reported in 20.7% of evolocumab-treated patients and 28.8% of ezetimibe-treated patients *(Nissen et al 2016).*
- The EVOPACS trial is the first randomized study to evaluate evolocumab in the acute phase of acute coronary syndrome (ACS) (*Koskinas et al 2019*). In EVOPACS, 308 patients hospitalized for ACS with elevated LDL-C levels were randomly assigned to SC evolocumab 420 mg (n = 155) or matching placebo (n = 153) administered in-hospital and after 4 weeks, in addition to atorvastatin 40 mg. The majority of enrolled patients (78.2%) had not received prior statin therapy. Results revealed that the difference in mean percentage change from baseline in LDL-C between groups was -40.7%, favoring evolocumab (p < 0.001) at week 8. Greater than 95% of evolocumab-treated patients achieved currently recommended target LDL-C levels at week 8 compared to 37.6% of patients administered placebo.

Longer term efficacy and safety

- ODYSSEY LONG TERM was a 78-week, DB, PC, RCT in which high CVD risk patients who were receiving maximally-tolerated statin therapy and had an LDL-C ≥ 70 mg/dL were randomized to receive alirocumab 150 mg SC Q2W (n = 1553) or placebo (n = 788) (*Robinson et al 2015*).
  - Compared with placebo, alirocumab reduced LDL-C by 61.9% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 78 weeks (56.0% vs placebo; p < 0.001).
  - In a post hoc analysis, patients treated with alirocumab had a lower rate of adjudicated composite CVD events (ie, CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization) compared with placebo (1.7% vs 3.3%, respectively; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.31 to 0.90; p = 0.02). However, there was no difference when including all positively adjudicated CVD events (ie, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization) (4.6% vs 5.1%, respectively; p = 0.68).
  - The frequency of AEs was similar in both groups (81.0% vs 82.5%, respectively), as were discontinuation rates (7.2% vs 5.8%, respectively).
- The OSLER studies enrolled 4465 patients who had completed a Phase 2 or Phase 3 trial with evolocumab, and randomly assigned them to OL evolocumab plus standard of care (SOC) or SOC alone. OSLER-1 enrolled patients from Phase 2 trials to receive evolocumab 420 mg SC Q4W, whereas OSLER-2 enrolled patients from Phase 3 trials to receive evolocumab 140 mg SC Q2W or 420 mg SC Q4W depending on patient choice. The parent trials included patients on statin therapy (70.1%), as well as patients who were statin intolerant or were not on other LLTs *(Koren et al 2014a, Sabatine et al 2015).*
  - Compared with SOC alone, evolocumab reduced LDL-C by 58.8% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 48 weeks (58.4% vs SOC; p < 0.001).
  - In a prespecified exploratory analysis, patients treated with evolocumab had a lower rate of CVD events (ie, death, MI, UA requiring hospitalization, coronary revascularization, stroke, transient ischemic attack [TIA], heart failure requiring hospitalization) (0.95% vs 2.18% with SOC; HR, 0.47; 95% CI, 0.28 to 0.78; p = 0.003).
  - The frequency of AEs was similar in both groups (69.2% vs 64.8%, respectively), as were serious AEs (7.5% in each group). Although uncommon overall, neurocognitive AEs were more frequent with evolocumab (0.9% vs 0.3% with SOC).
  - In 5-year results from OSLER-1, evolocumab demonstrated sustained mean LDL-C reductions over time, with patients maintaining a 56% reduction from baseline at year 5. Evolocumab was not associated with an increase in AEs or neutralizing antibodies over time *(Koren et al 2018 [abstract])*.
- DESCARTES was a 52-week RCT comparing evolocumab with placebo in 901 hypercholesterolemic patients with a range of CVD risk. Prior to the treatment phase, patients were assigned to 1 of 4 background LLT groups in a 4- to 12-week OL run-in period: diet alone, diet with atorvastatin 10 mg QD, diet with atorvastatin 80 mg QD, or diet with atorvastatin 80 mg QD and ezetimibe 10 mg QD. Patients were intensified to the next level of background LLT if they did not reach their LDL-C goal per current guidelines (Adult Treatment Panel [ATP] III). After the run-in period, patients were then randomized in a 2:1 ratio to evolocumab 420 mg SC Q4W (n = 599) or placebo (n = 302). After 52 weeks, evolocumab reduced LDL-C in all 4 LLT groups compared with placebo (55.7%, 61.6%, 56.8%, 48.5%, respectively; p < 0.001 for all comparisons) *(Blom et al 2014).*

Cardiovascular outcomes

- FOURIER, a DB, PC, RCT, was the first completed CV outcomes trial for the PCSK9 inhibitors. The trial enrolled 27,564 high-risk patients with CVD and LDL-C levels ≥ 70 mg/dL while receiving optimized LLT (99.7% of patients were receiving moderate- or high-intensity statins). Patients were randomized to receive evolocumab (either 140 mg SC Q2W or 420 mg SC Q4W) or placebo, while remaining on their baseline LLT. The primary endpoint was a composite of CV death, MI, stroke, hospitalization for UA, and coronary revascularization *(Sabatine et al 2017)*.
  - At 48 weeks, the least-squares mean (LSM) percentage reduction in LDL-C levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL to 30 mg/dL (p < 0.001).
  - The composite endpoint occurred in 9.8% of evolocumab-treated patients vs 11.3% of placebo-treated patients (treatment difference, 1.5%; HR, 0.85; 95% CI, 0.79 to 0.92; p < 0.001) during a median follow-up period of 26 months. The benefit was driven by reduction of MI, stroke, and coronary revascularization; no benefit was identified in CV death or death from any cause.
- ODYSSEY OUTCOMES was a DB, PC, RCT enrolling 18,924 patients who had experienced an ACS between 1 to 12 months prior and had inadequate control of their lipids (eg, LDL-C ≥ 70 mg/dL) despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (75 mg or 150 mg SC Q2W) or placebo in addition to their

baseline LLT to treat to an LDL-C target of 25 to 50 mg/dL. The primary endpoint was a composite of CHD death, non-fatal MI, ischemic stroke, and UA requiring hospitalization. Median follow-up was 2.8 years *(Schwartz et al 2018).*

- Compared to placebo, alirocumab reduced the overall risk of the primary composite outcome (alirocumab: 9.5% vs placebo: 11.1%; HR, 0.85; 95% CI, 0.78 to 0.93; p = 0.0003) and was associated with a lower risk of non-fatal MI (alirocumab: 6.6% vs placebo: 7.6%; HR, 0.86; 95% CI, 0.77 to 0.96; p = 0.006), ischemic stroke (alirocumab: 1.2% vs placebo: 1.6%; HR, 0.73; 95% CI, 0.57 to 0.93; p = 0.01), and UA (alirocumab: 0.4% vs placebo: 0.6%; HR, 0.61; 95% CI, 0.41 to 0.92; p = 0.02).
  - For the primary composite endpoint, the absolute benefit of alirocumab was greater among patients with a baseline LDL-C level ≥ 100 mg/dL (HR, 0.76; 95% CI, 0.65 to 0.87) compared to patients with lower baseline levels; however, the analysis on this subgroup was not prespecified.
- Alirocumab was associated with a lower risk of all-cause mortality (alirocumab: 3.5% vs placebo: 4.1%; HR, 0.85; 95% CI, 0.73 to 0.98; nominal p = 0.026), and there were also numerically fewer CHD deaths (alirocumab: 2.2% vs placebo: 2.3%; HR, 0.92; 95% CI, 0.76 to 1.11; p = 0.38).
- In a prespecified analysis of 8242 patients eligible for ≥ 3 years follow-up, alirocumab reduced death (HR, 0.78; 95% CI, 0.65 to 0.94; p = 0.01). A post hoc analysis found that patients with baseline LDL-C ≥ 100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR, 0.71; 95% CI, 0.56 to 0.90; *p*interaction = 0.007). Patients who achieved lower LDL-C values at 4 months (down to ~ 30 mg/dL) appeared to be at lower risk of subsequent death (*Steg et al 2019*).
- In another pre-specified analysis of ODYSSEY OUTCOMES, alirocumab reduced the risk of any stroke (HR, 0.72; 95% CI, 0.57 to 0.91) and ischemic stroke (HR, 0.73; 95% CI, 0.57 to 0.93) without increasing hemorrhagic stroke (HR, 0.83; 95% CI, 0.42 to 1.65) at a median follow-up of 2.8 years (*Wouter Jukema et al 2019*). Risk of hemorrhagic stroke was not dependent upon achieved LDL-C levels within the alirocumab group, which is significant as concerns have existed that very low LDL-C levels may increase the potential risk of this stroke type.

Meta-analyses

- A Cochrane Review of 24 studies (N = 60,997) comparing PCSK9 inhibitors with placebo or active treatment(s) for primary and secondary prevention of CVD was conducted *(Schmidt et al 2020)*. Eighteen trials randomized subjects to alirocumab and 6 to evolocumab. All subjects received background LLT or lifestyle counseling. Six alirocumab studies used an active treatment comparison vs 3 evolocumab studies.
  - Compared with placebo, alirocumab decreased the risk of CVD events, with an absolute risk difference (RD) of -2% (odds ratio [OR], 0.87; 95% CI, 0.80 to 0.94), decreased the risk of mortality (RD -1%; OR, 0.83; 95% CI, 0.72 to 0.96), MI (RD -2%; OR, 0.86; 95% CI, 0.79 to 0.94), and for any stroke (RD 0%; OR, 0.73; 95% CI, 0.58 to 0.91).
  - Compared with placebo, evolocumab decreased the risk of CVD events, with an absolute RD of -2% (OR, 0.84; 95% CI, 0.78 to 0.91), for mortality, the RD was < 1% (OR, 1.04; 95% CI, 0.91 to 1.19), MI (RD - 1%; OR, 0.72; 95% CI, 0.64 to 0.82), and for any stroke (RD < -1%; OR, 0.79; 95% CI, 0.65 to 0.94).
  - The evidence base of PCSK9 inhibitors compared with active treatment was much weaker, and it is unclear whether evolocumab or alirocumab might be effectively used as replacement therapies.
- A meta-analysis was conducted on 35 RCTs comparing treatment with a PCSK9 inhibitor to no PCSK9 inhibitor in adults with hypercholesterolemia (N = 45,539). Compared with no PCSK9 inhibitor use, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in MI (PCSK9 inhibitor: 2.3% vs control: 3.6%; OR, 0.72; 95% CI, 0.64 to 0.81), stroke (1.0% vs 1.4%; OR, 0.80; 95% CI, 0.67 to 0.96), and coronary revascularization (4.2% vs 5.8%; OR, 0.78; 95% CI, 0.71 to 0.86). Use of a PCSK9 inhibitor was not significantly associated with a decrease in all-cause mortality (1.9% vs 2.2%; OR, 0.71; 95% CI, 0.47 to 1.09) or CV mortality (1.1% vs 1.3%; OR, 1.01; 95% CI, 0.85 to 1.19) *(Karatasakis et al 2017).*
- In an updated meta-analysis involving 62,281 patients from 28 RCTs, the CV outcomes of PCSK9 inhibitor therapy (N = 33,204) vs placebo (N = 29,077) were assessed (*Casula et al 2019*). Results revealed no significant difference in all-cause mortality between the groups (OR, 0.93; 95% CI, 0.85 to 1.03). However, PCSK9 inhibitor therapy was associated with a significant reduction in CV events as compared to placebo (OR, 0.83; 95% CI, 0.78 to 0.87). Additionally, the occurrence of stroke and MI were significantly reduced with the PCSK9 inhibitors. CV mortality was not significantly different between the groups (OR, 0.94; 95% CI, 0.83 to 1.07).

CLINICAL GUIDELINES

- The updated ACC/AHA (2018) treatment guidelines for hypercholesterolemia emphasize reducing the risk of ASCVD through lipid management. In patients with clinical ASCVD, LDL-C should be reduced with high-intensity or maximally-tolerated statin therapy. In very high risk ASCVD, an LDL-C threshold of 70 mg/dL should be utilized to consider the addition of non-statins to maximally-tolerated statin therapy. If the addition of ezetimibe does not decrease LDL-C levels < 70 mg/dL, the addition of a PCSK9 inhibitor is reasonable. Similarly, in patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), high-intensity statin therapy should be initiated, but if the LDL-C level remains ≥ 100 mg/dL, adding ezetimibe may be reasonable. If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. The guideline notes that long-term safety (> 3 years) with the PCSK9 inhibitors is uncertain and cost-effectiveness is low at mid-2018 prices *(Grundy et al 2019)*.
- The NLA guideline (2015) recommends that the central focus of pharmacotherapy in hypercholesterolemia be moderate- or high-intensity statin therapy, and acknowledges that RCT evidence is limited in guiding combination drug therapy in patients receiving maximally-tolerated statin therapy whose atherogenic cholesterol remains elevated above treatment goals *(Jacobson et al 2015).*
  - The NLA Expert Panel evidence-based recommendations on treatment with PCSK9 inhibitors are summarized in Table 3. Patients with ASCVD and/or additional risk factors who have not met their LDL-C goals should be considered for adjunct therapy with a PCSK9 inhibitor; it is emphasized that clinicians should reinforce the importance of statin therapy and attention to lifestyle therapy with each patient visit *(Orringer et al 2017)*.

Table 3. 2017 NLA expert panel PCSK9 inhibitor recommendations

Disorder	LDL-C/Non-HDL-C for threshold for Rx (mg/dL)
ASCVD + additional risk factors	≥ 70/ ≥ 100
Progressive ASCVD	≥ 70/ ≥ 100
LDL-C ≥ 190, age 40 to 79 with no uncontrolled risk factors or key additional risk markers	≥ 100/ ≥ 130
LDL-C ≥ 190, age 40 to 79 with uncontrolled risk factors or key additional risk markers	≥ 70/ ≥ 100
LDL-C ≥ 190, age 18 to 39 with uncontrolled risk factors or key additional risk markers or FH causing mutation	≥ 100/ ≥ 130
HoFH phenotype	≥ 70/ ≥ 100
ASCVD + statin intolerance	Clinical judgment

- The AACE/ACE guidelines recommend LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. PCSK9 inhibitors should be considered as adjunct therapy in patients who are unable to reach their LDL-C goals with maximally-tolerated statin therapy *(Handelsman et al 2020).*

SAFETY SUMMARY

- Warnings/precautions
  - Hypersensitivity reactions (eg, pruritus, rash, urticaria), including some serious events (eg, hypersensitivity vasculitis, hypersensitivity reactions requiring hospitalization), have been reported with alirocumab and evolocumab treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment, treat according to the standard of care, and monitor until signs and symptoms resolve.
- Adverse effects
  - Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
- Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, symptoms associated with abetalipoproteinemia, a familial condition with minimal or nonexistent

LDL-C levels (eg, fat malabsorption syndromes, hepatic steatosis, progressive neurologic degenerative disease, retinitis pigmentosa, acanthocytosis), were not observed *(McKenney 2015).* Rates of overall AEs, serious AEs, and neurocognitive AEs among patients achieving very low LDL-C levels were similar to those among the overall group *(Robinson et al 2015, Sabatine et al 2015, Sabatine et al 2017).* The long-term effects of very low LDL-C levels by alirocumab or evolocumab are unknown *(Praluent Prescribing Information 2020, Repatha Prescribing Information 2020).*

- Neurocognitive AEs occurred infrequently, but more often in patients treated with alirocumab (1.2% vs 0.5% with placebo) and evolocumab (0.9% vs 0.3% with placebo) in longer-term safety analyses *(Robinson et al 2015, Sabatine et al 2015).*
  - The EBBINGHAUS trial evaluated cognitive function in 1204 patients enrolled in the FOURIER trial and identified no important cognitive differences between patients treated with evolocumab vs placebo over a median follow-up of 19 months *(Giugliano et al 2017).*
  - A meta-analysis of 14 Phase 2 and 3 alirocumab trials found no significant differences in rates of patient-reported neurocognitive treatment-emergent AEs between alirocumab and controls (placebo or ezetimibe). No association was found between neurocognitive treatment-emergent AEs and LDL-C < 25 mg/dL *(Harvey et al 2018).*
- There are no data available on use of alirocumab or evolocumab in pregnant or lactating women to inform a drug-associated risk.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Praluent (alirocumab)	Single-dose pre-filled syringe: 75 mg/mL, 150 mg/mL Single-dose pre-filled pen: 75 mg/mL, 150 mg/mL	SC	Starting dose: 75 mg every 2 weeks or 300 mg every 4 weeks If LDL-C response is inadequate, the dosage may be adjusted to the maximum dose of 150 mg every 2 weeks HeFH patients undergoing LDL apheresis: 150 mg every 2 weeks; can be administered without regard to timing of apheresis	The safety and efficacy of alirocumab have not been established in the pediatric population.
Repatha (evolocumab)	Single-dose pre-filled syringe: 140 mg/mL Single-dose pre-filled autoinjector: 140 mg/mL Single-dose pre-filled cartridge with on-body infusor: 420 mg/3.5 mL	SC	Established ASCVD or primary hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly HoFH: 420 mg once monthly	The safety and efficacy of evolocumab in combination with diet and other LDL-C lowering therapies in adolescents with HoFH were established based on data from a 12-week, PC trial that included 10 adolescents (ages 13 to 17 years old) with HoFH. Safety and effectiveness have not been established in pediatric patients with HoFH who are younger than 13 years old.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Safety and effectiveness have not been established in pediatric patients with primary hyperlipidemia or HeFH.

See the current prescribing information for full details

CONCLUSION

- CVD is the leading cause of death worldwide *(AHA 2020)*. Serum cholesterol is known to be related to ASCVD, with LDL-C being the dominant form of atherogenic cholesterol *(Grundy et al 2019).*
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit PCSK9, leading to substantial LDL-C reduction *(Navarese et al 2015*). The PCSK9 inhibitors are administered SC every 2 weeks or once monthly.
  - Alirocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C and to reduce the risk of MI, stroke, and UA requiring hospitalization in adults with established CVD.
  - Evolocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; as an adjunct to diet and other LLTs (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C; and to reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD.
- The efficacy and safety of alirocumab and evolocumab have been demonstrated across numerous clinical trials in various patient populations. The PCSK9 inhibitors offer substantial LDL-C lowering, and both have been shown to reduce CV events in high-risk patients, although benefit on mortality is still unclear.
- Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
  - Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, rates of overall AEs, serious AEs, and neurocognitive AEs among these patients were similar to those among the overall group. The long-term effects of very low LDL-C levels by alirocumab or evolocumab are still unknown.
- Current guidelines from the ACC/AHA *(Grundy et al 2019)*, AACE/ACE *(Handelsman et al 2020)*, and the NLA *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy, with ezetimibe and the PCSK9 inhibitors as potential second-line agents for patients not achieving adequate LDL-C lowering. Patients with ASCVD or at high risk for ASCVD may benefit from more aggressive LDL-C targets; however, there is no consensus on goal LDL-C levels.

