Therapeutic Class Overview
Respiratory Corticosteroid/Long-Acting β-Agonists Combinations

Therapeutic Class Overview/Summary: The combination inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) products include Advair® (fluticasone propionate/salmeterol), Breo Ellipta® (fluticasone furoate/vilanterol), Dulera® (mometasone/formoterol) and Symbicort® (budesonide/formoterol), with fluticasone furoate/vilanterol being the most recent agent to be approved by the Food and Drug Administration (FDA). Fluticasone propionate/salmeterol, mometasone/formoterol, budesonide/formoterol and fluticasone furoate/vilanterol are approved for the treatment of asthma; however, only fluticasone propionate/salmeterol, fluticasone furoate/vilanterol and budesonide/formoterol have been approved for the treatment of chronic obstructive pulmonary disease (COPD). The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. The LABAs have selective action on β_2 receptors which stimulate adenyl cyclase, thereby increasing intracellular cyclic adenosine monophosphate level, and subsequently relaxing bronchial smooth muscles. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity. All of the combination products are associated with similar adverse events, precautions and contraindications.[1-5] Moreover, the labeling for all of the combination products has been revised to reflect the results of an analysis which reported an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients treated with LABA-containing medications.[6] The combination ICS/LABA products appear to be equally efficacious for their respective indications, with the products differing in available dosage forms, dosing frequency (one vs two inhalations twice daily), pharmacokinetic profiles and ages for their FDA-approved indications.[1-5]

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

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Budesonide/ formoterol (Symbicort® HFA)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema* and treatment of asthma in patients 12 years of age and older	Meter dose aerosol inhaler (HFA): 80/4.5 µg 160/4.5 µg	-
Fluticasone propionate/ salmeterol (Advair Diskus®, Advair HFA®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema (Advair Diskus®)†, treatment of asthma in patients four years of age and older (Advair Diskus®) and treatment of asthma in patients 12 years of age and older (Advair HFA®)	Dry powder inhaler: 100/50 µg 250/50 µg 500/50 µg Meter dose aerosol inhaler (HFA): 45/21 µg 115/21 µg 230/21 µg	-
Fluticasone furoate/ vilanterol (Breo Ellipta®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease and treatment of asthma in patients 18 years of age and older	Dry Powder Inhaler: 100 µg/25 µg 200 µg/25 µg	-
Mometasone/ formoterol (Dulera®)	Treatment of asthma in patients 12 years of age and older	Meter dose aerosol inhaler (HFA): 100/5 µg 200/5 µg	-

HFA=hydrofluoroalkane
* Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
† Advair Diskus® 250/50 µg is the only strength FDA approved for this indication.

Evidence-based Medicine

- Fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, mometasone/formoterol and budesonide/formoterol have been studied for the treatment of asthma and COPD.[7-49]
- The safety and efficacy of mometasone/formoterol were established in two randomized, double-blind, parallel-group, multicenter trials of 12 and 26 week duration (N=1,509).
    - After 26 weeks of treatment, mometasone/formoterol was more effective than monotherapy with the individual components in controlling asthma and reducing the risk of asthma deteriorations in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICSs).[7]
    - After 12 weeks of treatment, mometasone/formoterol was more effective than mometasone monotherapy in improving asthma control and reducing nocturnal awakenings.
        - Patients poorly controlled on high-dose ICSs experienced significant improvements in asthma control, lung function and symptoms when treated with mometasone/formoterol compared to mometasone monotherapy.[8]
    - A long term safety trial demonstrated that treatment with mometasone/formoterol for up to one year is well tolerated.[9]
- A single prospective head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated noninferiority of mometasone/formoterol in regard to the forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours. Mometasone/formoterol treatment was also associated with a significantly quicker onset of action and increase in FEV_1 five minutes post dose compared to fluticasone propionate/salmeterol.[10]
- Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and results have generally demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms. Moreover, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.[11-36]
- Head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol have been conducted but failed to consistently demonstrate "superiority" of one product over the other.[37-46]
- Two studies comparing fluticasone propionate/salmeterol and fluticasone furoate/vilanterol did not demonstrate significant differences in improvement of 0 to 24 hour FEV_1.[47,48]
- A meta-analysis of 33 studies that compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol and budesonide/formoterol found that treatment with fluticasone furoate/vilanterol was noninferior to fluticasone propionate/salmeterol and budesonide/formoterol treatments.[49]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[50-53]
    - ICSs and β_2-agonists are well established treatment options in the management of both asthma and COPD.
    - The addition of a LABA is the preferred treatment option in asthma patients who fail to achieve adequate control with a low to medium dose ICS.
    - β_2-agonists are among the principal bronchodilators used in the treatment of COPD, and LABAs are more effective and convenient than short-acting bronchodilators.
    - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤60% predicted and repeated exacerbations.
    - ICS/LABA products are more effective than either component alone in reducing exacerbations or improving lung function in COPD patients.
    - No one ICS/LABA product is preferred over another for the treatment of asthma or COPD.

