OPTUMRx

Therapeutic Class Overview
Respiratory Corticosteroids

INTRODUCTION

- Inhaled corticosteroids (ICSs) are approved by the Food & Drug Administration (FDA) for the treatment of asthma. These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States, more than 25 million people are known to have asthma, including about 7 million children (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*NHLBI 2014*).
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007*).
- Long-term control medications include (*NHLBI 2007*):
  - Corticosteroids (ICSs for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
  - Cromolyn sodium and nedocromil
  - Immunomodulators (i.e., omalizumab)
  - Leukotriene modulators
  - Long-acting β-agonists (LABAs)
  - Methylxanthines (i.e., theophylline)
- Quick-relief medications include (*NHLBI 2007*):
  - Short-acting β-agonists (SABAs) as the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm
  - Anticholinergics (i.e. ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
  - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2018, Dupixent 2018, Fasenra 2017, Nucala 2017*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2018*).
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events including death. However, they are effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients with a history of exacerbations. An IL-5 antagonist or the immunoglobulin E (IgE) antagonist, omalizumab, may be added if patients require a higher level of care. Omalizumab is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma. SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma (*Fasenra prescribing information 2017, NHLBI 2007, Global Initiative for Asthma [GINA] 2018*).
- This review includes single-agent ICSs (ie, respiratory corticosteroids). While respiratory corticosteroids are commonly available in combination with other bronchodilators such as LABAs, combination agents are not included within this

review. Although inflammation is also a component of COPD pathogenesis, no single-entity ICS has been FDA-approved for use in COPD (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*).

- Of note, QVAR RediHaler, a new breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva, was approved by the FDA in August 2017 and was launched in February 2018, replacing the previous QVAR product (*Teva 2018*). Additionally, in January 2018, Mylan informed the FDA of the discontinuation of Aerospan (flunisolide) due to business reasons (*FDA Drug Shortages 2018*).
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alvesco (ciclesonide) inhalation aerosol	-
ArmonAir RespiClick (fluticasone propionate) dry powder inhaler	-
Arnuity Ellipta (fluticasone furoate) dry powder inhaler	-
Asmanex HFA (mometasone furoate) inhalation aerosol	-
Asmanex Twisthaler (mometasone furoate) dry powder inhaler	-
Flovent Diskus (fluticasone propionate) dry powder inhaler	-
Flovent HFA (fluticasone propionate) inhalation aerosol	-
Pulmicort Flexhaler (budesonide) dry powder inhaler	-
Pulmicort Respules (budesonide) solution for nebulization	✔
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Maintenance treatment of asthma as prophylactic therapy
Alvesco (ciclesonide) inhalation aerosol	✔ (age ≥ 12 years)
ArmonAir RespiClick (fluticasone propionate) dry powder inhaler	✔ (age ≥ 12 years)
Arnuity Ellipta (fluticasone furoate) dry powder inhaler	✔ (age ≥ 5 years)
Asmanex HFA (mometasone furoate) inhalation aerosol	✔ (age ≥ 12 years)
Asmanex Twisthaler (mometasone furoate) dry powder inhaler	✔ (age ≥ 4 years)
Flovent Diskus (fluticasone propionate) dry powder inhaler; Flovent HFA (fluticasone propionate) inhalation aerosol	✔ (age ≥ 4 years)
Pulmicort Flexhaler (budesonide) dry powder inhaler	✔ (age ≥ 6 years)
Pulmicort Respules (budesonide) solution for nebulization	✔ (age 12 months to 8 years)
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	✔ (age ≥ 4 years)

(*Prescribing information: Alvesco 2018, ArmonAir RespiClick 2018, Arnuity Ellipta 2018, Asmanex HFA 2018, Asmanex Twisthaler 2018, Flovent Diskus 2017, Flovent HFA 2017, Pulmicort Flexhaler 2016, Pulmicort Respules 2016, QVAR RediHaler 2018*)

- 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

- Several trials demonstrate the efficacy of ICSs compared to placebo for preventing exacerbations, improving FEV_1 and peak expiratory flow (PEF), improving symptoms, reducing use of SABAs, reducing oral corticosteroid requirements,

and/or improving quality of life (*Amar et al 2017, Baker et al 1999, Bleecker et al 2014, Fish et al 2000, Karpel et al 2007, Lotvall et al 2014, Meltzer et al 2009, Meltzer et al 2012, Nathan et al 2010, Nelson et al 1999, Rowe et al 1999, Sheffer et al 2005*).