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

INTRODUCTION

- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin *(American Diabetes Association [ADA] 2020[a]).*
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency; 2) Type 2 diabetes (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance; 3) Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation; and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) *(ADA 2020[b]).*
- In 2018, an estimated 34.2 million people, or 10.5%, of the United States (US) population had diabetes mellitus, with 7.3 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2020).*
- The insulin products are approved for use in the management of both T1DM and T2DM. Other pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β-cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis *(Powers 2018)*.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the US. These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain *(Powers 2018)*. Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
  - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units (U) per milliliter (U-200). In September 2017, Fiasp (insulin aspart) was approved *(Drugs@FDA 2020).* Fiasp is a new formulation of Novolog that contains niacinamide. Niacinamide helps to increase the speed of initial insulin absorption, resulting in an onset of appearance in the blood in an estimated 2.5 minutes. Additionally, in December 2017, Admelog (insulin lispro) was the first short-acting insulin approved as a "follow-on" product through the Food and Drug Administration's (FDA) abbreviated 505(b)(2) pathway *(FDA news release 2017).* A novel formulation of insulin lispro, Lyumjev (insulin lispro-aabc) was also approved in June 2020 (*Drugs@FDA 2020*). Lyumjev is a new formulation of Humalog with a quicker onset; appearance in the blood occurs approximately 1 minute after injection of Lyumjev (*Eli Lilly press release 2020, Lyumjev prescribing information 2020*).
  - Basal insulin products, also known as intermediate- or long-acting insulin, include neutral protamine Hagedorn (NPH) isophane, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a formulation of insulin glargine that provides 300 U of insulin glargine per mL and enables patients to utilize a higher dose in one injection (U-300). Additionally, Basaglar and Semglee (insulin glargine) were FDA approved via new drug applications (NDAs) under the 505(b)(2) pathway. As of March 2020, the NDA for Semglee was automatically

deemed to be a biologic licensing application (BLA) via section 351(a) via the Biologics Price Competition and Innovation Act *(Fierce Biotech FDA press release 2015, Drugs@FDA 2020, Hagen 2020).*

- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen, Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics, while the rest of the insulin products do not have a generic (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*). Of note, insulin products are available by prescription, as well as over-the-counter (OTC) (short- and intermediate-acting products only).
- This review will focus on the insulin preparations and combination insulin/GLP-1 agonist products outlined in Table 1 for their respective FDA-approved indications. FDA-approved products that do not have upcoming launch plans, such as Ryzodeg 70/30 (insulin degludec/insulin aspart), have been excluded from this review *(Novo Nordisk 2015*).
- Medispan Class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Rapid-Acting Insulins	
Admelog, Admelog SoloStar (insulin lispro)	-
Afrezza (insulin human) inhalation powder	-
Apidra, Apidra SoloStar (insulin glulisine)	-
Fiasp, Fiasp FlexTouch, Fiasp PenFill (insulin aspart)	-
Humalog, Humalog KwikPen, Humalog Junior KwikPen, Humalog Tempo Pen (insulin lispro)	✔ *
Lyumjev (insulin lispro-aabc)	-
Novolog, Novolog PenFill, Novolog FlexPen (insulin aspart)	✔ **
Short-Acting Insulins	
Humulin R (insulin, regular, human recombinant)	-
Humulin R U-500, Humulin R U-500 KwikPen (insulin, regular, human recombinant)	-
Novolin R, Novolin R FlexPen, Novolin R ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N FlexPen, Novolin N ReliOn (insulin, NPH human recombinant isophane)	-
Long-Acting Insulins	
Basaglar (insulin glargine)	-
Lantus, Lantus SoloStar (insulin glargine)	-
Levemir, Levemir FlexTouch (insulin detemir)	-
Semglee (insulin glargine)	-
Toujeo SoloStar, Toujeo Max SoloStar (insulin glargine U-300)	-
Tresiba, Tresiba FlexTouch (insulin degludec)	-
Combination Insulins, Rapid-Acting and Intermediate-Acting	
Humalog Mix 50/50, Humalog Mix 50/50 KwikPen (50% insulin lispro protamine/50% insulin lispro)	-
Humalog Mix 75/25, Humalog Mix 75/25 KwikPen (75% insulin lispro protamine/25% insulin lispro)	-
Novolog Mix 70/30, Novolog Mix 70/30 FlexPen, Novolog 70/30 PenFill (70% insulin aspart protamine/30% insulin aspart)	✔ **
Combination Insulins, Short-Acting and Intermediate-Acting	

Drug	Generic Availability
Humulin 70/30, Humulin 70/30 KwikPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Novolin 70/30, Novolin 70/30 ReliOn, Novolin 70/30 FlexPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Combination, Long-Acting Insulin and GLP-1 Receptor Agonist	
Soliqua 100/33 (insulin glargine/lixisenatide)	-
Xultophy 100/3.6 (insulin degludec/liraglutide)	-

*Eli Lilly launched an authorized generic of Humalog (vial and KwikPen) through its subsidiary, ImClone Systems (*Lilly 2019[a], Lilly 2019[b]*).
**Novo Nordisk launched an authorized generic of Novolog (vial, Penfil, and FlexPen) and Novolog Mix (vial and FlexPen) through its affiliate, Novo Nordisk Pharma Inc (*Novo Nordisk 2019*).

(Drugs@FDA 2020)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Insulins

Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins			
Admelog (insulin lispro)			✔
Afrezza (insulin human)		✔ §	
Apidra (insulin glulisine)			✔
Fiasp (insulin aspart)			✔
Humalog (insulin lispro)			✔
Lyumjev (insulin lispro-aabc)		✔ #	
Novolog (insulin aspart)			✔
Short-Acting Insulins			
Humulin R (insulin, regular, human recombinant)			✔ *
Novolin R (insulin, regular, human recombinant)			✔
Intermediate-Acting Insulins			
Humulin N (insulin, NPH human recombinant isophane)			✔
Novolin N (insulin, NPH human recombinant isophane)			✔
Long-Acting Insulins			
Basaglar (insulin glargine)			✔ ‡
Lantus (insulin glargine)			✔ ‡
Levemir (insulin detemir)			✔ †
Semglee (insulin glargine)			✔ †‡¶
Toujeo (insulin glargine U-300)			✔ †¶
Tresiba (insulin degludec)			✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	✔		
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)		✔	

Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Combination Insulins, Short-Acting and Intermediate-Acting			
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)		✔	
Novolin 70/30 (NPH, human insulin isophane/regular human insulin)			✔

* Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units.
† Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.
‡ Not indicated for children with T2DM.
§ Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.
‖ Indicated for patients 1 year of age and older with diabetes mellitus; the U-100 vial is recommended for pediatric patients requiring < 5 units daily.
¶ Indicated for patients 6 years and older with diabetes mellitus.
#Should generally be used in regimens with an intermediate or long-acting insulin.

(Prescribing information: Admelog 2019, Afrezza 2018, Apidra 2019, Basaglar 2019, Fiasp 2019, Humalog 2019, Humalog Mix 50/50 2019, Humalog Mix 75/25 2019, Humulin 70/30 2019, Humulin N 2019, Humulin R U-100 2019, Humulin R U-500 2019, Lantus 2019, Levemir 2020, Lyumjev 2020, Novolin 70/30 2019, Novolin N 2019, Novolin R 2019, Novolog 2019, Novolog Mix 70/30 2019, Semglee 2020, Toujeo 2019, Tresiba 2019)

Table 3. Food and Drug Administration Approved Indications – Insulins and GLP-1 Receptor Agonists

Indication	**Soliqua** (insulin glargine/ lixisenatide)	**Xultophy** (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	--
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(*Prescribing information: Soliqua 2020, Xultophy 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Rapid- and Short-Acting Insulins

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A number of comparative effectiveness reviews revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(Fullerton et al 2018, Plank et al 2005).* In patients with T1DM, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrated similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with T1DM and T2DM *(Dailey et al 2004, Garg et al 2005, Melo et al 2019, Nørgaard et al 2018, Rayman et al 2007).*
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with T1DM or T2DM *(Anderson et al 1997a, Chen et al 2006, Dailey et al 2004, Melo et al 2019, Nørgaard et al 2018, Raskin et al 2000, Vignati et al 1997).* Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin *(Anderson et al 1997b, Bretzel et al 2004, Chen et al 2006, Colquitt et al 2003, Dailey et al 2004, Fairchild et al 2000, Fullerton et al 2016, Fullerton et al 2018, Garg et al 2005, Home et al 2006, McSorley et al 2002, Mortensen et al 2006, Plank et al 2005, Raskin et al 2000, Vignati et al 1997).* One large trial of patients with T1DM reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin ($p < 0.001$) *(Anderson et al 1997a).* In another trial, a significantly lower frequency of nocturnal hypoglycemia was reported in patients with T2DM patients with insulin glulisine compared to regular insulin (9.1% vs 14.5%; $p = 0.029$) *(Rayman et al 2007).* A meta-analysis (MA) comparing rapid-acting agents with regular insulin in patients with T1DM found that rapid-acting agents are associated with less total hypoglycemic episodes (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.87 to 0.99), nocturnal hypoglycemia (RR, 0.55; 95% CI, 0.40 to 0.76), severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), post-prandial glucose (PPG) (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39), and lower HbA1c (MD, -0.13%; 95% CI, -0.16 to -0.10) (*Melo et al 2019).* In contrast, in a Cochrane review comparing rapid-acting insulins with regular insulin in adult, non-pregnant patients with T2DM, no clear significant differences were found between the groups for all-cause mortality or hypoglycemia events (*Fullerton et al 2018*).
- Afrezza was evaluated in both T1DM and T2DM patients; in a 24-week open-label (OL), active-controlled (AC), non-inferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or insulin aspart. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were significantly less with Afrezza compared to insulin aspart and fewer Afrezza patients achieved a HbA1c target of < 7% *(Bode et al 2015).* T2DM patients inadequately controlled on oral antidiabetic agents (OADs) were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo *(Rosenstock et al 2015[a]).* Afrezza was also compared to insulin lispro in a 16-week randomized-controlled trial (RCT) including 138 patients with T1DM. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline. PPG 90 minutes after a meal was significantly lower with Afrezza vs insulin lispro but the between-group difference diminished thereafter (*McGill et al 2020*).
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and post meal) to Novolog in patients with T1DM. Both mealtime and post meal Fiasp were demonstrated to be non-inferior to Novolog in change in HbA1c (Estimated treatment difference [ETD], -0.15; $p < 0.0001$; ETD 0.04%; $p < 0.0001$, respectively) *(Russell-Jones et al 2017)*. Onset 2 was a 26-week, Phase 3, DB, AC, RCT in T2DM patients on insulin and OADs. Patients were randomized to receive mealtime Fiasp (n = 345) or Novolog (n = 344). Fiasp demonstrated non-inferiority to Novolog in HbA1c lowering (ETD -0.02%; $p < 0.0001$) *(Bowering et al 2017)*. Onset 3 was an 18-week, Phase 3, OL, RCT in T2DM patients inadequately controlled on basal insulin and OADs. Patients were randomized to receive mealtime Fiasp + basal insulin (n = 116), or basal insulin alone (n = 120). The addition of Fiasp to basal insulin demonstrated superior HbA1c lowering from baseline (ETD -0.94%; $p < 0.0001$ for superiority) and significantly more patients achieved an HbA1c < 7.0% (60.3% vs 18.3%; OR, 9.31; $p < 0.0001$); however, with the addition of Fiasp, there was an increase in the frequency of severe or blood glucose-confirmed hypoglycemic episodes (RR, 8.24; $p < 0.0001$) and modest weight gain *(Rodbard et al 2017[b])*. Onset 9 was a 16-week RCT in adults with T2DM inadequately controlled on a basal-bolus insulin regimen. Patients were randomized to receive mealtime Fiasp + insulin degludec with or without metformin (n = 546) or Novolog + insulin degludec with or without metformin (n = 545). Change in HbA1c in Fiasp-treated patients was found to be non-inferior to Novolog-treated patients (ETD, -0.04%; 95% CI, -0.11 to 0.03). Fiasp demonstrated superior reduction in 1-hour PPG increment vs Novolog ($p = 0.001$), but differences at 2, 3, and 4 hours were not significant between groups. Treatment-emergent severe hypoglycemia or blood

glucose confirmed hypoglycemia was significantly lower with Fiasp vs Novolog (estimated treatment ratio, 0.81; 95% CI, 0.68 to 0.97) (*Lane et al 2020*).

- In 2020, Fiasp's indication was expanded to include children with diabetes based on results from the Onset 7 Trial *(Bode et al 2019*). This trial demonstrated non-inferiority of Fiasp to Novolog in 519 patients 1 to 17 years of age with T1DM. The estimated change from baseline to week 26 in HbA1c at meal time was −0.17% (95% CI −0.30 to −0.03) and post meal it was 0.13% (95% CI, −0.01 to 0.26); the change from baseline in HbA1c at meal time was statistically significant between groups in favor of Fiasp.
- The safety and efficacy of Admelog, the first "follow-on" rapid-acting insulin, were evaluated in two 26-week, Phase 3, OL, parallel group, RCTs in both T1DM (N = 506) (SORELLA 1; *Garg et al 2017)* and T2DM (N = 505) patients (SORELLA 2; *Derwahl et al 2018).* Patients were randomized to receive Admelog or its reference product, Humalog. Change in HbA1c in Admelog-treated patients was found to be non-inferior in both trials (SORELLA 1: least squares mean difference [LSMD], 0.06%; 95% CI, -0.084 to 0.197; SORELLA 2: LSMD, -0.07%; 95% CI, -0.215 to 0.067). Rates of hypoglycemia were similar between the treatment arms in both trials.
- The safety and efficacy of Lyumjev were evaluated in two 26-week, Phase 3, DB/OL, PG, RCTs in both T1DM (N = 1222) (PRONTO-T1D) and T2DM (N = 673) patients (PRONTO-T2D). Patients were randomized to receive Lyumjev or Humalog. The change in HbA1c for Lyumjev-treated patients was found to be noninferior in both trials (PRONTO-T1D: mealtime Lyumjev: estimated treatment difference [ETD], -0.08%; 95% CI, -0.16 to 0.00; p = 0.06 for noninferiority; post meal Lyumjev: ETD, +0.13%; 95% CI,0.04 to 0.22; p = 0.003 for noninferiority; PRONTO-T2D: mealtime Lyumjev: ETD, 0.06%; 95% CI, -0.05 to 0.16; noninferiority). Lyumjev significantly lowered PPG 1- and 2-hours post dose compared to Humalog. Rates of hypoglycemia were similar between the treatment arms in both trials *(Blevins et al 2020, Klaff et al 2020)*.
- Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA1c, achieving similar self-monitored glucose profiles, rates of hypoglycemia, and achieving glycemic goals in patients with T1DM *(Dreyer et al 2005, Philotheou et al 2011, Van Ban et al 2011).*

Long-Acting Insulins

- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in adults, adolescents, and children with T1DM and T2DM as demonstrated by the results of several active-comparator trials and MAs *(Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, Danne et al 2013, De Leeuw et al 2005, Fritsche et al 2003, Garber et al 2007, Haak et al 2005, Heller et al 2009, Hermansen et al 2004, Hermansen et al 2006, Herwig et al 2007, Home et al 2004, Horvath et al 2007, Kølendorf et al 2006, Lee et al 2012, Montañana et al 2008, Pan et al 2007, Pieber et al 2005, Philis-Tsimikas et al 2006, Raslová et al 2007, Ratner et al 2000, Riddle et al 2003, Robertson et al 2007, Rosenstock et al 2005, Russell-Jones et al 2004, Schober et al 2002, Siegmund et al 2007, Standl et al 2004, Tan et al 2004, Tricco et al 2014, Vague et al 2003, Yenigun et al 2009, Yki-Järvinen et al 2000, Yki-Järvinen et al 2006).*
- The safety and efficacy of the long-acting analog Toujeo (insulin glargine U-300) have been compared to that of Lantus (insulin glargine U-100) in OL, randomized, AC, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose with Toujeo were found to be similar to that of Lantus, including patients aged ≥ 65 years *(Home et al 2018, Bolli et al 2015, Home et al 2015, Riddle et al 2014[b], Ritzel et al 2018, Yki-Järvinen et al 2014).*
- A 2018 MA comparing Toujeo with Lantus in patients with T1DM and T2DM found that Toujeo was associated with a reduced risk of nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.69 to 0.95) and a slight benefit in HbA1 reduction (effect size, -0.08; 95% CI, -0.14 to -0.01) (*Diez-Fernandez et al 2019*).
- Tresiba (insulin degludec) was evaluated in more than 5,600 T1DM and T2DM patients throughout 9 pivotal studies and 5 extension studies (BEGIN clinical program).
  - In 8 of the pivotal trials, Tresiba was non-inferior to Lantus (insulin glargine U-100) or Levemir (insulin detemir) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in 5 trials, the rate of nocturnal hypoglycemia was significantly lower with Tresiba compared to Lantus or Levemir *(Davies et al 2014, Garber et al 2012, Gough et al 2013, Heller et al 2012, Mathieu et al 2013, Meneghini et al 2013[a], Onishi et al 2013, Zinman et al 2012).* It is noteworthy that 2 of the 8 Tresiba trials resulted in a nominally lower reduction in HbA1c for Tresiba compared to the active comparator basal insulin agents *(Davies et al 2014, Heller et al 2012).* The HbA1c and hypoglycemia trends were also observed in the published extension trials *(Bode et al 2013, Davies et al 2016, Hollander et al 2015, Rodbard et al 2013).* In the ninth pivotal trial, Tresiba lowered HbA1c significantly more than oral sitagliptin 100 mg

once daily in patients with T2DM who were receiving 1 or 2 concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; p < 0.001), but there were significantly more episodes of overall confirmed hypoglycemia (p < 0.0001) *(Philis-Tsimikas et al 2013).*
    - Across the BEGIN trials, a consistently increased risk of major adverse cardiovascular events (MACE) was observed with Tresiba. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified MA of MACE, which included a pooled analysis of 8,068 patients from 16 Phase 3 trials conducted for Tresiba monotherapy and insulin degludec/insulin aspart (Ryzodeg). According to the 2012 analysis, there was a consistent trend towards harm in the pooled insulin degludec groups compared to active comparators (hazard ratio [HR], 1.67; 95% CI, 1.01 to 2.75). Additional post-hoc analyses consistently trended towards harm regardless of endpoint, effect measure, analysis method, and subgroup analyses *(FDA Briefing Document 2012, Novo Nordisk Briefing Document 2012).*
    - The large, DB, active-comparator DEVOTE trial was subsequently initiated to prospectively and rigorously compare the cardiovascular (CV) safety of Tresiba to Lantus in patients with T2DM at high risk for CV events. The primary composite endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke occurred in 8.5% of the Tresiba group and 9.3% of the Lantus group (HR, 0.91; 95% CI, 0.78 to 1.06; p < 0.001 for non-inferiority), confirming non-inferiority of Tresiba to Lantus in terms of CV safety. Tresiba also demonstrated statistically significantly lower rates of severe hypoglycemia (odds ratio [OR] for severe hypoglycemic events, 0.73; 95% CI, 0.60 to 0.89; p < 0.001 for superiority) *(Marso et al 2017).*
- The efficacy of Tresiba vs Lantus in reducing the rate of symptomatic hypoglycemic episodes in patients with T1DM and T2DM was examined in the SWITCH 1 and SWITCH 2 trials, respectively. These 65-week, DB, crossover trials enrolled patients with hypoglycemia risk factors to receive Tresiba or Lantus. In both trials, Tresiba was found to cause fewer symptomatic hypoglycemic episodes (SWITCH 1: estimated rate ratio [ERR], 0.89; p < 0.001; SWITCH 2: ERR, 0.70; p < 0.001) and nocturnal hypoglycemic episodes (SWITCH 1: ERR, 0.64; p < 0.001; SWITCH 2: ERR, 0.58; p < 0.001) during the maintenance period than Lantus *(Lane et al 2017, Wysham et al 2017)*.
- A MA of 18 trials with 16,791 patients compared the safety and efficacy of Tresiba to Lantus, and similarly found that Tresiba was associated with a significant reduction in risk for all confirmed hypoglycemia during the maintenance treatment period (ERR, 0.81; 95% CI, 0.72 to 0.92; p=0.001), nocturnal confirmed hypoglycemia during the entire (ERR, 0.71; 95% CI, 0.63 to 0.80; p,0.001) and maintenance treatment periods (ERR, 0.65; 95% CI, 0.59 to 0.71; p,0.001), and a significantly lower fasting plasma glucose level (ETD -0.28 mmol/L; 95% CI, -0.44 to -0.11 mmol/L; p=0.001). Tresiba was found to reduce the incidence of severe hypoglycemia in patients with T2D, but not T1D (*Zhang et al 2018)*.
- A MA of 15 trials with 16,694 patients that compared Tresiba to Lantus found that Tresiba was associated with improved mean reduction in fasting plasma glucose (weighted mean difference, -5.2 mg/dL; 95% CI, -7.34 to -3.07; p < 0.00001) and less nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.75 to 0.88; p < 0.0001). However, fewer patients achieved HbA1c ≤ 7% with Tresiba compared with Lantus (RR, 0.92; 95% CI, 0.86 to 0.98; p = 0.01). The MA showed no statistically significant differences between Tresiba and Lantus for HbA1c reduction, body weight gain, and serious adverse events (AEs) (*Zhou et al 2019*).
- Additionally, Tresiba was evaluated for safety and efficacy in pediatric patients (ages 1 to 17) (N = 350) with T1DM in a 26-week, randomized, OL trial. Tresiba was non-inferior to Lantus with a difference in HbA1c reduction from baseline of 0.15% (95% CI, -0.03 to 0.33%) between the groups (pre-specified non-inferiority margin, 0.4%) *(Tresiba prescribing information 2016).*
- The safety and efficacy of Basaglar (insulin glargine U-100) compared to Lantus (insulin glargine U-100) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with T1DM (ELEMENT 1 trial) and T2DM (ELEMENT 2 trial), respectively. Both trials were multicenter (MC), parallel group, RCTs; ELEMENT 1 was OL and ELEMENT 2 was DB. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. OAD medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in HbA1c from baseline to 24 weeks. In both ELEMENT 1 and ELEMENT 2, Basaglar and Lantus had similar and significant (p < 0.001) within-group decreases in HbA1c values from baseline. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs -0.46%, respectively; LSMD, 0.108%; 95% CI, -0.002 to 0.219; p > 0.05; ELEMENT 2: -1.29% vs -1.34%, respectively; LSMD, 0.052%; 95% CI, -0.07 to 0.175; p > 0.05). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total, nocturnal, severe) at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 (p > 0.05 for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight

(ELEMENT 1, week 24 and 52: both p > 0.05; ELEMENT 2, week 24: p > 0.05) *(Blevins et al 2015, Rosenstock et al 2015[b]).* Basaglar has also been compared to Lantus when used in combination with OADs in patients with T2DM. ELEMENT 5 was a 24-week trial and included predominately Asian (48%) and White (46%) patients. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks (-1.25% vs -1.22%; LSMD, -0.04%; 95% CI, -0.22 to 0.15). Other 24-week efficacy and safety outcomes were similar between groups (*Pollom et al 2019*).