- Other Key Facts:
    - All LABA-containing medications carry a Black Box Warning regarding an increased risk of asthma-related deaths associated with their use.

- Budesonide/formoterol and fluticasone furoate/vilanterol have quicker onsets of action (15 and 16 minutes) compared to fluticasone propionate/salmeterol (30 to 60 minutes). The onset of action of mometasone/formoterol has not been reported.[1-5]
- All ICS/LABA products are available for twice-daily dosing, except fluticasone furoate/vilanterol which is administered once daily.[1-5]
- For the treatment of asthma, Advair® HFA (fluticasone propionate/salmeterol), Dulera® (mometasone/formoterol), Symbicort® (budesonide/formoterol) are approved for use in patients 12 years of age and older, whereas Advair Diskus® (fluticasone propionate/salmeterol) is approved for use in patients four years of age and older. Breo Ellipta® (fluticasone furoate/vilanterol) was recently approved for the treatment of asthma in patients 18 years of age and older.
- No generic products are available in this therapeutic class.

References

1. Symbicort® [package insert]. Wilmington (DE): AstraZeneca LP; 2016 Feb.
2. Advair Diskus® [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2016 Apr.
3. Advair HFA® [package insert]. Research Triangle Park (NC); GlaxoSmithKline: 2014 Dec.
4. Breo Ellipta® [package insert]. Triangle Park (NC): GlaxoSmithKline; 2015 Sep.
5. Dulera® [package insert]. Whitehouse Station (NJ): Schering Corporation; 2015 Jan.
6. FDA announces new safety controls for long-acting beta agonists, medications used to treat asthma [press release on the Internet]. Rockville (MD): Food and Drug Administration (US): 2010 Feb 18 [cited 2014 Jun 21]. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200931.htm.
7. Nathan RA, Nolte H, Pearlman DS. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 µg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. Allergy Asthma Proc. 2010;31:269-79.
8. Weinstein SF, Corren J, Murphy K, Nolte H, White M. Twelve–week efficacy and safety study of mometasone furoate/formoterol 200/10 microg and 400/10 microg combination treatments in patients with persistent asthma previously receiving high-dose inhaled corticosteroids (abstract). Allergy Asthma Proc. 2010;31:280-9.
9. Maspero JF, Nolte H, Cherrez-Ojeda I. Long-term safety of mometasone furoate/formoterol combination for treatment of patients with persistent asthma. J Asthma. 2010;47:1106-15.
10. Bernstein DI, Hebert J, Cheema A, Murphy KR, Cherrez-Ojeda I, Matiz-Bueno CE, et al. Efficacy and Onset of Action of Mometasone Furoate/Formoterol and Fluticasone Propionate/Salmeterol Combination Treatment in Subjects With Persistent Asthma. Allergy Asthma Clin Immunol. 2011 Dec 7;7(1):21. [Epub ahead of print]
11. Lalloo U, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared to increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest. 2003;123:1480-7.
12. Tal A, Simon G, Vermeulen, JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler vs inhaled corticosteroids alone in the treatment of asthma. Pediatr Pulmonol. 2002;34:342-50.
13. Zangrilli J, Mansfield LE, Uryniak T, O'Brien CD. Efficacy of budesonide/formoterol pressurized metered-dose inhaler vs budesonide pressurized metered-dose inhaler alone in Hispanic adults and adolescents with asthma: a randomized, controlled trial. Ann Allergy Asthma Immunol. 2011 Sep;107(3):258-65.e2
14. Pohl WR, Vetter N, Zwick H, Hrubos W. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double blind study. Respir Med. 2006;100(3):551-60.
15. Kuna P, Creemers JPHM, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared to twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. Respir Med. 2006;100(12):2151-9.
16. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. Int J Clin Pract. 2007;61(11):1874-83.
17. Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared to budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006;11:276-86.
18. Eid NS, Noonan MJ, Chipps B, Parasuraman B, Miller CJ, O'Brien CD. Once- vs twice-daily budesonide/formoterol in 6- to 15-year old patients with stable asthma. Pediatrics. 2010;126:e565-e75.
19. Kerwin EM, Oppenheimer JJ, LaForce C, Parasuraman B, Miller CJ, O'Dowd L, et al. Efficacy and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler in adults and adolescents with asthma previously stable with twice-daily budesonide/formoterol dosing. Ann Allergy Asthma Immunol. 2009;103:62-72.
20. Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized medtered-dose inhaler: randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. Allergy Asthma Proc. 2010;31:49-59.
21. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared to budesonide alone and formoterol alone in adolescents and adults with asthma. Clin Ther. 2007 May;29(5):823-43.
22. Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Ståhl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. Int J Clin Pract. 2002;56(6):427-33.

23. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma. Drugs. 2006;66(17):2235-54.
24. Chapman KR, Ringdal N, Backer V, Palmqvis M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Can Respir J. 1999;6:45-51.
25. Nelson HS, Wolfe JD, Gross G, Greos LS, Baitinger L, Scott C, et al. Efficacy and safety of fluticasone propionate 44 µg/salmeterol 21 µg administered in a hydrofluroalkane metered-dose inhaler as an initial asthma maintenance treatment. Ann Allergy Asthma Immunol. 2003;91:263-9.
26. Perrin K, Williams M, Wijesinghe M, James K, Weatherhall M, Beasley R. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting β-agonist inhaler therapy in asthma. J Allergy Clin Immunol. 2010;126:505-10.
27. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. J Allergy Clin Immunol. 2006;118:574-81.
28. Gappa M, Zachgo W, von Berg A, Kamin W, Stern-Strater C, Steinkamp G. Add-on salmeterol compared to double dose fluticasone in pediatric asthma: a double-blind, randomized trial (VIAPAED). Pediatr Pulmonol. 2009;44:1132-42.
29. Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, Brackel HJL, Gerrits GPJM, Hop WCJ, Duiverman EJ. Combination therapy salmeterol/fluticasone vs doubling dose of fluticasone in children with asthma. Am J Respir Crit Care Med. 2010;182:1221-7.
30. Bateman E, Boushey H, Bousquet J, Buss WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. Am J Respir Crit Care Med. 2004;170:836-44.
31. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone/salmeterol in a single inhaler is stepped down. J Allergy Clin Immunol. 2006;117(3):563-70.
32. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 µg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respir Med. 2001;95:136-46.
33. Pearlman DS, Peden D, Condemi JJ, Weinstein S, White M, Baitinger L, et al. Efficacy and safety of fluticasone/salmeterol HFA 134A MDI in patients with mild-moderate persistent asthma. J Asthma. 2004;41:797-806.
34. Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, et al. Efficacy and tolerability of fluticasone/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescents and adult patients with persistent asthma: a randomized, double blind, placebo-controlled, 12-week study. Clin Ther. 2006;28:73-85.
35. Lundback B, Ronmark E, Lindberg A, Jonsson AC, Larsson LG, Petavy, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. Respir Med. 2006;100:2-10.
36. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone and salmeterol inhaled from a single inhaler vs separate inhalers. J Allergy Clin Immunol. 2003;112:29-36.
37. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomized trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. Resp Med. 2006; 100:1152-62.
38. Bousquet J, Boulet Louis-Philippe, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. Respir Med. 2007:101:2437-46.
39. FitzGerald MJ, Boulet LP, Follows RM. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. Clin Ther. 2005;27(4):393-406.
40. Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared to formoterol-budesonide adjustable maintenance dosing: impact on health-related quality of life. Respir Res. 2007 Jul 4;8:46.
41. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomized, double-blind, comparison of Seretide (50/250 µg bd Diskus) vs formoterol (12 µg bd) and budesonide (800 µg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respir Med. 2002;96(11):851-61.
42. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/ formoterol pressurized metered-dose inhaler and fixed-dose fluticasone proprionate/salmeterol dry powder inhaler in asthma patients. J Allergy Clin Immuno. 2008;121:1407-14.
43. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinex-Jamenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. Int J Clin Pract. 2007;61(5):725-36.
44. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandström T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared to fixed-dose salmeterol/fluticasone in moderate to severe asthma. Curr Med Res Opin. 2004;20(2):225-40.
45. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation with budesonide/formoterol and salmeterol/fluticasone in single inhalers. Pulm Pharmacol Ther. 2001;14(1):29-34.
46. O'Connor PD, Patrick DL, Parasuraman B, Martin P, Goldman M. Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler vs fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. J Asthma. 2010;47:217-23.
47. Agustí A, de Teresa L, De Backer W, Zvarich MT, Locantore N, Barnes N, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2013 Oct 10.
48. Dransfield MT, Feldman G, Korenblat P, LaForce CF, Locantore N, Pistolesi M, et al. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 µg) versus twice-daily fluticasone propionate/salmeterol (250/50 µg) in COPD patients. Respir Med. 2014;108:1171-79.
49. Stynes G, Svedsater H, Wex J, Lettis S, Leather D, Castelnuovo E, et al. Once-daily fluticasone furoate/vilanterol 100/25 µg verse twice daily combination therapies in COPD – mixed treatment comparisons of clinical efficacy. Respiratory Research 2015;16:25.

50. National Heart, Lung, and Blood Institute and National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma full report 2007. [guideline on the internet]. 2007. [cited 2014 Jun 21]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.
51. Fitzgerald M, Bateman ED, Bousquet J, Cruz A, Haahtela T, O'Byrne P, et al. Global Initiative for Asthma. Global strategy for asthma management and prevention 2015 [guideline on the internet]. 2015. [cited 2015 Oct 22]. Available from: http://www.ginasthma.com.
52. Global Initiative for Chronic Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [guideline on the internet]. Global Initiative for Chronic Lung Disease World Health Organization; 2015 [cited 2015 Oct 22]. Available from: http://www.goldcopd.org/.
53. National Institute for Health and Clinical Excellence. Management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). [guideline on the internet]. 2010 [cited 2014 Jun21]. Available from: www.nice.org.uk/guidance/CG101.