- Numerous head-to-head trials have compared various ICS regimens to one another. Several clinical trials demonstrated no significant differences between different ICSs:
  - A trial comparing budesonide 750 mcg twice daily to fluticasone propionate 375 mcg twice daily in children 5 to 16 years of age demonstrated no statistically significant differences between treatment groups in PEF, symptom scores, physician/patient/parent assessment of efficacy, or frequency of exacerbations (*Fitzgerald et al 1998*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to various doses of mometasone furoate twice daily demonstrated comparable efficacy between fluticasone propionate and mometasone furoate for improvement in FEV_1, forced expiratory flow at 25 to 75% of forced vital capacity (FVC; i.e., forced expiratory flow $[FEF]_{25\text{ to }75\%}$), and PEF (*O'Connor et al 2001*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to mometasone furoate 400 mcg every evening demonstrated no significant differences between groups in FEV_1, FVC, PEF, albuterol use, or asthma symptom scores (*Wardlaw et al 2004*).
  - A trial comparing fluticasone propionate 500 mcg twice daily to mometasone furoate 500 mcg twice daily demonstrated no significant differences in PEF, FEV_1, symptom scores, or rescue albuterol use (*Harnest et al 2008*).
  - A trial comparing beclomethasone dipropionate 168 mcg twice daily to mometasone furoate 100 or 200 mcg twice daily demonstrated no significant differences in FEV_1, PEF, asthma symptoms, nocturnal awakenings, or albuterol use (*Nathan et al 2001*). The beclomethasone product evaluated in the trial is no longer commercially available.
  - A trial comparing ciclesonide 160 mcg every evening to budesonide 400 mcg every evening in children aged 6 to 11 years demonstrated no significant differences between groups in FEV_1, morning PEF, asthma symptom score, or need for rescue medication (*Von Berg et al 2007*).
  - A trial comparing fluticasone furoate 100 mcg daily to placebo also included fluticasone propionate 250 mcg twice daily as a reference arm; comparable results were seen between fluticasone propionate and fluticasone furoate for FEV_1, percentage of rescue-free days, and severe asthma exacerbations (*Lotvall et al* 2014).
  - A trial comparing fluticasone furoate 200 mcg daily to fluticasone propionate 500 mcg twice daily demonstrated that fluticasone furoate was non-inferior to fluticasone propionate based on effect on FEV_1 (*O'Byrne et al 2014*).
- Overall, comparative trials have not conclusively demonstrated one ICS to be significantly more effective than another. However, in several individual trials, significant differences in some endpoints were observed. For example, comparative trials have demonstrated:
  - In a trial comparing fluticasone propionate 200 mcg twice daily to budesonide 400 mcg twice daily in children 4 to 12 years of age, patients treated with fluticasone propionate had superior results for mean morning PEF compared to patients receiving budesonide (271 ± 82 and 259 ± 75 L/minute, respectively, P=0.002) (*Ferguson et al 1999*).
  - In a trial comparing budesonide 200 mcg twice daily to fluticasone propionate 100 mcg twice daily in children 6 to 9 years of age, effectiveness measures were comparable between groups; however, the mean growth velocity was significantly greater in the fluticasone propionate group (5.5 cm/year) compared to the budesonide group (4.6 cm/year) (*Ferguson et al 2007*).
  - A trial comparing beclomethasone dipropionate 168 or 336 mcg twice daily to fluticasone propionate 88 to 220 mcg twice daily demonstrated greater improvement in FEV_1 for fluticasone propionate-treated patients than beclomethasone dipropionate-treated patients. At endpoint, mean FEV_1 values in the low- and medium-dose fluticasone propionate groups improved by 0.31 (14%) and 0.36 L (15%), respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone dipropionate treatment groups, respectively. Improvements were also superior in the fluticasone propionate group for $FEF_{25\text{ to }75\%}$, FVC, morning PEF, and use of albuterol (*Raphael et al 1999*). Of note, the beclomethasone product evaluated in the trial is no longer commercially available.
  - In a trial comparing budesonide 400 mcg twice daily to various doses of mometasone furoate twice daily, the FEV_1 was significantly improved from baseline in the mometasone furoate 200 and 400 mcg treatment groups compared to the budesonide treatment group. In addition, morning wheezing scores were significantly improved in the mometasone furoate 400 mcg twice daily group compared to the budesonide group, and patients treated with mometasone furoate 200 or 400 mcg twice daily required significantly less albuterol compared to patients treated with budesonide (*Bousquet et al 2000*).
  - In a trial comparing budesonide 400 mcg once daily to mometasone furoate 440 mcg once daily, the mometasone furoate group had superior results for the percent change in FEV_1, $FEF_{25\text{ to }75\%}$, FVC, evening asthma symptom