- The safety and efficacy of Semglee and reference insulin glargine were compared in 2 OL RCTs enrolling 558 (INSTRIDE 1; *Blevins et al 2018*) and 127 (INSTRIDE 3) patients with T1DM. In both trials, patients also received mealtime insulin lispro. INSTRIDE 1 demonstrated non-inferiority of Semglee to reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.03%; standard error [SE], 0.046; 95% CI, −0.066 to 0.117), as did INSTRIDE 3 from baseline to week 36 (LSMD, 0.01%; 95% CI, -0.08 to 0.101). The safety profile of products did not significantly differ in either trial. Semglee was also compared to reference insulin glargine in 560 patients with T2DM in an OL RCT (INSTRIDE 2). This trial included patients who were insulin-naïve and insulin-non-naïve receiving OADs. Semglee was non-inferior to the reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.06%; 95% CI, -0.10 to 0.22). The safety profile was also similar between products in this trial; (*Blevins et al 2019, Blevins et al 2020[a]*).
- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting insulin analogs head-to-head, several trials have demonstrated non-inferiority among the products when used in the management of T1DM and as add-on therapy in patients with T2DM *(Heller et al 2009, Hollander et al 2008, Pieber et al 2007, Raskin et al 2009, Rosenstock et al 2008, Swinnen et al 2010).*
  - In one head-to-head trial of Lantus and metformin vs Levemir and metformin, Lantus had greater HbA1c lowering, but Levemir demonstrated less weight gain and hypoglycemia *(Meneghini et al 2013[b]).*
  - A 2011 Cochrane review (included 4 trials; N = 2250) concluded that Lantus and Levemir are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events *(Swinnen et al 2011).* A 2018 MA similarly found no differences in HbA1c reduction between insulin degludec, detemir, or glargine in T1DM and T2DM patients, but the incidence of hypoglycemia was less with degludec as compared to glargine (nocturnal hypoglycemia; T1DM: RR, 0.68; 95% CI, 0.56 to 0.81; T2DM: RR, 0.73; 95% CI, 0.65 to 0.82) (*Holmes et al 2018).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (NMA) (included 41 trials, of which 25 trials included patients on basal-oral therapy; N = 15,746) evaluated the safety and efficacy of Toujeo (insulin glargine U-300) vs other basal insulin therapies in the treatment of T2DM. The authors found that the change in HbA1c was comparable between Toujeo and Levemir (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and Tresiba (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events *(Freemantle et al 2016).*
  - The safety of Tresiba was compared to Toujeo in the 2019 CONCLUDE trial that included 1609 patients with T2DM. In this trial, the rate of overall symptomatic hypoglycemia, the primary endpoint, was similar between Tresiba and Toujeo (RR, 0.88; 95%, CI 0.73 to 1.06). However, the rates of nocturnal symptomatic hypoglycemia and severe hypoglycemia (both of which were exploratory endpoints) were lower with Tresiba vs Toujeo (RR, 0.63; 95% CI, 0.48 to 0.84 and RR, 0.20; 95% CI 0.07 to 0.57, respectively) (*Philis-Tsimikas et al 2020*).
- In 2019, Toujeo's indication was expanded to include children with diabetes mellitus as young as 6 years of age based on results of the EDITION JUNIOR trial. In this study, Toujeo demonstrated non-inferiority to Lantus for the primary endpoint of change in HbA1c from baseline to week 26 (mean reduction, 0.4% in both groups; 95% CI, –0.17 to 0.18) with comparable numbers of patients experiencing ≥ 1 episode of hypoglycemia *(Danne et al 2019).*

Combination Insulins

- A direct comparative trial evaluating 2 types of premixed biphasic insulin (insulin lispro 50/50 and insulin aspart 70/30) demonstrated similar results in terms of reducing HbA1c *(Domeki et al 2014).* Another trial comparing biphasic insulin to basal plus prandial insulin in T2DM demonstrated that basal plus prandial insulin therapy was slightly more effective than premixed insulin with less hypoglycemia *(Riddle et al 2014[a]).*

Other Evidence

- A systematic review (SR) that included 11 studies and compared the efficacy and safety of biosimilar insulins (Basaglar and Admelog) to their reference products found comparable pharmacokinetic and/or pharmacodynamic parameters, clinical efficacy and immunogenicity, and AEs between the biosimilar agents and their reference products (*Tieu et al 2018)*. Similar conclusions were made in a 2020 SR (*Ampudia-Blasco 2020).*
- Insulin therapies have been compared to GLP-1 agonists with mixed study results. A study comparing glycemic control with Lantus vs exenatide demonstrated that better glycemic control was sustained with exenatide *(Diamant et al 2012).* Other studies have demonstrated that GLP-1 agonists are statistically non-inferior to Lantus for change in HbA1c *(Inagaki et al 2012, Weissman et al 2014).* Studies comparing the addition of GLP-1 agonists to Lantus were found to be non-inferior to the addition of thrice daily insulin lispro to Lantus *(Diamant et al 2014, Rosenstock et al 2014, Rosenstock et al 2020).*
- In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy (DCCT 1993, UKPDS 1998). Neither trial indicated the specific insulin formulations utilized; however, in the UKPDS, the risk reduction in microvascular complications was related more toward tight glycemic control rather than to one specific therapy (UKPDS, 1998).

Combination Products: Long-Acting Insulin and GLP-1 Receptor Agonist

- A 2017 SR and MA evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai et al 2017*). The analysis included 8 trials. The absolute HbA1c change relative to baseline with insulin glargine/lixisenatide was -1.50% and -1.89% with insulin degludec/liraglutide; comparisons between the groups revealed no significant differences. Additionally, there was no significant difference between the groups with regard to body weight changes.

Soliqua (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in 2 Phase 3, AC, OL, RCTs, titled the LIXILAN trials:
  - T2DM patients uncontrolled on basal insulin:
    - The LIXILAN-L trial was a 2-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least 6 months at stable daily doses ± OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (n = 366) or insulin glargine 100 U/mL (n = 365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the LSMD between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, −0.5%; 95% CI, −0.6 to −0.4; p < 0.0001) *(Aroda et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
    - A 2020 MA including 8 RCTs (N = 3828) compared insulin glargine/lixisenatide to other treatment intensification strategies in people whose T2DM was inadequately controlled (*Home et al 2020*). The estimated difference in HbA1c reduction with insulin glargine/lixisenatide vs premixed insulin, three times daily mealtime insulin + basal insulin, and once daily mealtime insulin + basal insulin was -0.50 %-units (95% CI, -0.93 to -0.06), -0.35 %-units (-95% CI, -0.89 to 0.13) and -0.68 %-units (95% CI, -1.18 to -0.17), respectively. Safety was similar or improved with insulin glargine/lixisenatide vs other insulin regimens.
  - Comparative data vs GLP-1 receptor agonists: The LIXILAN-O trial was a 3-treatment arm study in 1167 patients with T2DM who were inadequately controlled on metformin ± OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (n = 468), insulin glargine 100 U/mL (n = 466), or lixisenatide (n = 233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, −0.3%; 95% CI, −0.4 to −0.2; p < 0.0001) and also demonstrated superiority for the endpoint (p < 0.0001). At week 30, the LSMD in HbA1c reduction between insulin glargine/lixisenatide and lixisenatide was also statistically significant (LSMD, −0.8%; 95% CI, −0.9 to −0.7; p < 0.0001) *(Rosenstock et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
  - Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin

glargine/lixisenatide and insulin glargine; however, fewer lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs 25.6%, respectively) *(Aroda et al 2016, Rosenstock et al 2016, FDA summary review [Soliqua] 2016).*

Xultophy (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in 9 Phase 3, parallel-group, AC, RCTs, titled the DUAL trials *(Xultophy dossier 2016).*
  - T2DM patients uncontrolled on basal insulin and/or OADs:
    - The DUAL I trial was a 3-treatment arm, OL study in 1,663 T2DM patients that compared fixed-dose combination of insulin degludec/liraglutide (n = 834) to insulin degludec (n = 414) and liraglutide (n = 415) components. Prior to randomization, patients were receiving metformin ± pioglitazone. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for fixed-dose combination insulin degludec/liraglutide, -1.4% for insulin degludec, and -1.2% for liraglutide. The ETD for HbA1c showed that the fixed-dose combination insulin degludec/liraglutide is non-inferior to insulin degludec (ETD, -0.47%; 95% CI -0.58 to -0.36; p < 0.0001) and superior to liraglutide (ETD, -0.64%; 95% CI, -0.75 to -0.53, p < 0.0001) (*Gough et al 2014*).
    - The DUAL II trial was a 2-treatment arm, DB study in 413 T2DM patients that compared insulin degludec/liraglutide (n = 207) to insulin degludec (n = 206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; p < 0.0001) *(Buse et al 2014).*
    - The DUAL IV trial was a DB study in 435 T2DM patients that compared insulin degludec/liraglutide (n = 289) to placebo (n = 146). Prior to randomization, uncontrolled patients were receiving sulfonylurea ± metformin. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -0.5% for placebo. The ETD for HbA1c statistically favored insulin degludec/liraglutide over placebo (ETD, -1.02%; 95% CI, -1.18 to -0.87; p < 0.001) (*Rodbard et al 2017[a]*).
    - The DUAL V trial was a 2-treatment arm, OL, non-inferiority study in 557 T2DM patients that compared insulin degludec/liraglutide (n = 278) to insulin glargine (n = 279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI < 0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; p < 0.001 for non-inferiority) *(Lingvay et al 2016).*
    - The DUAL VI trial was a 32-week, OL, non-inferiority study in 420 T2DM patients that compared insulin degludec/liraglutide titrated once weekly (n = 210) to insulin degludec/liraglutide titrated twice weekly (n = 210). Prior to randomization, patients were receiving metformin ± pioglitazone. The mean HbA1c reduction from baseline after 32 weeks was -2% with once-weekly titration and -2% with twice-weekly titration. The ETD revealed a non-inferiority between the 2 treatment regimens (ETD, 0.12%; 95% CI -0.04 to 0.28) (*Harris et al 2017*).
    - The DUAL VII trial was a 2-treatment, OL study in 506 T2DM patients that compared insulin degludec/liraglutide (n = 252) to insulin glargine + insulin aspart (n = 254). Prior to randomization, patients were receiving metformin and insulin glargine. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -1.5% for insulin glargine with insulin aspart. The ETD revealed non-inferiority between the 2 treatments (ETD, -0.02%; 95% CI -0.16 to 0.12) (*Billings et al 2018*).
    - The DUAL VIII trial was a 26-week, OL, randomized study in patients with T2DM that compared once daily insulin degludec/liraglutide (n=506) with insulin glargine (n=506) (*Aroda et al 2019*). Prior to randomization, patients were uncontrolled on stable doses of oral antidiabetic agents. Results demonstrated that patients who received insulin degludec/liraglutide had a longer time to initiation of therapy intensification (met when HbA1c was ≥ 7% at 2 consecutive visits after 26 weeks of treatment) compared to insulin glargine (>2 years vs 1 year).
    - The DUAL IX trial was a 26-week, OL, randomized study that compared once daily insulin degludec/liraglutide (n=210) with insulin glargine (n=210) in patients with T2DM uncontrolled with SGLT2 inhibitors (*Philis-Tsimikas et*

al 2019). The results of this study demonstrated that treatment with insulin degludec/liraglutide was non-inferior to insulin glargine with respect to the primary outcome of change in HbA1c from baseline to week 26 (-1.9% and -1.7%, respectively). In a confirmatory analysis, insulin degludec/liraglutide was also found superior to insulin glargine for the primary outcome with an estimated treatment difference of -0.36% (95% CI, -0.50 to -0.21).

- T2DM patients uncontrolled on GLP-1 receptor agonists:
  - The DUAL III trial was a 2-treatment arm, OL study in 438 T2DM patients that compared insulin degludec/liraglutide (n = 292) to the currently administered maximum dose of GLP-1 receptor agonist (n = 146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; p < 0.001) *(Linjawi et al 2017).*
- Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However, compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; p < 0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine with a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; p < 0.001) *(Buse et al 2014, Lingvay et al 2016, Linjawi et al 2017, Xultophy dossier 2016).*

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous MI, stroke, angina, or revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary outcomes of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (HR, 1.02; 95% CI, 0.94 to 1.11; p = 0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; p = 0.27) *(Gerstein et al 2012).*
  - ELIXA, a MC, DB, randomized, placebo-controlled (PC) trial (N = 6068) was conducted to evaluate the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups *(Pfeffer et al 2015)*.
  - LEADER, a MC, DB, randomized, PC trial (N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, nonfatal MI, or nonfatal stroke) occurred in fewer patients in the liraglutide group (13%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for non-inferiority; p = 0.01 for superiority). Mortality from CV causes was lower in the liraglutide group (4.7%) vs the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). Additionally, the rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group *(Marso et al 2016).*

CLINICAL GUIDELINES

- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. Either multiple daily injections or a continuous infusion can be considered, with some recent data demonstrating modest advantages with pump therapy such as increased HbA1c lowering and reduced severe hypoglycemia rates. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2020[b], Chiang et al 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2020[b], Buse et al 2020, Garber et al 2020, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2020[b], Buse et al 2020, Garber et al 2020, Handelsman et al 2015).*
  - The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACA) T2DM management algorithm identifies lifestyle therapies such as weight loss, comprehensive management of lipids and blood pressure, safety, and simplicity as crucial factors of a T2DM regimen. The guideline notes that patients are unlikely to achieve glycemic targets with a third oral antihyperglycemic agent if their HbA1c level is > 8% or in those with long-standing disease. A GLP-1 agent may be considered, but many patients will eventually require insulin. The guideline suggests basal (long-acting) insulin for those who are symptomatic with an entry HbA1c > 9.0%. Basal insulin analogs are preferred over NPH. If an intensified regimen is needed, the addition of a GLP-1 agonist, SGLT2 inhibitor, or DPP-4 inhibitor can be considered. The combination of basal insulin with a GLP-1 receptor agonist may offer greater efficacy than the oral agents. Prandial (rapid-acting) insulin prior to meals can be considered when the total daily dose of basal insulin exceeds 0.5 U/kg *(Garber et al 2020).*
    - The guideline also states that newer basal insulin formulations (glargine U-300, and degludec U-100 and U-200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U-100 and detemir. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, compared to glargine U-100 and detemir insulin; however, no recommendation for specific insulin products is given.
  - The ADA and European Association for the Study of Diabetes (EASD) offer similar emphasis on lifestyle modifications and CV disease risk management. In the 2020 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. The ADA guideline states that insulin therapy (with or without additional agents) should be initiated in patients with newly diagnosed T2DM with evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (≥ 10%) or blood glucose levels (≥ 300 mg/dL) are very high. The ADA and EASD recommend that, in most patients who require an injectable therapy, a GLP-1 agonist should be the first choice ahead of insulin. For patients with T2DM and established ASCVD, the level of evidence for MACE benefit is greatest for GLP-1 agonists. GLP-1 agonists are also suggested for patients without CVD but with indicators of high risk. Due to the progressive nature of the disease, patients may eventually require insulin therapy (*ADA 2020[b], Buse et al 2020)*.
    - Certain patient factors can influence the choice of insulin therapy. For patients with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), insulin therapies with demonstrated CV disease safety (degludec and glargine U-100) should be considered. For patients with hypoglycemia issues, a basal insulin with lower risk of hypoglycemia should be considered (risk of hypoglycemia: degludec/glargine U-300 < glargine U-100/detemir < NPH).
    - A basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with HbA1c > 10% and/or if the patient is above the target HbA1c by > 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm.
- The American College of Cardiology published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das et al 2020*). For the GLP-1 agonists, albiglutide [discontinued in the US], dulaglutide, liraglutide, and

injectable semaglutide have proven benefits of reducing CV events. Exenatide once weekly and oral semaglutide have demonstrated numerically favorable but not statistically significant reductions in CV events. In contrast, lixisenatide is not associated with a reduction in ASCVD event risk. Thus, both the ACC pathway and ADA guideline consider dulaglutide, liraglutide, and injectable semaglutide as the preferred GLP-1 agents (*ADA 2020[b], Das et al 2020*).

- The Endocrine Society released a guideline for the treatment of diabetes in older adults. The general recommendations focus on selecting treatment that would minimize hypoglycemia in patients 65 years and older with diabetes. The guideline does not provide specific targets. Metformin with lifestyle changes is the preferred initial treatment in patients without significant kidney function impairment. Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin. The guideline advises using insulin sparingly to decrease the risk for hypoglycemia in patients 65 years and older. The addition of a long-acting insulin may be the initial step to control fasting glucose. Insulin degludec and insulin glargine U-300 may cause less hypoglycemia compared to insulin glargine U-100. Older adults typically have more postprandial hyperglycemia rather than fasting hyperglycemia. Therefore, adding a premeal insulin may be more optimal than titrating a long-acting basal insulin in certain cases (*LeRoith et al 2019*).

SAFETY SUMMARY

Insulins

- Contraindications:
  - Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
  - In addition, Afrezza is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.
- Boxed Warnings:
  - Afrezza has a boxed warning for the risk of acute bronchospasm in patients with chronic lung disease. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.
- Warnings/Precautions:
  - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
  - Changes in insulin regimen, including insulin manufacturer, type, strength, injection site, or method of administration, may affect glycemic control and lead to hypoglycemia or hyperglycemia. Frequent glucose monitoring and close medical supervision is recommended when making changes to a patient's insulin regimen.
  - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
  - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
  - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
  - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
  - Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products. If hypersensitivity reactions occur, the insulin product should be discontinued.
  - Administration of Humulin R U-500 in syringes other than U-500 insulin syringes has resulted in dosing errors. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The prescribed dose should always be expressed in units of insulin.
  - Afrezza has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- AEs:
  - Hypoglycemia is the most commonly observed AE. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
  - Weight gain, sodium retention and edema, and injection site reactions can occur.

- Additional AEs observed with the inhaled insulin, Afrezza, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.

- Drug Interactions:
  - β-blockers, clonidine, guanethidine, and reserpine may mask hypoglycemic reactions.
  - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
  - Refer to the prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Contraindications:
  - Both combination agents are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
  - Xultophy (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Warnings/Precautions:
  - Warnings and precautions are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
  - Additional warnings and precautions for Soliqua include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control and a lack of clinical studies showing macrovascular risk reduction. Additional warnings for Xultophy include a potential increased risk for acute gallbladder disease.
- AEs:
  - The most common AEs reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common AEs include hypoglycemia and allergic reactions with Soliqua and increased lipase with Xultophy.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.

DOSING AND ADMINISTRATION

- Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
- Dose adjustments in patients with renal and/or hepatic dysfunction may be required with the insulin products.
- In elderly patients, caution should be taken with initial insulin dosing and subsequent dose changes to avoid hypoglycemic reactions.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Rapid-Acting Insulins				

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Admelog (insulin lispro)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons with a single dosage and in titration packs with multiple dosages	Inhalation	Generally given 3 times daily at the beginning of a meal.	Safety and efficacy in pediatric patients or in renal or hepatic dysfunction have not been established.
Apidra (insulin glulisine)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 4 years with T1DM or in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Fiasp (insulin aspart)	100 U/mL: FlexTouch pen, vial, PenFill cartridges	SC, IV	Administer at the start of a meal or within 20 minutes after starting a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Humalog (insulin lispro)	100 U/mL: cartridge, KwikPen, Junior KwikPen, Tempo Pen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lyumjev (insulin lispro-aabc)	100 U/mL: cartridge, KwikPen, Junior KwikPen, Tempo Pen, vial	SC, IV (U-100 only)	Administer at the start of the meal or within 20 minutes after starting the meal.	Safety and efficacy in children have not been established. Use prefilled pens with caution in patients with visual

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	200 U/mL: KwikPen		Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	impairment who rely on audible clicks to dial their dose.
Novolog (insulin aspart)	100 U/mL: cartridge (PenFill), FlexPen, Vial	SC, IV	Novolog: Should be injected immediately (within 5 to 10 minutes) before a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. Use FlexPen and PenFill cartridges with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Short-Acting Insulins				
Humulin R (insulin, regular, human recombinant)	100 U/mL: cartridge, vial 500 U/mL KwikPen, vial	SC, IV (U-100 only)	When given SC, generally given 3 or more times daily before meals (within 30 minutes). U-500: Generally given 2 to 3 times daily before meals. U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	U-500: well-controlled studies in children not available. Dosing in pediatric patients must be individualized. Dose conversion should not be performed when using the U-500 KwikPen or a U-500 insulin syringe. Only a U-500 insulin syringe should be used with the Humulin U-500 vial. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin R (insulin, regular, human recombinant)	100 U/mL: Vial	SC, IV	Administration should be followed by a meal within 30 minutes of administration. Often used in combination with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM or in children with T2DM have not been established. Use in pumps is not recommended due to risk of precipitation.
Intermediate-Acting Insulins				
Humulin N (insulin, NPH, human recombinant isophane)	100 U/mL: KwikPen, vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	Has not been studied in children. Dosing in pediatric patients must be individualized. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Novolin N (insulin, NPH, human recombinant isophane)	100 U/mL: Vial, Flexpen	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	
Long-Acting Insulins				
Basaglar (insulin glargine)	100 U/mL: KwikPen	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Semglee (insulin glargine)	100 U/mL; prefilled pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use Semglee prefilled pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Levemir (insulin detemir)	100 U/mL: FlexTouch pen, vial	SC	Daily to twice daily Once daily administration should be given with evening meal or at bedtime. Twice daily administration should be given in the morning and then 12 hours later with evening meal or at bedtime.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Toujeo (insulin glargine U-300)	300 U/mL: SoloStar pen, Max SoloStar pen	SC	Daily May be administered at any time of day, but at the same time every day.	To minimize the risk of hypoglycemia, the dose of Toujeo should be titrated no more frequently than every 3 to 4 days. The Toujeo Max SoloStar pen carries 900 U of Toujeo U-300

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				(twice as many as the regular SoloStar pen) and is recommended for patients that require at least 20 U per day Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Tresiba (insulin degludec)	100 U/mL: FlexTouch pen, vial 200 U/mL: FlexTouch pen	SC	Daily May be administered at any time of day (should be same time of day in pediatric patients).	Safety and efficacy in children < 1 year have not been established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days. Pediatric patients requiring < 5 units daily should use the U-100 vial. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically dosed twice daily.	Safety and efficacy in children have not been established. Use Humalog Mix KwikPen and Novolog Mix FlexPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: cartridge, FlexPen, vial	SC	Twice daily T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: KwikPen, vial	SC	Twice daily 30 to 45 minutes before a meal	Safety and efficacy in children have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin 70/30 (NPH, human insulin	100 U/mL: FlexPen, vial	SC	Twice daily 30 to 60 minutes before a meal	

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
isophane/regular human insulin)				
Combination Products, Long-Acting Insulin and GLP-1 Receptor Agonist				
Soliqua 100/33 (insulin glargine/ lixisenatide)	100 U/mL; 33 mcg/mL: SoloStar pen	SC	Once daily within the hour prior to the first meal of the day	The pen delivers doses from 15 to 60 U of insulin glargine with each injection. Not recommended for use in end-stage renal disease (ESRD). Frequent BG monitoring and dose adjustment may be necessary in hepatic impairment.
Xultophy 100/3.6 (insulin degludec/ liraglutide)	100 U/mL; 3.6 mg/mL: pen	SC	Once daily at the same time each day with or without food	The pen delivers doses from 10 to 50 U of insulin degludec with each injection. Has not been studied in patients with hepatic impairment or severe renal impairment. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit
*Dose and frequency of insulin products should be individualized per patient needs.
See the current prescribing information for full details

(Clinical Pharmacology 2020)

CONCLUSION

Insulins

- The insulin products are approved for use in the management of both T1DM and T2DM. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products are classified by their onset and duration of actions and may fall into one of four categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by SC injection, which allows for prolonged absorption and less pain compared to IM injection. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen, Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics or products that contain the same insulin (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*).
- Safety profiles of the injectable rapid-acting insulins are comparable, with the exception of Afrezza, a rapid-acting inhaled insulin. The inhalation route offers a less invasive alternative route of administration and improved convenience of administration compared with injectable rapid-acting insulins. Afrezza has a boxed warning for bronchospasm and is contraindicated in patients with chronic lung disease. Due to this different route of administration, the most common AEs associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation.
- The safety and efficacy of insulin therapy in the management of diabetes are well established. Clinical trials have demonstrated that the newer rapid- and long-acting insulin analogs are as effective as regular and isophane (NPH) insulin in terms of glucose management. The data also suggest that long-acting insulin analogs are superior to NPH in

decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data do not consistently demonstrate the superiority of one rapid- or long-acting insulin analog over another.

- In terms of clinical outcomes, intensive glycemic control with insulin has been shown to significantly reduce the rate of onset and progression of diabetic complications when compared to standard therapy.
- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2020[b], Chiang 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2020[b], Buse 2020, Garber et al 2020, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2020[b], Davies 2018, Garber et al 2020, Handelsman et al 2015).*
- The ADA and EASD recommend that in most patients who require an injectable therapy a GLP-1 agonist should be the first choice, ahead of insulin. For patients with T2DM and established ASCVD, the level of evidence for MACE benefit is greatest for GLP-1 agonists. GLP-1 agonists are also suggested for patients without CVD but with indicators of high risk. Certain patient factors can influence the choice of insulin therapy and recommendations for certain products are made for those with ASCVD, CKD, and those with hypoglycemia issues (*ADA 2020[b], Buse 2020)*.

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Insulin glargine/lixisenatide (Soliqua) and insulin degludec/liraglutide (Xultophy) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise to improve glycemic control in adult T2DM patients.
- The medications are administered through a fixed ratio pen. Soliqua may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while Xultophy may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.
- These agents have been studied in combination with metformin, sulfonylureas, pioglitazone, and meglitinides. In studies, Soliqua demonstrated HbA1c reductions ranging from 0.3 to 0.5% vs insulin glargine and 0.8% vs lixisenatide. Xultophy demonstrated estimated treatment differences in HbA1c reductions of 1% vs insulin degludec monotherapy, 0.6% vs insulin glargine monotherapy, and 0.9% vs a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, Xultophy and Soliqua were associated with both weight losses and gains. Hypoglycemia rates were mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with fewer hypoglycemic events *(Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, Home et al 2020, Lingvay et al 2016, Linjawi et al 2017, Rosenstock et al 2016).* Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo *(Gerstein et al 2012, Marso et al 2016, Marso et al 2017, Pfeffer et al 2015).*
- Overall, the safety profiles of these agents are similar. Xultophy has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. Other key warnings for these products include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Soliqua has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common AEs include gastrointestinal effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- The ADA and EASD guidelines note that a basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with HbA1c > 10% and/or if above the target HbA1c by more than

2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm (*ADA 2020[b], Buse 2020).*

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Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (*Longstreth 2020a*).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (*Hesketh, 2020; Hesketh 2019*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth 2020a*).
- Three distinct types of CINV have been defined, including (*Hesketh 2020, Hesketh 2019*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours
  - Delayed emesis, occurring beyond 24 hours after chemotherapy
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (*Longstreth 2020a*).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (*Feyer et al 2020)*.
- Nausea with or without vomiting is common in early pregnancy. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (*American College of Obstetrics and Gynecologists [ACOG] 2018 [reaffirmed in 2019], Smith et al 2020*).
- Nausea is common in motion sickness and symptoms may also include vomiting and headache. Motion sickness is thought to result from incongruent vestibular, visual, and somatosensory sensory cues *(Priesol 2020)*.
- The mechanism of action for the 5-hydroxytryptamine (5-HT3, or serotonin) agents results from the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the CNS. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (*Mannix et al 2006*).
- The substance P/neurokinin 1 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
- Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol and nabilone. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
- The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown (*Diclegis and Bonjesta prescribing information 2018*).
- Dopamine receptor antagonists, such as prochlorperazine (a phenothiazine) and trimethobenzamide (a benzamide), primarily work by blocking D_2-dopamine receptors in the postrema area of the midbrain. They also have M1-muscarinic and H1-histamine antagonizing effects *(Longstreth 2020b).* Scopolamine, an anticholinergic drug, is an M1-muscarinic receptor antagonist. Antihistamines are used for motion sickness *(Longstreth 2020b).*

- The 5-HT3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The D_2 antagonist Barhemsys (amisulpride) is FDA-approved for treatment and prevention of PONV.
- The substance P/NK1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, Akynzeo, contains palonosetron, a 5-HT3 receptor antagonist, and a substance P/NK1 receptor antagonist: netupitant in the oral formulation and fosnetupitant in the injectable formulation. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- Diclegis and Bonjesta are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. Diclegis and Bonjesta are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
  - The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin. However, this product was removed from the market in 1983 due to lawsuits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis *(*MA) of controlled studies on outcome of pregnancies exposed to Bendectin reported no increase in the incidence of birth defects (*Smith et al 2020*).
- Prescription meclizine is FDA-approved for vertigo; however, over-the-counter products are used for n/v and dizziness associated with motion sickness. Transdermal scopolamine is FDA-approved for n/v associated with motion sickness and for PONV. Prochlorperazine is FDA-approved for treatment of severe n/v, promethazine is approved for motion sickness and n/v associated with certain anesthesia and surgery, and trimethobenzamide is approved for PONV and nausea related to gastroenteritis.
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV, PONV, or n/v associated with other conditions such as pregnancy and motion sickness, with a focus on CINV. Other agents including glucocorticoids may also be effective antiemetics; however, they have been excluded from this review. Although certain agents are FDA-approved for other indications, only those related to n/v are included in this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Dopamine Antagonist; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Akynzeo (palonosetron/netupitant) capsule	–
Akynzeo (palonosetron/fosnetupitant) IV solution	–
Aloxi (palonosetron) IV solution	✔
Anzemet (dolasetron) tablets*	–
Barhemsys (amisulpride) IV solution	–
Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	–
Cesamet (nabilone) capsule*	–
Cinvanti (aprepitant) IV emulsion	–
Compro (prochlorperazine) rectal suppository	✔
Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	✔
Emend (aprepitant) oral suspension	–
Emend (aprepitant) capsule, combination pack	✔
Emend (fosaprepitant) IV solution	✔
granisetron injection, tablets	✔ ‡
Marinol (dronabinol) capsule‖	✔
meclizine over-the-counter products	✔
ondansetron injection	✔ ‡
Phenergan (promethazine) injection	✔
prochlorperazine injection, tablet	✔
Promethegan (promethazine) rectal suppository	✔

Drug	Generic Availability
promethazine injection, tablet, syrup, oral solution	✔
Sancuso (granisetron) transdermal patch	–
Sustol (granisetron) extended-release subcutaneous injection	–
Syndros (dronabinol) oral solution	–
Tigan (trimethobenzamide) capsule	✔
Tigan (trimethobenzamide) injection	-
Transderm Scop (scopolamine) transdermal film	✔
Varubi (rolapitant) tablet†	–
Zofran (ondansetron) oral solution, tablet	✔ ‡
Zofran (ondansetron) ODT	✔ ‡
Zuplenz (ondansetron) oral soluble film	–

Abbrv: IV=intravenous, ODT=orally disintegrating tablet

*This product has been discontinued.

‡Generic available in at least 1 dosage form and/or strength.

†The FDA website shows the IV rolapitant product as discontinued. The manufacturer of IV rolapitant suspended further distribution of the product in February 2018 due to reports of anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions associated with its use.

‖Marinol brand has been discontinued, but generic dronabinol is available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
	Anorexia in patients with AIDS											
Anorexia associated with weight loss in adults with AIDS									✔			
	CINV											
N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments									✔	✔		
Highly emetogenic cancer chemotherapy (HEC) – prevention of acute n/v associated with initial and repeat courses in adults				✔								
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC including high-dose cisplatin in patients ≥ 6 months of age						✔* (oral suspension)	✔*					
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years				✔								
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin as a single dose regimen, in adults						✔* (IV emulsion)						
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC in combination with dexamethasone											✔ (capsule)	

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC in combination with dexamethasone											✔ ¥ (IV)	
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in patients ≥ 12 years of age						✔ * (capsule)						
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC								✔ *				
Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m^2			✔ (tablet, ODT, oral solution, oral soluble film)									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		✔ (injection, tablets)										
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age			✔ (injection)									
Moderately emetogenic cancer (MEC) chemotherapy – prevention of n/v associated with initial and repeat courses in adults				✔								
Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days		✔ (TD)										
Prevention of n/v associated with initial and repeat courses of MEC			✔									

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
			(tablet, ODT, oral solution, oral soluble film)									
Prevention of n/v associated with MEC, including initial and repeat courses in ages ≥ 2 years	✔											
Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age						✔ (oral suspension)						
Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens.		✔ * (ER injection)										
Prevention of delayed n/v associated with initial and repeat courses of MEC in patients ≥ 6 months of age							✔ *					
Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age						✔ * (capsule)						
Prevention of n/v associated with initial and repeat courses of MEC as a 3 day regimen, in adults						✔ * (IV emulsion)						
Prevention of delayed n/v associated with initial and repeat courses of MEC as a single dose regimen, in adults						✔ * (IV emulsion)						
	NVP											
Treatment of NVP in women who do not respond to conservative management												✔
	PONV											
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been				✔								

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
demonstrated; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, Aloxi injection is recommended even where the incidence of PONV is low												
Prevention of PONV in adults			✔ (tablet, ODT, oral solution)			✔ (generic aprepitant only)						
Prevention and treatment of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.		✔ (injection)			✔							
Prevention of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.			✔ (injection†, oral soluble film)									
	RINV											
Prevention of n/v associated with RT, including TBI and fractionated abdominal RT		✔ (tablets)										
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose			✔									

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
fraction to the abdomen, or daily fractions to the abdomen			(tablet, ODT, oral solution, oral soluble film)									

Abbrv: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, ER = extended release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, NVP = nausea and vomiting of pregnancy, NK1 = neurokinin 1, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch, THC = delta-9-tetrahydrocannabinol

* When used in combination with other antiemetic agents.

† For patients who do not receive prophylactic ondansetron injection and experience n/v postoperatively, ondansetron injection may be given to prevent further episodes.

¥ Not studied for prevention of n/v associated with anthracycline plus cyclophosphamide chemotherapy.

Table 2 (cont.) Food and Drug Administration Approved Indications.

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
PONV					
Treatment of PONV					✔ † (capsules, injection)

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
Prevention and control of n/v associated with certain types of anesthesia and surgery		✔ ¥ (injection, suppository, solution, syrup, tablet)			
Antiemetic therapy in postoperative patients		✔ ¥ (suppository, solution, syrup, tablet)			
Prevention of PONV associated with recovery from anesthesia and/or opiate analgesia and surgery				✔	
Motion Sickness					
Prevents and treats n/v or dizziness associated with motion sickness	✔ *				
Prevention of n/v associated with motion sickness				✔	
Active treatment of motion sickness		✔ ¥ (injection)			
Active and prophylactic treatment of motion sickness		✔ ¥ (suppository, solution, syrup, tablet)			
Nausea associated with gastroenteritis					
Nausea associated with gastroenteritis					✔ † (capsules, injection)
Severe nausea and vomiting					
Control of severe n/v			✔ ** (tablets, injection, suppository)		

Abbrv: n/v = nausea and vomiting, FDA = Food and Drug Administration; ODT = orally disintegrating tablets, PONV = postoperative nausea and vomiting

*Antivert (meclizine) is FDA-approved for treatment of vertigo; however, over-the-counter meclizine prevents and treats nausea, vomiting or dizziness associated with motion sickness.
†Tigan not recommended to use in pediatric patients due to risk of extrapyramidal signs and symptoms, other CNS effects, and risk of exacerbating underlying disease in patients with Reye's syndrome or other hepatic impairment.
¥Promethazine is also FDA-approved for multiple indications including those related to allergic conditions, surgical analgesia, and sedation.
**Prochlorperazine is also FDA-approved for treatment of schizophrenia and anxiety.