scores, albuterol use, percentage of asthma symptom-free days, and physician–evaluated response to therapy (*Corren et al 2003*).

- Meta-analyses have evaluated ciclesonide and mometasone furoate compared to other ICS agents:
  - A meta-analysis comparing ciclesonide to other ICS agents (budesonide or fluticasone propionate) in children with asthma demonstrated no significant differences between ciclesonide and budesonide on asthma symptom scores, symptom-free days, rescue medication-free days, or exacerbations. When ciclesonide and fluticasone propionate were compared, no significant differences were found in asthma symptoms or rescue medication-free days. One of the four studies of ciclesonide vs fluticasone propionate demonstrated a higher incidence of exacerbations with ciclesonide; however, the dose of fluticasone propionate was relatively higher in this study (*Kramer et al 2013*).
  - A meta-analysis comparing mometasone furoate to other ICS agents (beclomethasone dipropionate [QVAR formulation which is no longer marketed], budesonide, or fluticasone propionate) in patients with moderate to severe asthma demonstrated superior results with mometasone furoate for pulmonary function measures (FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and morning PEF). Mometasone furoate was also shown to be superior on some symptom indices (morning difficulty breathing scores and rescue medication use), but not others (morning wheeze scores, morning cough scores, and nocturnal awakenings). However, based on the pooled results for the comparative arms, it is not possible to make conclusions about the relative efficacy of mometasone furoate compared to other individual agents (*Yang et al 2012*).
- Fluticasone propionate has also been compared to a leukotriene receptor, montelukast, in several randomized controlled trials in both adults and children. Although differences were not detected for all endpoints, in general these trials demonstrated superior outcomes for fluticasone propionate for FEV_1, symptom-free days, asthma symptom scores, nighttime awakenings, rescue albuterol use, physician's global assessments, frequency of exacerbations, and/or quality of life measures (*Busse et al 2001, Garcia et al 2005, Sorkness et al 2007, Szefler et al 2005, Zeiger et al 2006*).
- The safety and efficacy of ArmonAir RespiClick were evaluated in 2,130 patients with asthma, including two 12-week confirmatory trials, a 26-week safety trial, and two dose-ranging trials. The efficacy of ArmonAir RespiClick is based primarily on the dose-ranging and confirmatory trials (*Bernstein et al 2017, Kerwin et al 2017, Mansfield et al 2017, Raphael el at 2017, Sher et al 2017*).
  - The first Phase 3 trial (n=647, of which 389 were randomized to ArmonAir RespiClick or placebo) was a randomized, double-blind, placebo-controlled efficacy and safety study that compared ArmonAir RespiClick 55 mcg and 113 mcg one inhalation twice daily, AirDuo RespiClick (fluticasone propionate/salmeterol) 55/14 mcg and 113/14 mcg one inhalation twice daily, and placebo in patients ≥12 years of age with persistent symptomatic asthma despite low-dose or mid-dose ICS or ICS/LABA therapy. For the primary endpoint of change from baseline in trough FEV_1, a significantly greater improvement was seen in ArmonAir RespiClick 55 mcg and 113 mcg as compared to placebo at the end of 12 weeks (least squares means [LSM] change of 0.172 L, 0.204 L, and 0.053 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF, total daily use of rescue medication, and Asthma Quality of Life Questionnaire improvement were also evaluated and supported efficacy of ArmonAir RespiClick (*Raphael el at 2017*).
  - The second Phase 3 trial (n=728, of which 437 were randomized to ArmonAir RespiClick or placebo) was similarly designed, but evaluated an increased ICS dose: ArmonAir RespiClick 113 mcg and 232 mcg, AirDuo RespiClick 113/14 mcg and 232/14 mcg, and placebo. Results for the primary endpoint of change from baseline in trough FEV_1 mirrored that of Trial 1, with significantly greater improvement in the ArmonAir RespiClick 113 mcg and 232 mcg groups as compared to placebo at the end of 12 weeks (LSM change of 0.119 L, 0.179 L, and -0.004 L, respectively). Secondary endpoints of weekly average of daily trough morning PEF and total daily use of rescue medication also supported efficacy of ArmonAir RespiClick (*Sher et al 2017*).
- The safety and efficacy of QVAR RediHaler were evaluated in 1,858 patients with persistent symptomatic asthma, including two 12-week and one 6-week Phase 3 confirmatory trials in patients ≥12 years of age, and one 12-week Phase 3 confirmatory trial in patients 4 to 11 years of age (*Amar et al 2016, Hampel et al 2017, Vandewalker et al 2017*).
  - The first 12-week Phase 3 trial (N=270) was a randomized, double-blind, placebo-controlled trial study that compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used low-dose ICS or non-corticosteroid therapy. For the primary endpoint of change from baseline in trough FEV_1 area under the effect curve 0 to 12 weeks ($AUEC_{0\text{-}12wk}$), a significantly greater improvement was seen with QVAR RespiClick 80 mcg and 160 mcg as compared to placebo (difference of LSM from placebo of 0.124 L and 0.116 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF and a reduction in asthma symptoms vs placebo (*Hampel et al 2017*).