(*Prescribing information: Akynzeo 2020, Aloxi 2020, Antivert 2019, Anzemet tablets 2019, Barhemsys 2020, Bonjesta 2018, Cesamet 2020, Cinvanti 2019, Compro 2016, Diclegis tablets 2018, Emend capsules and oral suspension 2019, Emend for injection 2019, granisetron injection 2020, granisetron tablets 2019, Marinol 2017, meclizine chewable tablets 2019, meclizine soluble film 2019, meclizine tablets ODT 2020, ondansetron injection 2019, Promethegan suppository 2014, prochlorperazine injection 2019, prochlorperazine tablets 2018, promethazine injection 2016, promethazine oral solution 2019, promethazine syrup 2018, promethazine tablets 2019, Sancuso 2020, Sustol 2017, Syndros 2018, Tigan capsules 2017, Tigan injection 2016, Transderm Scop 2019, Varubi 2018, Zofran tablets ODT oral solution 2017, Zuplenz 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Anorexia in patients with AIDS

- A 2015 MA (N = 6,462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in HIV/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), and a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials). A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

CINV

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone, are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. There are no published clinical trials comparing dronabinol to nabilone for CINV. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Dolasetron has been shown to be an effective therapy in the treatment of CINV in comparative studies with palonosetron, ondansetron, and placebo (*Eberhart et al 2004, Eisenberg et al 2003, Karamanlioglu et al 2003, Lofters et al 1997, Meyer et al 2005, Walker et al 2001*).
- Granisetron and ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of 1 over another, but this has not been a consistently proven outcome (*Billio et al 2010, Dabbous et al 2010, del Giglio et al 2000, Dempsey et al 2004, Gan et al 2005, Jaing et al 2004, Kalaycio et al 1998, Lacerda et al 2000, Orchard et al 1999, White et al 2006*).
- Sancuso (granisetron) patch was noninferior to orally administered granisetron for CINV in a randomized trial (*Boccia et al 2011*). However, a MA of 3 studies found oral granisetron significantly reduced the odds of CINV compared with transdermal granisetron *(Chua et al 2020)*.
- Palonosetron was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (*Aapro et al 2005, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gralla et al 2003, Kaushal et al 2010, Likun et al 2011, Massa et al 2009, Suzuki et al 2016, Chow et al 2018, Matsumoto et al 2020*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal Phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving HEC or MEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was noninferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs and are superior to placebo (*Billio et al 2010, del Giglio et al 2000, George et al 2009, Singhal et al 2012, Tang et al 2012*). A 2016 MA comparing ondansetron to other 5-HT3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (*Simino et al 2016*).

- A 2016 Cochrane review found that 5-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).
- A randomized, DB, noninferiority study comparing single-dose palonosetron 20 mcg/kg to multi-dose ondansetron 150 mcg/kg x 3 doses for the prevention of CINV in pediatric patients, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was noninferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*). A randomized, DB study in pediatric patients, aged 0 to 18 years, receiving HEC found complete response rates were not significantly different during the acute phase between palonosetron 5 mcg/kg, 10 mcg/kg and ondansetron 150 mcg/kg x 3 doses *(Tan et al 2018).* Palonosetron 10 mcg/kg was superior to ondansetron and palonosetron 5 mcg/kg in the delayed phase. In a randomized, open-label study, palonosetron was found to be noninferior and cost-effective in comparison to ondansetron for the prevention of acute CINV in children (2 to 18 years of age) with cancer (*Jain et al* 2018).
- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron IV was not more efficacious than granisetron IV at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (*Suzuki et al 2016*).
- A phase 3, randomized, DB trial compared oral with IV palonosetron in cancer patients receiving MEC *(Cui et al 2020)*. The primary endpoint, complete response rate in the acute phase, was not significantly different between treatment arms, and the authors concluded oral palonosetron was noninferior to IV palonosetron.
- One MC, DB, RCT evaluated dexamethasone compared to aprepitant in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 antagonists and/or dexamethasone (*Herrington et al 2008, Rapoport et al 2010, Yeo et al 2009, Herrstedt et al 2005, Warr et al 2005, Gralla et al 2005, De Wit et al 2004, Poli-Bigelli et al 2003, Hesketh et al 2003, Martin et al 2003, Gore et al 2009, Jordan et al 2009, Grunberg et al 2009*).
- Oral aprepitant- and IV fosaprepitant-based regimens were compared in a phase 3, randomized, DB trial for the prevention of CINV in patients treated with cisplatin-based chemotherapy *(Zhang et al 2020)*. The primary endpoint, complete response during the overall phase, was not significantly different between treatment arms, and the authors concluded the IV fosaprepitant-based regimen was noninferior to the oral aprepitant-based regimen.
- In combination regimens with granisetron and dexamethasone, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*).
- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- Trimethobenzamide has limited data supporting its use in CINV *(Hurley and Eshelman 1980).*
- In a large MA (13 dronabinol studies and 16 nabilone studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).
- In a second MA, authors concluded that with regard to antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI,

0.47 to 0.96; NNT = 3.4). Nabilone was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; p = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).

- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).

NVP

- In a MA on interventions for hyperemesis gravidarum, drowsiness, dizziness, and dystonia were experienced by more women treated with promethazine compared to metoclopramide in a single study. In another study, duration of hospital admission was not different between promethazine and ondansetron, but sedation was more common with promethazine *(Boelig et al 2016).*
- FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on 1 DB, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (p = 0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis group compared to a 1.8 point decrease in the placebo group (p = 0.005) (*Koren et al 2010*).
  - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (*Koren et al 2015*).

PONV

- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 antagonists and NK1 antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).
- In prevention of PONV, amisulpride was studied in 2 randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2020, Gan et al 2017, Kranke et al 2018)*. In one study, patients received amisulpride monotherapy; in another, patients received amisulpride in combination with IV ondansetron, dexamethasone, or betamethasone. The primary endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.
- In treatment of PONV, amisulpride was studied in 2 unpublished randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2020, Candiotti et al 2020, Habib et al 2020)*. In one study, patients received no PONV prophylaxis; in another, patients received and failed PONV prophylaxis with an antiemetic of another class. The primary endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.

RINV

- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving TBI, which is associated with high emetogenic risks. The study was only powered to demonstrate a difference between each active treatment groups and historical controls. In the intention-to-treat population, significantly

more patients given granisetron (33.3%) or ondansetron (26.7%) had zero emetic episodes over 4 days, the primary efficacy end point, than those within the historical control group (0%) ($p < 0.01$) (*Spitzer et al 2000).*

- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

Motion Sickness

- In a MA of 14 studies, scopolamine prevented symptoms of motion sickness more effectively than placebo (RR 0.48; 95% CI, 0.32 to 0.73), but conclusions could not be made regarding its efficacy compared to antihistamines and calcium channel blockers *(Spinks and Wasiak 2011).*

CLINICAL GUIDELINES

- The 5-HT3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV. Treatment of CINV, RINV or PONV generally involves the use of multiple agents that affect different receptor types (*American Gastroentrological Association [AGA] 2001, Herrstedt et al 2017, Hesketh et al 2017, Gan et al 2014, Gupta et al 2016, Roila et al 2010).*
- The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (*Gupta et al 2016*):
  - All patients should receive PONV prophylaxis during the perioperative period.
  - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
- The 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2017*):
  - For the prevention of n/v induced by HEC, a 4 drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC, other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended.
  - For children receiving HEC or MEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant cannot be given; palonosetron and aprepitant can be used if dexamethasone cannot be given.
  - Cannabinoids (eg, nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).
  - Dopamine receptor antagonists (eg, prochlorperazine, metoclopramide) are included as agents that may be added on to regimens for patients who experience n/v despite optimal prophylaxis.
- The 2020 National Comprehensive Cancer Network (NCCN) antiemesis guideline recommends the following regimens for prevention of CINV depending on emetic risk (order does not imply preference) *(NCCN 2020):*
  - For high emetic risk IV chemotherapy on day 1: 1) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) olanzapine, NK-1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Additional agents depending on the regimen are used on days 2, 3, and 4.
  - For moderate emetic risk IV chemotherapy on day 1: 1) 5-HT3 receptor antagonist plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone. Additional agents depending on the regimen are used on days 2 and 3.
  - For low emetic risk IV chemotherapy: dexamethasone, metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For low to minimal emetic risk oral chemotherapy: metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.

- For breakthrough treatment for CINV (add an agent for a different drug class to the current regimen): olanzapine, lorazepam, dronabinol or nabilone, haloperidol, metoclopramide, scopolamine, prochlorperazine or promethazine, 5-HT3 receptor antagonist, or dexamethasone.

- The NCCN guideline recommends granisetron ± dexamethasone or ondansetron ± dexamethasone for pretreatment for RINV in patients receiving radiation therapy (upper abdomen/localized site) or total body irradiation *(NCCN 2020).*
- The 2018 ACOG Practice Bulletin for NVP recommends the following algorithm (*ACOG 2018 [reaffirmed 2019]*):
  - First-line nonpharmacologic options: Change the prenatal vitamin to 1 that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
  - If symptoms persist, escalate to first-line pharmacologic interventions: pyridoxine (vitamin B6) monotherapy or pyridoxine in combination with doxylamine in various doses.
  - If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
  - If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
  - If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
    - If symptoms continue to persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

SAFETY SUMMARY

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated. Ondansetron is also contraindicated with apomorphine.
- The 5-HT3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. Ondansetron and granisetron have QTc prolongation as a general precaution. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Ondansetron and granisetron may mask progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
- The D_2 antagonist amisulpride carries a warning for QT prolongation, and it should be avoided in patients with congenital long QT syndrome and patients taking droperidol. Electrocardiogram (ECG) monitoring is recommended in patients with pre-existing arrhythmia, electrolyte abnormalities, congestive heart failure, and patients taking other drugs or with other conditions that prolong the QT interval.
- Aprepitant and fosaprepitant are weak-to-moderate inhibitors of CYP3A4 and aprepitant is an inducer of CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated in patients taking CYP substrates of the respective enzymes that have a narrow therapeutic index, pimozide and thioridazine. Increased plasma concentrations may result in QT prolongation and torsades de pointes.
- Fosaprepitant, aprepitant, and rolapitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant, fosaprepitant, or rolapitant IV in patients who experience hypersensitivity symptoms with first-time use. Infusion site reactions have been reported with fosaprepitant IV; avoid infusion into small veins or through a butterfly catheter.
- Dronabinol and nabilone have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).
- Dronabinol and nabilone are contraindicated in individuals who are allergic to cannabinoids. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol and nabilone may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- Common adverse events with cannabinoids were dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance.

- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. Additional warnings and precautions include:
  - Avoid dronabinol in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of dronabinol cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking dronabinol.
- Meclizine may cause drowsiness and should be used with caution in patients with asthma, glaucoma, or an enlarged prostate due to its anticholinergic effects. Headache, fatigue, and vomiting are other common adverse events.
- Promethazine has a boxed warning that it should not be used in patients < 2 years old because of the risk of fatal respiratory depression. It should be used with caution in pediatric patients 2 years and older. The injection has a boxed warning for severe tissue injury. Promethazine is also contraindicated in comatose states, hypersensitivity, or for treatment of lower respiratory tract symptoms including asthma. Promethazine injection should not be administered by intra-arterial injection or subcutaneously. Warnings related to promethazine include CNS depression, respiratory depression, lower seizure threshold, bone-marrow depression, and neuroleptic malignant syndrome (NMS).
- Prochlorperazine has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. Contraindications include hypersensitivity, comatose states or in the presence of large amounts of CNS depressants, pediatric surgery, in pediatric patients < 2 years or weighing < 20 pounds, or for use in pediatric conditions that the dose has not been determined. Other warnings include tardive dyskinesia, NMS, and falls. Adverse events include drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, and hypotension.
- Transdermal scopolamine is contraindicated in acute closure glaucoma and hypersensitivity. Warnings and precautions include acute angle closure glaucoma, neuropsychiatric adverse reactions, and eclamptic seizures in pregnant women. Scopolamine may cause reduced gastrointestinal motility, urinary retention, and also blurred vision if it comes into contact with eyes. Additionally, patients may experience withdrawal symptoms, and transdermal scopolamine should be removed prior to magnetic resonance imaging. The most common reactions for motion sickness include dry mouth, drowsiness, blurred vision, and pupil dilation, and for PONV include dry mouth, dizziness, somnolence, agitation, visual impairment, confusion, mydriasis, and pharyngitis.
- Trimethobenzamide is contraindicated in hypersensitivity. Warnings and precautions include acute dystonic reactions and other extrapyramidal symptoms, other CNS reactions (eg, coma, depression of mood, disorientation, and seizures), hepatotoxicity, and impairment of mental and/or physical activities. Other adverse events include blurred vision, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, and muscle cramps.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAOIs), as they intensify and prolong the adverse effects of the agent. The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, are not recommended (unless cleared to do so by a health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties. It should be used with caution in women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. Additionally, false positive urine screening tests for methadone, opiates, and phencyclidine have been reported with doxylamine/pyridoxine use.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
5-HT$_3$ Receptor Antagonists				
Dolasetron	Tablet	Oral	Take within 1 hour before chemotherapy.	Indicated in both pediatric (age 2 to 16 years based on adult PK data) and adults.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				ECG monitoring recommended in patients with renal impairment and the elderly.
Granisetron	Tablet, injection, injection ER, TD patch	Oral, IV, SC, TD	Take orally within 1 hour before chemotherapy or radiation, or twice daily. Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week.	Injection approved for CINV in children 2 to 16 years. Tablet, injection ER, and TD patch have not studied in pediatrics. Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment. Apply patch to upper outer arm. The patch may be worn for up to 7 days depending on the duration of the chemotherapy regimen.
Ondansetron	Tablet, oral solution, ODT, oral soluble film, IV solution, injection	Oral, lingual, IV, IM	Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy. IV administrations vary: (1) administer IV over 15 minutes	Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥10). There is no experience beyond first-day administration in these patients. Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery. Administer IM as a single dose.	
Palonosetron	IV solution	IV	IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	IV solution approved for prevention o CINV in pediatric patients aged ≥ 1 month.
D2 antagonist				
Amisulpride	IV solution	IV	Prevention of PONV: 5 mg as a single IV injection over 2 minutes at induction of anesthesia Treatment of PONV: 10 mg as a single IV injection over 1 to 2 minutes	Use for prevention of PONV may be as monotherapy or in combination with an antiemetic of a different class. Use for treatment of PONV may be in patients who received prophylaxis with an agent of a different class or who have not received prophylaxis. Avoid use in patients with severe renal impairment.
Substance P/NK$_1$ Receptor Antagonists				
Aprepitant	Capsule, combination pack,	Oral, IV	Take orally within 1 hour before chemotherapy and once daily for 2 additional days	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	oral suspension, IV emulsion		Administer IV over 2 minutes or 30 minutes completing the administration approximately 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3).	Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years. Give with or without food. Use with caution in severe hepatic impairment.
Fosaprepitant	IV solution	IV	Adults: Administer IV over 20 to 30 minutes before chemotherapy. Administer IV over 30 minutes (12 to 17 years) or 60 minutes (6 months to <12 years) (for the 3-day regimen, continue capsules or oral suspension on days 2 and 3). Complete infusion approximately 30 minutes prior to chemotherapy	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Use with caution in severe hepatic impairment.
Rolapitant	Tablet	Oral	Administer orally within 2 hours prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Avoid use in severe hepatic impairment; if use cannot be avoided, monitor for adverse events.
THC derivatives				
Dronabinol	Capsule, oral solution	Oral	Take orally 1 to 3 hours before chemotherapy and subsequent doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day or; take orally twice daily, one hour prior to lunch and dinner.	If adverse effects occur and do not resolve in 1 to 3 days with continued use, consider dose reductions. In elderly, consider decreasing the initial dose to reduce risk of CNS adverse reactions. Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water (oral solution).
Nabilone	Capsule	Oral	Take orally twice daily; initial dose is given 1 to 3 hours before	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			chemotherapy and subsequent doses 2 to 3 times daily.	
Other single-agent products				
Meclizine	Chewable, immediate-release, and ODT	Oral	Take orally 1 hour before travel (may repeat every 24 hours as needed)	Start at the lowest dose for elderly patients due to anticholinergic effects
Promethazine	Tablet, oral syrup, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration (motion sickness): Take orally 30 to 60 minutes before departure, then repeated in 8 to 12 hours as needed Oral and rectal administration (PONV): Take orally or rectally every 4 to 6 hours as needed IV and IM (PONV): Administer IV or IM every 4 to 6 hours as needed	Deep IM injection is the preferred parenteral route of administration
Prochlorperazine	Tablet, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration: 3 to 4 times per day Rectal administration: Twice daily IV or IM administration: Administer 3 to 4 hours as needed; or administer 1 to 2 hours (IM) or 15 to 30 minutes (IV) before induction of anesthesia and repeat once if necessary	Lower doses are usually sufficient for elderly patients; increase doses gradually
Scopolamine	Transdermal	Trans-dermal	Motion sickness: Apply patch at least 4 hours before antiemetic effects are needed – for use up to 3 days PONV: Apply patch the evening before scheduled surgery; remove 24 hours after surgery.	Apply to hairless area of the skin behind the ear
Trimethobenzamide	Capsule, IM solution	Oral IM	Oral: Take orally 3 to 4 times daily IM: Administer 3 to 4 times per day as needed	Reduce daily oral dose in elderly and patients with renal impairment
Combination products				
Palonosetron/ netupitant Palonosteron/ fosnetupitent	Capsule Powder for injection	Oral IV	Oral administration: Take orally within 1 hour before chemotherapy	Given as part of a regimen that includes a corticosteroid. Do not use in severe renal or hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			IV administration: Infuse over 30 minutes starting 30 minutes before chemotherapy.	
Doxylamine succinate/ pyridoxine HCl	Tablet ER, tablet DR	Oral	Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR).	Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water.

Abbrv: CINV = chemotherapy-induced nausea and vomiting, DR = delayed release, ECG = electrocardiogram, ER = extended release, HEC = highly emetogenic cancer chemotherapy, IM = intramuscular, IV = intravenous, ODT = orally disintegrating tablet, PONV = post-operative nausea and vomiting, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal
See the current prescribing information for full details.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v (*Longstreth 2020a*)
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or radiation therapy. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms (*AGA 2001, ACOG 2018, Hesketh et al 2017, Longstreth 2020a, Longstreth 2020b, Roila et al 2010; NCCN 2020).*
- Guideline recommendations vary according to indication. The 2017 ASCO antiemetic guidelines recommend a 4-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for regimens other than carboplatin area AUC ≥ 4 mg/mL/min or a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min (*Hesketh et al 2017*). A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (*Gupta et al 2016*). The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first-line pharmacologic therapy (*ACOG 2018 [reaffirmed 2019]*).
- The 5-HT3 antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include dolasetron, granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials haven't demonstrated a clear treatment leader between dolasetron, granisetron, and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV. The 5-HT3 receptor antagonists are the only agents in this class review with demonstrated efficacy and, of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV. The 5-HT3 receptor antagonists are generally well tolerated, with mild headache the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with dolasetron, granisetron, and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists (*Aapro et al 2005, AGA, 2001, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gan et al 2014, Gralla et al 2003, Gupta et al 2016, Herrstedt et al 2017, Hesketh et al 2017, Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2020b, Roila et al 2010, Salvo et al 2012, Simino et al 2016, Spitzer et al 2000, Suzuki et al 2016*).
  - All 5-HT3 antagonist formulations are available generically with the exception of Anzemet (dolasetron) tablets, Sancuso (granisetron) transdermal patch, Sustol (granisetron) extended-release injection, and Zuplenz (ondansetron) oral soluble film.
- The substance P/NK1 receptor antagonists are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists that are generally effective for acute emesis only. These include aprepitant,

fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically a 5-HT3 antagonist, a glucocorticoid, ± olanzapine, for patients receiving HEC. One MA concluded aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization (*AGA 2001, Gralla et al 2005, Grunberg et al 2011, Hesketh et al 2017, Herrington et al 2008, Herrstedt et al 2005, Longstreth 2020b, Rapoport et al 2010, Roila et al 2010, Singh et al 2016, Warr et al 2005, Yeo et al 2009)*.
  - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and combination pack.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. The agents include nabilone and dronabinol. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have little clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol and nabilone are recommended for later line therapy *(Hesketh et al 2017, Lane et al 1991, Longstreth 2020b, Meiri et al 2007, Machado Rocha et al 2008, Tramer et al 2001)*.
  - Only Marinol (dronabinol) oral capsules are available generically.
- Amisulpride is approved for prevention and treatment of PONV. Supporting evidence includes randomized trials in each indication demonstrating superiority over placebo *(Barhemsys prescribing information 2020)*.
  - Amisulpride is not available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine) and Akynzeo (palonosetron/netupitant and palonosetron/fosnetupitant). Doxylamine succinate/pyridoxine is the only agent in this class FDA-approved for NVP and is guideline-recommended as a first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available over-the-counter (*ACOG 2018 [reaffirmed 2019])*. The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.
- Other agents used for n/v include meclizine, promethazine, prochlorperazine, scopolamine, and trimethobenzamide. Meclizine and scopolamine are generally used for motion sickness. Prochlorperazine may be used in low emetic risk chemotherapy while prochlorperazine, scopolamine, or promethazine may be used for breakthrough treatment *(NCCN 2020)*.