- The second 12-week Phase 3 trial (n=532) was a randomized, double-blind, placebo-controlled trial that compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs QVAR 160 mcg and 320 mcg twice daily and placebo in patients who previously used mid- to high-dose ICS or ICS/LABA therapy. The baseline-adjusted trough morning FEV_1 $AUEC_{0\text{-}12wk}$ increased in all active treatment groups vs placebo, although the differences were not significant. Overall, the safety profiles of QVAR and QVAR RediHaler were comparable (*Amar et al 2016*).
- The 6-week randomized, double-blind, parallel-group, placebo-controlled trial compared QVAR RediHaler 160 mcg and 320 mcg twice daily vs placebo, with a QVAR 160 mcg twice daily reference arm, in patients previously using non-corticosteroid, ICS ± LABA, or combination asthma therapy. For the primary endpoint of change from baseline in trough FEV_1 $AUEC_{0\text{-}6wk}$, a significantly greater improvement was seen with QVAR RespiClick 160 mcg and 320 mcg vs placebo (difference of LSM from placebo of 0.144 L and 0.150 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF, reduced rescue medication use, and a reduction in asthma symptoms vs placebo, with similar results demonstrated with QVAR 160 mcg treatment (*Ostrom et al 2018*).
- The 12-week randomized, double-blind, parallel-group, placebo-controlled trial in pediatric patients compared QVAR RediHaler 40 mcg and 80 mcg twice daily vs placebo in patients who previously used non-corticosteroid or low-dose ICS ± LABA therapy. Treatment with the QVAR RediHaler did not demonstrate a statistically significant difference vs placebo for the primary endpoint of FEV_1 $AUEC_{0\text{-}12wk}$; however, the change in weekly average of daily morning PEF was 11.3 L/min and 8.5 L/min for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, with nominal significance (*Vandewalker et al 2017*).

CLINICAL GUIDELINES

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICSs are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The GINA guideline also provides a stepwise approach to asthma management. It recommends an ICS as a preferred controller medication choice, with an increased ICS dose and/or addition of a LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (e.g., tiotropium, omalizumab, mepolizumab, reslizumab, benralizumab) (*GINA 2018*).