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Established Drug Classes

Therapeutic Class Overview
Beta-adrenergic Blocking Agents

INTRODUCTION

- Approximately 121.5 million American adults have at least 1 type of cardiovascular (CV) disease according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. The age-adjusted prevalence of all types of heart disease was 10.6% in 2017. CV disease deaths were most often caused by coronary heart disease (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (HF; 9.4%), and other causes (17.6%) *(Virani et al 2020)*.
- Beta-adrenergic blocking agents (beta-blockers) are a group of drugs that block the sympathomimetic effects of catecholamines on beta receptors. This results in negative inotropic and chronotropic effects and relaxation of smooth muscle.
- Beta-blockers have varied pharmacologic properties.
  - Cardioselective beta-blockers preferentially interact with $beta_1$-receptors, which are predominantly found in the heart. Non-cardioselective beta-blockers also interact with $beta_2$-receptors found on smooth muscle in the lungs, blood vessels, and other tissues. The cardioselectivity of beta-blockers is dose-dependent; therefore, $beta_2$ blockade can occur at higher doses with certain cardioselective agents.
  - Some beta-blockers (acebutolol and pindolol) have intrinsic sympathomimetic activity (ISA), which may result in a lower incidence of bradycardia and bronchoconstriction *(Facts and Comparisons 2020)*. In addition, some beta-blockers (nebivolol and propranolol) have higher lipophilicity, which may increase the risk for central nervous system-related adverse events *(Facts and Comparisons 2020)*.
  - Carvedilol and labetalol also block alpha-adrenergic receptors and may reduce peripheral resistance more than other beta-blockers *(Clinical Pharmacology 2020)*.
- Specific indications for the beta-blockers vary by product. Most beta-blockers (all except sotalol) are approved to treat hypertension (HTN). The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2017).* Nearly half of American adults (46%) have HTN based on this definition. Other indications for 1 or more beta-blockers include, but are not limited to: angina pectoris, arrhythmias, myocardial infarction (MI), HF, left ventricular dysfunction following MI, treatment of essential tremor, and migraine prophylaxis.
- Most of the beta-blockers are available generically. There are no generics available for Bystolic (nebivolol) and branded Levatol (penbutolol), which was discontinued in 2014. Brand Hemangeol is an oral solution of propranolol in a strength of 4.28 mg/mL (equivalent to 3.75 mg); however generic oral solutions of propranolol are available in strengths of 4 and 8 mg/mL.
- There has been extensive experience with beta-blockers in clinical practice, and clinical trials do not consistently demonstrate a clinical advantage of one agent over another for most Food and Drug Administration (FDA)-approved indications. In general, treatment guidelines do not recommend the use of one beta-blocker over the other, as recommendations regarding the use of these agents are made for the class as a whole. There are some exceptions, however. Guidelines do recognize the role of 3 beta-blockers (carvedilol, bisoprolol, and extended release metoprolol) for the reduction of mortality and hospitalization in patients with HF *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017)*. Also, sotalol has some unique properties and is considered separately from the other beta-blockers, as this agent is not indicated to treat HTN and is instead used to treat certain ventricular arrhythmias or for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter.
- Although some single-ingredient beta-blockers have several indications, the beta-blocker/diuretic combination products are FDA-approved only for the treatment of HTN. Patients with HTN frequently require the use of 2 or more agents from different therapeutic classes in order to adequately reduce BP, and the dose of each product should be titrated to its desired effect. Thus, the place in therapy for the beta-blocker/diuretic combinations is for patients who require both agents at doses for which a combination product is available. Several of the combination products (all except for Dutoprol and Ziac) contain specific wording in their prescribing information stating that the product is not approved for initial therapy *(Gradman 2012)*.
- Both beta-blockers and diuretics are well established in the management of HTN. The choice of antihypertensive agent(s) for a particular patient will depend on the patient's comorbidities.

- All of the beta-blockers contained within the combination products are also available generically as single-entity agents. The diuretics hydrochlorothiazide (HCTZ) and chlorthalidone are available generically as single-entity agents. All of the combination products except for Dutoprol (metoprolol succinate extended release/HCTZ) are available generically. Dutoprol is not available as a generic but its individual components are.
- Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence to therapy *(Mancia et al 2013)*.
- This class includes the orally-administered beta-blockers, as well as the orally-administered alpha/beta-blocking agents, carvedilol and labetalol, and the beta-blocker/diuretic combination products. Several beta-blockers are also available in intravenous (IV) forms for in-hospital use; however, the IV formulations are not included within the scope of this review.
- Medispan drug class: Beta Blockers - Beta Blockers Non-Selective; Beta Blockers Cardio-Selective; Alpha-Beta Blockers; Antihypertensive Combinations - Beta Blocker & Diuretic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Beta-blockers	
acebutolol*	✔
Betapace, Betapace AF, Sorine, Sotylize (sotalol)	✔ ‖
betaxolol*	✔
bisoprolol*	✔
Bystolic (nebivolol)	-
Coreg, Coreg CR (carvedilol)	✔
Corgard (nadolol)	✔
Hemangeol, Inderal LA, Inderal XL, Innopran XL (propranolol)*	✔ ‡
Toprol XL, Kapspargo Sprinkle (metoprolol succinate extended release)	✔ †
labetalol*	✔
Lopressor (metoprolol tartrate)	✔
pindolol*	✔
Tenormin (atenolol)	✔
timolol*	✔
Beta-blocker/Diuretic Combinations	
Dutoprol (metoprolol succinate extended release/HCTZ)	-
Lopressor HCT (metoprolol tartrate/HCTZ)	✔
propranolol/HCTZ*	✔
Tenoretic (atenolol/chlorthalidone)	✔
Ziac (bisoprolol/HCTZ)	✔

‡ Hemangeol (propranolol oral solution), Inderal XL, and Innopran XL are brand-name only.
† Kapspargo Sprinkle (metoprolol succinate extended release capsule) is brand name only.
‖ Sotylize (sotalol oral solution) is brand-name only.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications for Single-Entity Beta-blockers

Generic Name	Hypertension	Angina pectoris	Cardiac arrhythmias*	Myocardial infarction	Heart failure	Pheochromocytoma	Migraine prophylaxis	Hypertrophic subaortic stenosis	Proliferating infantile hemangioma requiring systemic therapy	Essential tremor	Left ventricular dysfunction following myocardial infarction
acebutolol	✔ †		✔								
atenolol	✔ †	✔ ‡		✔ §							
betaxolol	✔ †										
bisoprolol	✔ ‖										
carvedilol	✔ †¶				✔ #						✔ **
labetalol	✔ ††										
metoprolol	✔ §§	✔ ‖‖		✔ ¶¶	✔ ##						
nadolol	✔ †	✔ ***									
nebivolol	✔ ‖										
pindolol	✔ †										
propranolol	✔ †,†††	✔ ‡‡‡	✔	✔ §§§		✔ ‖‖‖	✔	✔ ¶¶¶	✔ ††††	✔ ###	
sotalol			✔								
timolol	✔ †			✔ ****			✔				

* See Table 3 for the specific cardiac arrhythmias for which these agents are indicated.
† May be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
‡ Indicated for the long term management of patients with angina pectoris due to coronary atherosclerosis.
§ Indicated for the management of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality.
‖ May be used alone or in combination with other antihypertensive agents.
¶ Indicated for the management of essential HTN.
# Indicated for the treatment of mild to severe chronic HF of ischemic or cardiomyopathic origin, usually in addition to diuretics, angiotensin converting enzyme inhibitors and digitalis to increase survival, and also to reduce the risk of hospitalization.
** Indicated to reduce CV mortality in clinically stable patients who survived the acute phase of an MI and have a left ventricular ejection fraction ≤ 40% (with or without symptomatic HF).
†† Labetalol tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.
§§ Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets may be used alone or in combination with other antihypertensive agents.
‖‖ Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets are indicated in the long term treatment of angina pectoris.
¶¶ Metoprolol tartrate tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality when used alone or in conjunction with IV metoprolol tartrate. Oral therapy can be initiated after IV therapy or, alternatively, oral treatment can begin within 3 to 10 days of the acute event.
Metoprolol succinate extended release tablets are indicated for the treatment of stable, symptomatic (New York Heart Association Class II or III) HF of ischemic, hypertensive or cardiomyopathic origin. Metoprolol succinate extended release capsules are indicated for the treatment of patients with HF to reduce the risk of CV mortality and HF-related hospitalization.
*** Indicated for the long term management of patients with angina pectoris.
††† Inderal XL and Innopran XL are indicated for the treatment of HTN only.
‡‡‡ Indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris due to coronary atherosclerosis.
§§§ Propranolol tablets and oral solution are indicated to reduce CV mortality in patients who have survived the acute phase of an MI and are clinically stable.
‖‖‖ Propranolol tablets and oral solution are indicated as an adjunct to alpha-adrenergic blockade to control BP and reduce symptoms of catecholamine-secreting tumors.
¶¶¶ Improves New York Heart Association functional class in symptomatic patients with hypertrophic subaortic stenosis.
Propranolol tablets and oral solution are indicated for the management of familial or hereditary essential tremor.
**** Indicated in patients who have survived the acute phase of an MI, and are clinically stable, to reduce CV mortality and the risk of reinfarction.

†††† Only approved for Hemangeol oral solution. Hemangeol is not FDA-approved for any other indication.

(Prescribing information: acebutolol 2017, betaxolol 2020, bisoprolol 2019, Betapace and Betapace AF 2018, Bystolic 2019, Coreg 2017, Coreg CR 2020, Corgard 2019, Hemangeol 2020, Inderal LA 2019, Inderal XL 2017, Innopran XL 2017, Kapspargo 2018, labetalol 2019, Lopressor 2017, pindolol 2017, propranolol solution 2017, propranolol tablets 2019, Sorine 2020, Sotylize 2015, Tenormin 2017, timolol 2018, Toprol XL 2019)

Table 3. FDA-Approved Cardiac Arrhythmia Indications

Indication	acebutolol	propranolol	sotalol
Control ventricular rate in patients with atrial fibrillation and a rapid ventricular response		✔ (oral solution, tablet)	
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AFIB/AFL] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm*			✔
Management of ventricular premature beats	✔		
Treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia**			✔

* Limitations of use: Because sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol.
** Limitations of use: Sotalol may not enhance survival in patients with ventricular arrhythmias. Because of the proarrhythmic effects of Betapace/Betapace AF, including a 1.5 to 2% rate of Torsade de Pointes (TdP) or new ventricular tachycardia/fibrillation (VT/VF) in patients with either non-sustained ventricular tachycardia (NSVT) or supraventricular arrhythmias (SVT), its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Avoid treatment of patients with asymptomatic ventricular premature contractions.

(Prescribing information: acebutolol 2017, propranolol solution 2017, propranolol tablets 2019, Betapace and Betapace AF 2018, Sorine 2020, Sotylize 2015)

Table 4. FDA-Approved Indications for Beta-blocker/Diuretic Combinations

Drug	HTN
Dutoprol (metoprolol succinate extended release/HCTZ)	✔
Lopressor HCT (metoprolol tartrate/HCTZ)	✔*
propranolol/HCTZ	✔*
Tenoretic (atenolol/chlorthalidone)	✔*
Ziac (bisoprolol/HCTZ)	✔

*The fixed-dose combination product is not indicated for initial therapy of HTN. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

(Prescribing information: Dutoprol 2020, Lopressor HCT 2012, propranolol and HCTZ 2020, Tenoretic 2018, Ziac 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials demonstrating the safety and efficacy of beta-blockers for their FDA-approved indications have demonstrated that beta-blockers are superior to placebo and efficacious compared to active comparators for these varied indications, including:
  - HTN (*Dahlöf et al 1991, Davidov et al 1988, Dhakam et al 2008, Dietz et al 2008, Fogari et al 1997, Giles et al 2014, Greathouse 2010, Materson et al 1990, Neutel et al 2010, Stoschitzky et al 2006, Van Bortel et al 2005, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1977, Wald et al 2008*)
  - Angina (*Pandhi et al 1985, van der Does et al 1999, Weiss et al 1998*)
  - Arrhythmia (*Lui et al 1983, Seidl et al 1998*)
  - Heart failure (*Bristow et al 1996, CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, Dargie et al 2001, Di Lenarda et al 1999, Flather et al 2005, Goldstein et al 2001, Krum et al 1995, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Waagstein et al 1993*)

- Infantile hemangiomas (*Bauman et al 2014, Novoa et al 2018*)
- Essential tremor (*Calzetti et al 1981, Gironell et al 1999, Yetimalar et al 2005*)
- Migraine prophylaxis (*Ashtari et al 2008, Domingues et al 2009, Jackson et al 2019, Rao et al 2000, Schellenberg et al 2008, Tfelt-Hansen et al 1984*)

- Head-to-head trials have demonstrated that no one beta-blocker is consistently superior compared to the others for the treatment of HTN *(Czuriga et al 2003, Davidov et al 1988, Dhakam et al 2008, Fogari et al 1997)*.
- Trials have demonstrated CV advantages with beta-blocker use in patients with prior MI; however, recent post-hoc analyses examining the use of beta-blockers have been mixed *(Bangalore et al 2014, Dahl Aarvik et al 2019, Freemantle et al 1999, Gottlieb et al 2001, Jonsson et al 2005, Olsson et al 1992)*.
- For the treatment of HF, a survival benefit has been demonstrated with bisoprolol, carvedilol, and sustained release metoprolol succinate; however, only carvedilol and metoprolol succinate extended release are FDA-approved for the treatment of HF. Carvedilol has demonstrated superiority to other beta-blockers in certain populations. Beta-blockers that have been shown to reduce mortality in patients with systolic dysfunction include carvedilol, bisoprolol, and long-acting metoprolol *(Bristow et al 1996, CIBIS-II Investigators and Committees 1999, Dargie 2001, Di Lenarda et al 1999, Goldstein et al 2001, Hamaad et al 2007, Maack et al 2001, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Sanderson et al 1999)*. In elderly patients with HF, nebivolol demonstrated a significant improvement in a composite measure of death or CV hospitalization; however, differences for the individual components of the composite measure did not reach statistical significance *(Flather et al 2005)*.
  - Head-to-head trials have compared metoprolol to carvedilol in patients with HF; however, available trials used the immediate release formulation of metoprolol rather than the extended release formulation that has FDA approval for this indication *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Poole-Wilson et al 2003, Sanderson et al 1999)*. Most of the comparative trials have been small and have evaluated outcomes other than mortality *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Sanderson et al 1999)*. One larger trial, COMET (N = 3029), demonstrated that all-cause mortality was significantly lower in patients treated with carvedilol compared to patients treated with metoprolol tartrate (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.74 to 0.93; p = 0.0017). However, questions have been raised about the choice of metoprolol formulation and its dosing for this trial, so definitive conclusions could not be made *(Kveiborg et al 2007)*.
  - A meta-analysis (MA) that included trials that evaluated immediate and sustained release metoprolol revealed that treatment with carvedilol improved mean left ventricular ejection fraction significantly more than treatment with metoprolol *(Packer et al 2001[a])*.
  - Another MA found that carvedilol significantly reduced the incidence of post-operative atrial fibrillation when compared to metoprolol in patients following a coronary artery bypass grafting (CABG) procedure *(DiNicolantonio et al 2014)*.
  - Several meta-analyses have confirmed the mortality benefit of beta-blockers for the treatment of HF *(Brophy et al 2001, Chatterjee et al 2013, Lechat et al 1998, Whorlow et al 2000)*.
- For the treatment of infantile hemangiomas, a systematic review (SR) and MA of 28 trials concluded that oral propranolol probably improves clinician-assessed clearance vs placebo (risk ratio, 16.61; 95% CI, 4.22 to 65.34) and provides a clinician-assessed reduction in mean hemangioma volume by 45.9% (95% CI, 11.60 to 80.20) *(Novoa et al 2018)*. Compared with topical timolol, oral propranolol was not significantly different in the proportion of patients with clinician-assessed reductions of 50% or greater in hemangioma size. Another SR of 9 trials supports the efficacy of oral atenolol for the treatment of infantile hemangioma based on a response rate of 0.90 (95% CI, 0.85 to 0.93) and an overall rate of adverse events of 0.26 (95% CI, 0.12 to 0.47) (*Wang et al 2018*).

Combination products

- Most trials compared the combination product to placebo or to 1 or both of the individual product components. Results demonstrate that:
  - The combination products are superior to placebo (*de Leeuw et al 1997, Lewin et al 1993, Nissinen et al 1980*).
  - Additional BP lowering is achieved when the combination therapy is compared to 1 or both of the individual drug components administered as monotherapy *(Dafgard et al 1981, Fogari et al 1984, Frishman et al 1994, Frishman et al 1995, Hansson et al 1999, Leonetti et al 1986, Liedholm et al 1981, Smilde et al 1983, Stevens et al 1982)*.
  - The CAPPP study compared an angiotensin converting enzyme (ACE) inhibitor to treatment with a diuretic and/or beta-blockers. For both diabetic and non-diabetic patients, both regimens were equally effective in preventing the composite of fatal and non-fatal MI, stroke, and CV deaths *(Hansson et al 1999)*. A sub-analysis of diabetic patients

within the CAPPP trial found that in hypertensive diabetic patients, captopril (ACE inhibitor) was superior to a diuretic and/or beta-blocker antihypertensive treatment regimen in preventing CV events, especially in those with metabolic decompensation *(Niskanen et al 2001)*. Further studies should be performed to validate beta-blockers in combination with a diuretic and their place in therapy with diabetic patients.

CLINICAL GUIDELINES

- Hypertension:
  - The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2017)* offers updated classifications of HTN and goals of treatment (see Table 5).

Table 5. Classification of BP measurements

BP Category	BP	Treatment or follow-up
Normal	SBP < 120 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is > 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbrv: ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, CKD = chronic kidney disease, CVD = cardiovascular disease, DBP= diastolic blood pressure, DM = diabetes mellitus, SBP = systolic blood pressure

  - In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
    - First-line antihypertensive agents include: thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or angiotensin II receptor blockers (ARBs).
    - Diuretics, ACE inhibitors, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
      - Beta-blockers are not recommended as first-line agents unless the patient has ischemic heart disease (IHD) or HF.
      - Cardioselective beta-blockers (atenolol, betaxolol, bisoprolol, metoprolol tartrate and succinate) are preferred in patients with bronchospastic airway disease requiring a beta-blocker.
      - Non-cardioselective beta-blockers (ie, nadolol, propranolol) should be avoided in patients with reactive airways disease.
      - Bisoprolol, carvedilol, and metoprolol succinate are preferred in patients with HF with reduced ejection fraction (HFrEF).
      - In general, beta-blockers with ISA (ie, acebutolol, carteolol, penbutolol, pindolol) should be avoided, especially in patients with IHD or HF.
  - Most HTN guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a CCB as first line therapy *(Go et al 2014, James et al 2014, Mancia et al 2013, Weber et al 2014, Whelton et al 2017, Williams et al 2018)*.

- In the treatment of severe HTN in pregnancy, labetalol is outlined as an option with consideration of maternal and fetal side effects *(American Diabetes Association 2020, Bushnell et al 2014, de Boer et al 2017, Weber et al 2014)*.
- Beta-blockers have strong clinical outcome benefits in hypertensive patients with a history of MI, HF, acute coronary syndrome, and in the management of angina pectoris. Some guidelines endorse beta-blockers for first-line therapy in these populations *(Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014, Williams et al 2018)*.
- Patients with resistant HTN (defined as above-goal elevated BP despite concurrent use of 3 drug classes) may require additional treatment *(Carey et al 2018)*. Guidelines from the AHA/ACC for the treatment of resistant HTN suggest beta-blockers may be helpful in patients with obstructive sleep apnea, coarctation of the aorta, and patients without bradycardia who have failed multiple other antihypertensives. No specific beta-blocker is preferred by this guideline.

- The beta-blockers are also a mainstay of HF treatment, as evidenced by recommendations within treatment guidelines *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017)*. Of note, carvedilol and metoprolol succinate extended release are the only 2 beta-blockers that are FDA-approved for the treatment of HF, but a mortality benefit has also been shown for bisoprolol in clinical trials, and all 3 are recognized as appropriate options in clinical guidelines *(CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, MERIT-HF Study Group 1999, Ponikowski et al 2016, Waagstein et al 1993, Yancy et al 2013, Yancy et al 2017)*.
  - Conclusive data on the medical management of HF in patients with a systemic right ventricle (RV) are lacking, despite the high incidence of late clinical HF and sudden death in this population. Use of conventional HF medications may be problematic because of preexisting sinus node dysfunction, heart block, baffle stenosis, nondistensible atria, and restrictive RV physiology. Beta-blockade may exacerbate bradyarrhythmias, whereas vasodilation could be counterproductive in patients with nondistensible atria or restrictive physiology *(Stout et al 2016)*.
- Guidelines also support the use of beta-blockers for additional CV diseases including stable ischemic heart disease, unstable angina, MI (acute and long-term after MI), rate control in atrial fibrillation and atrial flutter, maintenance of normal sinus rhythm in atrial fibrillation (sotalol), non-ST-segment elevation acute coronary syndromes, select ventricular and supraventricular arrhythmias, complications following CABG, valvular heart disease, and hypertrophic cardiomyopathy *(Amsterdam et al 2014[a,b], Brugada et al 2019, Fihn et al 2012, Fihn et al 2014, Gersh et al 2011, Ibanez et al 2018, January et al 2014[a,b], January et al 2019, Jneid et al 2012, Knuuti et al 2019, Montalescot et al 2013, Neumann et al 2018, Nishimura et al 2014[a,b], Nishimura et al 2017, O'Gara et al 2013, Page et al 2016, Priori et al 2015, Roffi et al 2016, Rosendorff et al 2015)*.
- Metoprolol, propranolol, and timolol are established as effective for migraine prevention *(Silberstein et al 2012, Snow et al 2002, American Headache Society 2019, Oskoui 2019)*.
- Propranolol is the only beta-blocker that is FDA-approved for the treatment of essential tremor. Guidelines recommend propranolol, long-acting propranolol, or primidone for limb tremor in essential tremor, depending on concurrent medical conditions and potential side effects *(Zesiewicz et al 2011)*.
- A 2019 treatment guideline on infantile hemangioma was published by the American Academy of Pediatrics. If pharmacologic therapy is needed, oral propranolol should be used as a first-line agent. No other systemic beta-blockers are recommended due to a lack of high-quality data (*Krowchuk et al 2019*).

SAFETY SUMMARY

- Beta-blockers have a number of contraindications related to their pharmacologic properties. They should be avoided in patients with sinus bradycardia and second- or third-degree heart block. They also should not be initiated in patients with uncontrolled HF or cardiogenic shock. Based on their ability to block $beta_2$ receptors in the lung, beta-blockers should generally not be used (or used with caution) in patients with asthma and/or chronic obstructive pulmonary disease. This is particularly a concern with non-selective beta-blockers. Other contraindications vary based on the specific drug and the clinical use.
- A boxed warning exists for atenolol, metoprolol (non-boxed warning for metoprolol succinate extended release capsules), nadolol, propranolol extended release capsules, and timolol: worsening angina, MI, and arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with beta-blockers. When discontinuing a chronically administered beta-blocker, particularly in patients with IHD, the dosage should be gradually reduced over a period of 1 to 2 weeks, and the patient should be carefully monitored. Sotalol also carries a boxed warning, noting that patients initiated or reinitiated on sotalol or sotalol AF should be placed for a minimum of 3 days (on

their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Creatinine clearance (CrCL) should be calculated prior to dosing.

- Hemangeol has specific contraindications for use in premature infants with corrected age < 5 weeks, infants weighing < 2 kg, BP < 50/30 mm Hg, and pheochromocytoma.
- Key additional warnings and precautions include:
  - Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in peripheral vascular disease.
  - Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge when taking a beta-blocker. Such patients may also be unresponsive to the usual doses of epinephrine used to treat allergic reactions.
  - Beta-blocker therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
  - Some beta-blockers may potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
  - Beta-blockers should not be given to patients with untreated pheochromocytoma. In patients with this condition, a beta-blocker should be given only after an alpha-blocker has been initiated.
  - Bradycardia and/or hypotension may occur.
  - Sotalol can provoke new or worsened ventricular arrhythmias in some patients. This may include Torsades de Pointes, the risk of which increases with increasing prolongation of the QT interval. Use with particular caution if the QTc is > 500 milliseconds. Use is contraindicated in patients with congenital or acquired long QT syndrome or if serum potassium < 4 mEq/L.
  - The value of using betaxolol in psoriatic patients should be carefully weighed since it has been reported to cause an aggravation in psoriasis.
  - Hemangeol has demonstrated an increased risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Infants with large facial infantile hemangioma should be investigated for potential arteriopathy associated with PHACE syndrome prior to therapy.
- Common adverse reactions (occurring in > 10% of patients for at least 1 medication) include: bradycardia, chest pain, hypotension, palpitations, dizziness, drowsiness, fatigue, headache, insomnia, lightheadedness, hyperglycemia, diarrhea, nausea, weight gain, decreased sexual ability, weakness, and dyspnea.

Combination products

- Based on the beta-blocker component, the beta-blocker/diuretic combinations are contraindicated in patients with sinus bradycardia, second-or third-degree heart block, cardiogenic shock, and overt cardiac failure.
- Based on the diuretic component, the beta-blocker/diuretic combinations are contraindicated in patients with anuria, hypersensitivity to the ingredients, or hypersensitivity to sulfonamide-derived drugs.
  - Lopressor HCT and Dutoprol are contraindicated in patients with sick sinus syndrome, which includes patients with sinus bradycardia and patients with sinus pauses or arrest.
  - Lopressor HCT is contraindicated in those with severe peripheral arterial circulatory disorders.
  - Propranolol/HCTZ is contraindicated in patients with bronchial asthma.
- A precaution is included in some package inserts (Lopressor HCT and Ziac) related to the diuretic component of HCTZ-containing products regarding the risk for non-melanoma skin cancer. Patients taking HCTZ should protect skin from the sun and undergo regular skin cancer screening.
- Boxed warning for Dutoprol, Lopressor HCT, and propranolol/HCTZ: Do not discontinue abruptly; withdraw gradually with appropriate monitoring to avoid potential exacerbation of IHD. This is also a warning for Tenoretic and Ziac (although not boxed).
- Avoid in overt HF; use with caution in patients with controlled HF.
- Avoid in patients with bronchospastic disease. Low doses of $beta_1$ selective agents may be used in patients with bronchospastic disease when no acceptable alternative exists.
- Dutoprol has a warning for bradycardia, particularly in patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders. Concomitant use of beta adrenergic blockers, non-dihydropyridine CCB, digoxin, or clonidine increases the risk. The drug also has additional warnings for increased risk of acute renal failure in patients with chronic kidney disease, severe HF, or volume depletion; and reduced effectiveness of epinephrine when treating anaphylaxis.

- Some beta-blockers may cause hypoglycemia or potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
- Thyrotoxicosis: Beta blockade may mask certain clinical signs of thyrotoxicosis (eg, tachycardia). Abrupt withdrawal of beta blockade may precipitate a thyroid storm.
- Thiazides should be used with caution in severe renal disease, as they may precipitate azotemia in this setting.
- Thiazides should be used with caution in patients with impaired hepatic function because minor alterations of fluid/electrolyte balance may precipitate hepatic coma.
- Adverse reactions reported in > 5% of patients in clinical trials for Dutoprol and Lopressor HCT include bradycardia, dizziness/vertigo, drowsiness/somnolence, fatigue/lethargy, and headache.
- Adverse reaction rates for the other fixed-dose combination products (propranolol/HCTZ, Tenoretic, and Ziac) are not specifically listed in the prescribing information; however, adverse reactions are known based on experience with their components. Notable adverse reactions include HF, intensification of atrioventricular block, bradycardia, peripheral vascular insufficiency, heart rhythm/conduction disturbance, depression, nausea, vomiting, diarrhea, constipation, orthostatic hypotension, dizziness, fatigue, vertigo, headache, hypersensitivity, hyperglycemia, hyperuricemia, and bronchospasm.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity Beta-blockers				
acebutolol	Capsules	Oral	Cardiac arrhythmias (ventricular): Twice daily HTN: Once to twice daily	Dosage adjustment in renal impairment is required. Older patients have an approximately 2-fold increase in bioavailability and may require lower maintenance doses; avoid doses above 800 mg.
atenolol	Tablets	Oral	Angina pectoris: Once daily HTN: Once daily Acute MI*: After initial IV dosing in the acute setting, 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, once or twice daily for a further 6 to 9 days or until discharge.	Dosage adjustment in renal impairment is required. Atenolol can cause fetal harm when used in pregnancy. Low birth weights have been reported with use; drug is excreted in breast milk; use with caution. Neonates may be at risk for hypoglycemia and bradycardia.
betaxolol	Tablets	Oral	HTN: Once daily	Dosage adjustment in renal impairment is required. Consideration should be given to reducing the starting dose to 5 mg in elderly patients.
bisoprolol	Tablets	Oral	HTN: Once daily	Dosage adjustment in renal and hepatic impairment is required.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
carvedilol	ER capsules (Coreg CR), tablets (Coreg)	Oral	HF: ER capsule: Once daily; Tablet: Twice daily HTN: ER capsule: Once daily; Tablet: Twice daily Left ventricular dysfunction following MI: ER capsule: Once daily; Tablet: Twice daily	Patients controlled with immediate release (IR) tablets may be switched to ER capsules (see prescribing information for details). When switching from the higher doses of IR carvedilol to ER, a lower starting dose is recommended for the elderly. Contraindicated in severe hepatic dysfunction. ER capsule: Take once daily in the morning with food. Should be swallowed as a whole capsule or may alternatively be opened, and the beads sprinkled over a spoonful of applesauce. Tablet: Take with food.
labetalol	Tablets	Oral	HTN: Twice daily	Dose adjustment is required in the elderly. Use with caution in hepatic dysfunction; metabolism of the drug may be diminished.
metoprolol	ER tablets (succinate; Toprol XL), ER capsules (succinate; Kapspargo), tablets (tartrate)	Oral	Angina pectoris: ER tablet or ER capsule: once daily; Tablet: daily in 2 divided doses HF: ER tablet (NYHA Class II): once daily [start with 25 mg/day]; ER tablet (severe HF): once daily [start with 12.5 mg/day]; ER capsule: once daily [start with 25 mg/day] HTN: ER tablet or ER capsule: once daily; Tablet: daily in single or divided doses MI: Tablet: After initial IV dosing in the acute setting, initiate tablets at 50 mg every 6 hours 15 minutes after the last IV dose and continue for 48 hours; thereafter, the maintenance dose is 100 mg twice daily	Hepatic dosage adjustment may be necessary; initiate at low doses with cautious gradual titration. ER tablet or ER capsule: Dosing recommendations are available for pediatric hypertensive patients ≥ 6 years of age; product is not recommended in patients < 6 years. ER tablet: Take with or immediately after meals. ER tablets are scored and can be divided, but not crushed or chewed. ER capsule: swallow whole or sprinkle capsule contents over soft food; mix contents with water for nasogastric tube administration ER capsule: 1 to 1 dose conversion with ER tablet

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Tablet: Take with or immediately after meals. Do not chew.
nadolol	Tablets	Oral	Angina pectoris: Once daily HTN: Once daily	Dosage adjustment in renal impairment is required.
nebivolol	Tablets (Bystolic)	Oral	HTN: Once daily	Dosage adjustment in renal and hepatic impairment is required.
pindolol	Tablets	Oral	HTN: Twice daily	Poor hepatic function may cause blood levels to increase substantially; use with caution.
propranolol	ER capsules (Inderal LA), ER beads capsules (Inderal XL, Innopran XL), oral solution (Hemangeol), oral solution (generic), tablets (generic)	Oral	Angina pectoris: ER capsule (Inderal LA): Once daily; Oral solution, tablet: Daily in 2, 3 or 4 divided doses Cardiac arrhythmias (atrial fibrillation): Oral solution, tablet: Three to 4 times daily before meals and at bedtime Essential tremor: Oral solution, tablet: Twice daily HTN: ER capsules (all): Once daily; Oral solution, tablet: Twice daily; if control is not adequate, a larger dose, or 3 times daily therapy may achieve better control Hypertrophic subaortic stenosis: Oral solution, tablet: Three to 4 times daily before meals and at bedtime; ER capsule (Inderal LA): Once daily Infantile hemangioma: Oral solution (Hemangeol): Twice daily Migraine prophylaxis: Oral solution, tablet: Daily in divided doses; ER capsule (Inderal LA): Once daily MI: Oral solution, tablet: Twice or 3 times daily Pheochromocytoma: Oral solution, tablet (operable	Propranolol is not indicated for the treatment of hypertensive emergencies. With propranolol, hepatic insufficiency increases plasma concentration and prolongs the half-life; use with caution. Hemangeol is not intended for pregnant or nursing women. Hemangeol should be initiated at ages 5 weeks to 5 months. Administer doses at least 9 hours apart and during or after feeding. Monitor heart rate and BP for 2 hours after first dose or increasing dose. Of 460 infants (aged 5 weeks to 5 months), 60% had complete or near complete resolution of hemangioma at week 24. Inderal XL and Innopran XL should be administered once daily at bedtime and should be taken consistently either on an empty stomach or with food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			tumors): Daily in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade; Oral solution, tablet (inoperable tumors): Daily in divided doses as adjunct to alpha-adrenergic blockade	
sotalol	Tablets (Betapace, Betapace AF, Sorine), oral solution (Sotylize)	Oral	Cardiac arrhythmias (maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter): Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function Cardiac arrhythmias (ventricular): Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function	Pediatric dosing is available for the treatment of cardiac arrhythmias (ventricular and symptomatic atrial fibrillation/atrial flutter). Dosage adjustment in renal impairment is required. For treatment of atrial fibrillation or flutter, use is contraindicated if CrCL is < 40 mL/min. See the Betapace or Sorine prescribing information for instructions on compounding an oral solution from the tablets.
timolol	Tablets	Oral	HTN: Twice daily Migraine prophylaxis: Twice daily MI: Twice daily	During maintenance therapy for migraine prophylaxis, doses of 10 mg or 20 mg may be given once daily. Dosage reductions may be necessary in kidney and hepatic dysfunction as timolol is substantially excreted by the kidney (ie, risk of toxic reactions may be increased) and is partially metabolized in the liver.
Beta-blocker/Diuretic Combinations				
Dutoprol (metoprolol succinate extended release/HCTZ)	Tablets	Oral	Once daily	Safety and effectiveness in severe renal impairment (CrCL ≤ 30 mL/min) have not been established; no dose adjustment necessary in patients with moderate renal impairment. Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lopressor HCT (metoprolol tartrate/ HCTZ)	Tablets	Oral	Daily in single or divided doses	While once-daily dosing is effective and can maintain a reduction in BP throughout the day, lower doses may not maintain a full effect at the end of the 24-hour period; larger or more frequent doses may be required. Should be taken with or immediately following meals.
propranolol/ HCTZ	Tablets	Oral	Twice daily	Use with caution in severe renal disease.
Tenoretic (atenolol/ chlorthalidone)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required. Atenolol can cause fetal harm when used in pregnancy and thiazide diuretics have caused adverse reactions for the fetus in pregnancy; use in pregnancy only if clearly needed. Excreted in breast milk; use with caution. Clinically significant bradycardia and hypoglycemia in nursing infants has been reported.
Ziac (bisoprolol/ HCTZ)	Tablets	Oral	Once daily	Use with caution when dosing/titrating patients with renal and hepatic impairment; discontinue use with progressive renal impairment.

See the current prescribing information for full details
Abbrv: BP = blood pressure, CrCL = creatinine clearance, ER = extended release, HCTZ=hydrochlorothiazide, IV = intravenous, MI = myocardial infarction, NYHA = New York Heart Association
* Dosing from the package insert is summarized for completeness, but an IV formulation of atenolol is no longer marketed.

CONCLUSION

- Beta-blockers are a group of drugs that block the effects of catecholamines on beta receptors.
- Beta-blockers have a range of FDA-approved indications as the agents within the class differ in pharmacologic and pharmacokinetic properties. Such differences may include adrenergic-receptor blocking activity, ISA, and lipophilicity.
- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of beta-blockers. All of the agents within the class, with the exception of sotalol, are FDA-approved for the treatment of HTN. Most guidelines recommend that the selection of an antihypertensive agent be based on compelling indications for use; the 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults recommends the use of beta-blockers as secondary agents after thiazide diuretics, ACE inhibitors, ARBs, and CCBs *(Whelton et al 2017)*.
- The choice of a beta-blocker for a specific patient will depend on several factors. In addition to considering the clinical trial data and FDA-approved indications, patient diagnoses and comorbidities should be considered when selecting a product; for example:
  - Beta-blockers are best avoided in patients with asthma and chronic obstructive pulmonary disease; however, if no suitable alternatives exist, a $beta_1$-selective agent is preferred.

- For patients with HF, bisoprolol, carvedilol, or metoprolol extended release should be considered as these have demonstrated a reduction in mortality; some guidelines recommend nebivolol as an option in certain HF patients *(Ponikowski et al 2016, Rosendorff et al 2015)*.
- For patients with hepatic or renal disease, drugs that are not hepatically or renally eliminated, respectively, are preferred.
- For patients receiving concomitant therapy with a cytochrome (CYP) 2D6 inhibitor, beta-blockers that are not CYP2D6 substrates are preferred *(Clinical Pharmacology 2020)*.
- For patients with HTN and acute coronary syndrome, initial therapy should include a short-acting $beta_1$-selective beta-blocker without ISA (metoprolol tartrate or bisoprolol) *(Rosendorff et al 2015)*.

- Most beta-blockers are available generically, including those that are recognized as effective for providing a mortality benefit in patients with HF *(Drugs@FDA 2020, Yancy et al 2013, Yancy et al 2017)*. Available generic products will provide ample options for the majority of patients and clinical situations.
- The beta-blocker/diuretic combination products are FDA-approved for the treatment of HTN and are well-established for this indication.
- The beta-blocker/diuretic combinations are more effective compared to placebo and compared to the individual components given alone. There are currently no head-to-head trials comparing the various combination products to one another or any trials to demonstrate differences in clinical outcomes when the drug components are administered as separate agents concurrently versus the fixed-dose combination products.
- Many patients with HTN require more than 1 antihypertensive medication to achieve BP goals. Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence *(Mancia et al 2013)*.
- HTN guidelines recommend combination therapy as a treatment option in patients who have BP that is not at goal with monotherapy *(James et al 2014, Mancia et al 2013, Weber et al 2014)*.
- Most guidelines agree that beta-blockers are of particular value for hypertensive patients with certain co-morbid diseases, such as HF, post-MI, angina pectoris, coronary artery disease, and ventricular dysfunction *(Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014)*. Other guidelines recommend beta-blockers for atrial fibrillation and diabetes *(Go et al 2014, Mancia et al 2013)*. Diuretics also offer benefits in terms of diseases associated with edema, such as HF *(Go et al 2014, Mancia et al 2013, Weber et al 2014)*. However, caution should be exercised as some guidelines do not recommend the use of beta-blockers in combination with a diuretic in patients at risk for diabetes as they have adverse effects associated with glucose metabolism *(Weber et al 2014)*.

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Therapeutic Class Overview
Urinary antispasmodics

INTRODUCTION

- Overactive bladder (OAB) is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of a causative infection or pathological conditions. 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 (*American Urological Association 2019, Coyne et al 2008, Haab 2014, International Continence Society 2015).*
  - Children with OAB usually have detrusor overactivity as diagnosed through cystometric evaluation. Neurogenic detrusor overactivity is predominantly caused by a congenital neural tube defect in children (*Austin et al 2016, Franco et al 2020*).
- Behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training and fluid management) are considered first-line treatment in all patients with OAB *(American Urological Association 2019).*
- Urinary antispasmodics are used as first-line pharmacological therapy in OAB (*American College of Obstetricians and Gynecologists 2015, American Urological Association 2019, Blok et al 2020, Burkhard et al 2018*).
  - Anticholinergic therapy has been frequently used in patients with neurogenic detrusor overactivity, but there are limited data in this specific population (*Haab 2014*).
- The urinary antispasmodics used for the treatment of OAB belong to 2 classes of drugs, which include anticholinergic compounds known as muscarinic receptor antagonists, and the beta-3 adrenergic agonist (AR), mirabegron.
  - The anticholinergic agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions.
    - Oral immediate-release (IR) and extended-release (ER) formulations (LA, XL, and XR) are available for oxybutynin (Ditropan), tolterodine (Detrol), and trospium. Darifenacin (Enablex) and fesoterodine (Toviaz) are also supplied as oral ER tablet formulations.
    - Oxybutynin is also formulated as a topical gel (Gelnique) and transdermal patch (Oxytrol, Oxytrol for Women). Oxytrol for Women is an over-the-counter (OTC) product previously available as a prescription; it is specifically indicated for women ≥ 18 years of age with 2 or more of the following symptoms for at least 3 months: urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours), urinary urgency (a strong need to urinate right away), and urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate) *(Oxytrol for Women Drug Facts 2016).*
    - Vesicare LS (solifenacin) is a recently approved oral suspension formulation of solifenacin and is approved for use in pediatric patients ≥ 2 years of age with neurogenic detrusor overactivity.
  - Myrbetriq (mirabegron) is an agonist of the human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR, which increases bladder capacity.
- All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of OAB.
  - Flavoxate is FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis.
  - The IR formulation of oxybutynin is also indicated for the relief of symptoms of neurogenic or reflex neurogenic bladder, and the ER tablet is approved for the treatment of detrusor overactivity.
- The anticholinergic urinary antispasmodics have demonstrated a similar safety and efficacy profile compared to one another; 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 have suggested 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 *(Brown et al 2018).*
- The development of ER formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events (AEs). Oxybutynin undergoes first-pass metabolism to an active metabolite with a high incidence of dry mouth; however, transdermal oxybutynin formulations bypass this metabolism, maintaining the efficacy of oxybutynin with a lower incidence of AEs *(Dmochowski et al 2005).*
- Trospium, a water-soluble compound, has low penetration through the blood brain barrier and the gut; however, clinical studies have not demonstrated a lower incidence of AEs with trospium compared to other agents within the class.

- Fesoterodine, a prodrug, is rapidly metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.
- Botox injection (onabotulinumtoxinA) also has 2 FDA-approved indications for OAB. The OAB indications for BOTOX include the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]) in adults who have an inadequate response to or are intolerant of an anticholinergic medication *(Botox prescribing information 2020).* Botox is not included in this review.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review focuses on the use of the urinary antispasmodics for OAB.
- Medispan class: Urinary Antispasmodics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anti-muscarinic (Anticholinergic)	
Detrol (tolterodine)	✔
Detrol LA (tolterodine ER)	✔
Ditropan XL (oxybutynin ER)	✔
Enablex (darifenacin ER)	✔
Gelnique (oxybutynin 10% topical gel)	-†
oxybutynin	✔
Oxytrol (oxybutynin transdermal patch)	-
Oxytrol for Women (oxybutynin transdermal patch)*	-
trospium‡	✔
trospium ER‡	✔
Toviaz (fesoterodine)	-†
Vesicare (solifenacin)	✔
Vesicare LS (solifenacin)§	-
Beta-3 Adrenergic Agonists	
Myrbetriq (mirabegron)	-
Direct Muscle Relaxants	
flavoxate	✔

*OTC product
†The FDA approved a generic oxybutynin topical gel AB rated to Gelnique and a fesoterodine tablet AB rated to Toviaz; neither generic agents are currently commercially available.
‡Branded product (Sanctura) is no longer available.
§Vesicare LS is projected to launch in late 2020.

(*Astellas 2020, Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	darifenacin (Enablex)	fesoterodine (Toviaz)	flavoxate	mirabegron (Myrbetriq)	oxybutynin (Ditropan XL, Gelnique, Oxytrol)‡‡	solifenacin (Vesicare)	solifenacin (Vesicare LS)	tolterodine (Detrol, Detrol LA)	trospium
Treatment of OAB	✔ *	✔ *		✔ *	✔ * (patch, gel, XL)	✔ *		✔ *	✔ *
Treatment of OAB in combination with solifenacin				✔ *					
Treatment of detrusor overactivity					✔ † (XL)				
Treatment of bladder instability in patients with uninhibited neurogenic or reflex neurogenic bladder					✔ (IR)				
Symptomatic relief of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis			✔						
Treatment of neurogenic detrusor overactivity							✔ §		

***** In patients with symptoms of urge urinary incontinence, urgency, and urinary frequency; Vesicare is indicated in adults only.
† In pediatric patients ≥ 6 years of age with symptoms of detrusor overactivity associated with a neurological condition.
‡ Oxytrol for Women is available OTC and is approved for women ≥ 18 years of age with ≥ 2 of the following symptoms for at least 3 months: urinary frequency, urinary urgency, and urge incontinence; Oxytrol is approved for overactive bladder in men.
§ In pediatric patients ≥ 2 years of age

(Oxytrol for Women Drug Facts 2016; Prescribing information: Detrol 2016, Detrol LA 2018, Ditropan XL 2019, Enablex 2016, flavoxate 2018, Gelnique 2019, Myrbetriq 2018, oxybutynin tablets 2020, oxybutynin syrup 2020, Oxytrol 2017, Toviaz 2017, trospium tablets 2018, trospium extended-release capsules 2014, Vesicare 2020, Vesicare LS 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A 2018 Agency for Healthcare Research and Quality (AHRQ) systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al 2018*). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo. Additionally, anticholinergics overall were found to improve quality of life compared with no treatment, but there was inconsistency both within and across studies regarding the comparative effect of these medications on various aspects of quality of life.
- Although used for urinary incontinence, flavoxate is no more effective than other drugs used for urge incontinence or related disorders *(Micromedex 2020).* No recent clinical trials have been published with flavoxate.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective vs placebo with regard to improvements in micturition frequency, urgency and urge incontinence episodes *(Chapple et al 2004, Chapple et al 2007, Dmochowski et al 2003, Dmochowski et al 2008, Dmochowski et al 2010, Herschorn et al 2010(b), Kaplan et al 2011, Kay et al 2006, Khullar et al 2011, MacDiarmid et al 2011, Mattiasson et al 2010, Nitti et al 2007, Nitti et al 2013, Salinas-Casado et al 2015, Sand et al 2011, Staskin et al 2007, Staskin et al 2009, Wagg et al 2013, Zinner et al 2005).*
- Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class *(Anderson et al 1999, Anderson et al 2006, Appell et al 2001, Barkin et al 2004, Batista et al 2015, Chapple et al 2005, Chapple et al 2007, Davila et al 2001, Diokno et al 2003, Dmochowski et al 2003, Dmochowski et al 2010, Ercan et al 2015, Halaska et al 2003, Harvey et al 2001, Herschorn et al 2010(a), Herschorn et*

al 2010(b), Hsiao et al 2011, Kaplan et al 2011, Kay et al 2006, Kilic et al 2006, Kinjo et al 2018, Kobayashi et al 2018, Sand et al 2004, Versi et al 2000, Zellner et al 2009).

- The evidence to support the efficacy and safety of the oxybutynin transdermal patch (Oxytrol for Women) as an OTC product was based on the completed studies with the prescription product *(Dmochowski et al 2002, Dmochowski et al 2003, FDA Oxytrol for Women Medical Review 2013*). The Oxytrol for Women transdermal patch is the same formulation and dose as the prescription Oxytrol transdermal patch.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- Another review demonstrated that all anticholinergics for OAB showed similar small benefits. For urgency urinary incontinence, the drugs showed 20% or less difference from placebo in the rate of achieving urinary continence or improvement in urinary continence. The numbers needed to treat (NNT) to achieve continence in 1 woman were similar across drugs (range for NNT, 6 to 12). Dose-related efficacy effects were evident for fesoterodine, solifenacin, and oxybutynin. Small differences were apparent in the AEs among the anticholinergics. Dry mouth and constipation were the most common AEs. Treatment discontinuation due to AEs was greater than with placebo for all drugs except darifenacin and tolterodine (*Shamliyan et al 2012*).
- A network meta-analysis of 5 randomized controlled trials ranked the antispasmodics for treatment of OAB in women in the following order from highest to lowest efficacy: solifenacin 10 mg once daily, oxybutynin 3 mg 3 times daily, solifenacin 5 mg once daily, darifenacin 15 mg once daily, fesoterodine 8 mg once daily, darifenacin 7.5 mg once daily, and tolterodine 4 mg once daily. However, solifenacin 10 mg had the most AEs while darifenacin 7.5 mg once daily caused the least AEs. The authors concluded that solifenacin 5 mg once daily was preferred for OAB followed by oxybutynin 3 mg 3 times daily based on efficacy, AEs, and cost (*Nalliah et al 2017*).
- A network meta-analysis that compared solifenacin 5 mg/day to other antimuscarinic agents found that solifenacin was more effective than tolterodine 4 mg/day for incontinence and urgency. In addition, solifenacin had a lower risk of dry mouth compared to other antimuscarinics (*Nazir et al 2018*).
- A 2019 network meta-analysis of 128 studies of anticholinergics concluded that all the anticholinergic medications were better than placebo for patients with OAB; however, there was no clear best treatment for cure or improvement. In this analysis, transdermal oxybutynin was shown to cause less dry mouth than the other treatments (*Herbison et al 2019*).
- Three 12-week, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of mirabegron 25 mg, 50 mg, or 100 mg once daily vs placebo. Mirabegron significantly reduced the mean number of incontinence episodes and the mean number of micturitions per 24 hours compared to placebo *(Nitti et al 2013).*
- Mirabegron compared with either tolterodine IR or tolterodine LA demonstrated comparable efficacy in 2 trials. However, tolterodine IR patients had more AEs *(Kuo et al 2015, Yamaguchi et al 2014).* A 2-period, 8-week crossover trial comparing mirabegron and tolterodine ER found greater tolerability with mirabegron; however, patient treatment preference and symptoms were similar between treatments (*Staskin et al* 2018). An indirect treatment comparison meta-analysis concluded that mirabegron had similar efficacy to most other antispasmodics; however, solifenacin demonstrated improved symptom control compared to mirabegron *(Obloza 2017).* Another systematic review and meta-analysis concluded that mirabegron demonstrated similar efficacy to tolterodine and solifenacin with regard to improvement in micturitions, incontinence, and nocturia with a lower incidence of dry mouth and no higher risk of hypertension (*Chen et al 2018*).
- A systematic review compared treatment with mirabegron 50 mg to several different active treatments (including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) in regard to micturitions, incontinence, and dry rate (*Kelleher et al 2018*). Mirabegron had similar efficacy to other active treatments with a few exceptions: solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 50 mg were found to be more efficacious at reducing micturition frequency than mirabegron 50 mg; solifenacin 5 mg plus mirabegron 25/50 mg and fesoterodine 8 mg were found to be more efficacious at reducing urgency urinary incontinence than mirabegron 50 mg; and solifenacin 5 mg plus mirabegron 25/50 mg, trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg were associated with an improved dry rate when compared to mirabegron 50 mg. In general, mirabegron was associated with a significantly lower frequency of AEs compared to other active treatments.
- Studies examining combination therapy of mirabegron and solifenacin have demonstrated decreased frequency of incontinence, urgency episodes, and/or micturition frequency with a similar AE profile to monotherapy *(Drake et al 2016, Herschorn et al 2017, Kosilov et al 2015, Yamaguchi et al 2015).* A 12-month long-term trial of mirabegron and solifenacin also found the combination to be well tolerated with greater improvement in OAB symptoms as compared to

monotherapy with either agent (*Gratzke et al 2018*). Similarly, the combination of low-dose trospium and solifenacin has also resulted in decreased frequency of incontinence in elderly patients with moderate symptoms *(Kosilov et al 2014).*

- The efficacy and safety of solifenacin suspension for the treatment of pediatric patients (6 months to < 18 years of age of age) with neurogenic detrusor overactivity were evaluated in 2 open-label, baseline-controlled, Phase 3 studies. Patients were treated with sequential doses of solifenacin 2.5 to 10 mg for 12 weeks to determine an optimal dose, followed by a fixed dose for ≥ 40 weeks. The primary outcome was the change in maximum cystometric capacity from baseline to 24 weeks. Results revealed that maximum cystometric capacity significantly improved after 24 weeks of treatment (37 mL for children 6 months to < 5 years of age; $p < 0.001$ and 57.2 mL for children 5 to < 18 years of age; $p < 0.001$). Improvement continued through 52 weeks of treatment. Results for all secondary endpoints were also significant at week 24. Treatment-emergent AEs were mostly mild or moderate in nature (*Franco et al 2020*).

CLINICAL GUIDELINES

- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy *(American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014).*
- The American Geriatrics Society recommends avoiding anticholinergics, including oral antimuscarinics and flavoxate, in elderly patients with delirium, dementia or cognitive impairment due to worsening central nervous system AEs *(American Geriatric Society 2019).*
- No one urinary antispasmodic is recommended over another; however, ER formulations are associated with lower incidences of AEs and similar efficacy as compared to IR products. Due to different tolerability profiles, patients experiencing an AE or inadequate efficacy (despite dose optimization) with one antispasmodic agent may be switched to another agent within the class *(American Urological Association 2019, Burkhard et al 2018).* The American College of Physicians recommends the choice of pharmacologic treatment be based on AEs, tolerability, convenience, and cost *(Qaseem et al 2014)*.

SAFETY SUMMARY

- The anticholinergic urinary antispasmodics are contraindicated with uncontrolled narrow angle glaucoma and urinary retention. Flavoxate is contraindicated in patients with achalasia, pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, gastrointestinal hemorrhage, and obstructive uropathy.
- Warnings and precautions for most of the anticholinergic agents include the risk of angioedema, decreased gastrointestinal motility, urinary retention, and central nervous system effects such as dizziness, somnolence, confusion, and hallucinations. Anticholinergic agents should be used with caution in patients with myasthenia gravis or ulcerative colitis. Ditropan XL should be used with caution in patients with Parkinson's disease.
- In general, due to the anticholinergic mechanism of action of the urinary antispasmodics, these agents are commonly associated with anticholinergic-related AEs. The most common AEs include dry mouth and constipation. AEs for mirabegron include hypertension, nasopharyngitis, urinary tract infection, and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Darifenacin	Tablet (ER)	Oral	Once daily	• Dose should not exceed 7.5 mg/day with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors; not recommended for use in severe hepatic impairment (Child-Pugh C).
Fesoterodine	Tablet (ER)	Oral	Once daily	• Not recommended for use in severe hepatic impairment (Child-Pugh C).

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Dose should not exceed 4 mg/day in severe renal impairment (CrCl < 30 mL/min) or when co-administered with potent CYP3A4 inhibitors.
Flavoxate	Tablet	Oral	3 to 4 times daily	• With improvement of symptoms, the dose may be reduced.
Mirabegron	Tablet (ER)	Oral	Once daily	• Not recommended for use in ESRD or severe hepatic impairment (Child-Pugh C). • Dose should not exceed 25 mg/day in patients with severe renal impairment (CrCL 15 to 29 mL/min) or moderate hepatic impairment (Child-Pugh B).
Oxybutynin	Tablet (IR), tablet (ER), syrup, gel, transdermal patch	Oral, transdermal	Tablet (IR), Syrup: twice to 3 times daily Tablet (ER): once daily Gel: once daily Patch: once every 3 to 4 days (Oxytrol); once every 4 days (Oxytrol for Women)	• FDA-approved for use in children ≥ 5 years of age (IR) and ≥ 6 years of age (ER) • Dose adjustment of tablets (IR) is recommended in the frail elderly due to prolonged elimination half-life.
Solifenacin	Tablet, suspension	Oral	Once daily	Tablet: • Dose should not exceed 5 mg/day in patients with severe renal impairment (CrCL < 30 mL/min), when co-administered with potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C). Suspension: • Recommended daily dose is based on patient weight. • Administration of dose should be followed with liquid (eg, water or milk). • The recommended starting dose should not be exceeded in patients with severe renal impairment (CrCL < 30 mL/min), when coadministered with potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C).
Tolterodine	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Dose adjustment is required for the capsule (ER) in patients with severe renal impairment, mild to moderate hepatic impairment, and those co-administered potent CYP3A4 inhibitors (2 mg once daily); not recommended for use in severe hepatic impairment (Child-Pugh C). • Capsule (ER) is not recommended in patients with CrCl < 10 mL/min.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Dose adjustment is required for the tablet in patients with significantly reduced hepatic or renal function or those currently taking potent CYP3A4 inhibitors (1 mg twice daily).
Trospium	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Should be administered at least 1 hour before meals or on an empty stomach. • Dose adjustment is recommended in severe renal impairment for the tablet (20 mg once daily); capsule (ER) not recommended for use in severe renal impairment (CrCL < 30 mL/min). • Should be used with caution in patients with moderate to severe hepatic dysfunction.

Abbreviations: CrCl = creatinine clearance, CYP = cytochrome P450, ER = extended-release, ESRD = end-stage renal disease, IR = immediate-release

See the current prescribing information for full details.

CONCLUSION

- The urinary antispasmodics (with the exception of flavoxate) are FDA-approved for the management of OAB, defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.
  - In the absence of treatment, urinary incontinence has been shown to greatly reduce quality of life in areas such as physical and social functioning, as well as mental and general health *(Coyne et al 2008).*
  - Solifenacin suspension is approved for use in pediatric patients ≥ 2 years of age with neurogenic detrusor overactivity.
- The urinary antispasmodics include 2 classes of medications: muscarinic receptor antagonists include darifenacin (Enablex), fesoterodine (Toviaz), flavoxate, oxybutynin, solifenacin (Vesicare, Vesicare LS), tolterodine (Detrol), and trospium; and the beta-3 adrenergic agonist, mirabegron (Myrbetriq). The anticholinergic agents antagonize the effects of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle tissue in the bladder and consequently decreasing bladder contractions. To reduce dosing frequency and AEs, ER (LA, XL, and XR) formulations are available for oxybutynin (Ditropan XL), tolterodine (Detrol LA), and trospium.
  - Oxybutynin is the only agent that is also available in a topical gel (Gelnique) and transdermal patch (Oxytrol). Oxytrol for Women is an OTC transdermal patch indicated in women ≥ 18 years of age for OAB treatment.
  - Mirabegron has a different mechanism of action and AE profile.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective compared to placebo in regard to improvements in micturition frequency, urgency, urge incontinence episodes, and cystometric capacity (solifenacin suspension). Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more so than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- A 2018 AHRQ systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al* 2018). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (OR, 1.80; 95% CI, 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo.
- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy. Anticholinergics

should be avoided in elderly patients with delirium, dementia, or cognitive impairment. In general, ER formulations of urinary antispasmodics are associated with lower incidences of AEs with similar efficacy as compared to IR products. Pharmacologic treatment should be based on AEs, tolerability, convenience, and cost *(American Geriatric Society 2019, American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014*).

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