SAFETY SUMMARY

- ICS agents are generally contraindicated in patients with hypersensitivity to components of the product. ArmonAir RespiClick, Arnuity Ellipta, Asmanex Twisthaler, Flovent Diskus, and Pulmicort Flexhaler are also contraindicated in patients with hypersensitivity to milk proteins. All ICSs are contraindicated as primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- ICSs have no boxed warnings. Key warnings and precautions are similar among products, and generally include:
  - The occurrence of *Candida albicans* infections in the mouth and pharynx
  - Eosinophilic conditions and Churg-Strauss Syndrome
  - Glaucoma, increased intraocular pressure, and cataracts
  - Hypercorticism and adrenal suppression
  - The risk of oral corticosteroid withdrawal or adrenal insufficiency in patients transitioning from oral to ICS agents
  - Paradoxical bronchospasm
  - Reduction in bone mineral density with long-term use
  - Reduction in growth velocity in pediatric patients

- Adverse effects are similar among products. Common adverse effects include allergic rhinitis, back pain, conjunctivitis, cough, bronchitis, diarrhea, dyspepsia, dysphonia, ear infections, epistaxis, fever, gastrointestinal discomfort, gastroenteritis, headache, increased asthma symptoms, musculoskeletal pain, nasal congestion, nasopharyngitis/pharyngitis, nausea and vomiting, oral candidiasis, pharyngolaryngeal pain, rash, sinusitis, throat irritation, and upper respiratory infection.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alvesco (ciclesonide)	Inhalation aerosol (HFA): 80 or 160 mcg per actuation	Inhalation	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an ICS: initial, 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with oral corticosteroids: initial, 320 mcg twice daily; maximum, 320 mcg twice daily	Not indicated for children < 12 years of age.
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per inhalation	Inhalation	Patients ≥ 12 years of age: initial, 55, 113, or 232 mcg twice daily (dependent on asthma severity); maximum, 232 mcg twice daily	Not indicated for children < 12 years of age.
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler: 50, 100 or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg once daily; maximum, 200 mcg once daily Patients treated previously with an ICS: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily	Age 5 to 11 years: 50 mcg once daily
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Inhalation	Patients previously receiving a medium-dose ICS: 100 mcg, 2 inhalations twice daily Patients previously receiving a high-dose ICS: 200 mcg, 2 inhalations twice daily Patients currently receiving oral corticosteroids: 200 mcg, 2 inhalations twice daily	Not indicated for children < 12 years of age.
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler: 110 or 220 mcg per actuation	Inhalation	Patients treated previously with bronchodilators alone or an ICS: initial, 220 mcg once daily in the evening; maximum, 440 mcg administered as once daily in the evening or as 220 mcg twice daily	Children 4 to 11 years of age: initial, 110 mcg once daily in the evening; maximum, 110 mcg per day.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Patients treated previously with oral corticosteroids: initial, 440 mcg twice daily; maximum, 880 mcg per day	When administered once daily, should be taken only in the evening.
Flovent Diskus (fluticasone propionate)	Dry powder inhaler: 50, 100, or 250 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 100 mcg twice daily; maximum, 1000 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: initial, 50 mcg twice daily; maximum, 100 mcg twice daily
Flovent HFA (fluticasone propionate)	Inhalation aerosol (HFA): 44, 110, or 220 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 88 mcg twice daily; maximum, 880 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: 88 mcg twice daily
Pulmicort Flexhaler (budesonide)	Dry powder inhaler: 90 or 180 mcg per actuation	Inhalation	Patients ≥ 18 years of age: initial, 360 mcg twice daily (selected patients can be initiated at 180 mcg twice daily); maximum, 720 mcg twice daily	Children 6 to 17 years of age: initial, 180 mcg twice daily (selected patients can be initiated at 360 mcg twice daily); maximum, 360 mcg twice daily
Pulmicort Respules (budesonide)	Suspension for nebulization: 0.25 mg/2 mL, 0.5 mg/2 mL, or 1 mg/2 mL	Inhalation	Children 12 months to 8 years of age treated previously with only bronchodilators: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 0.5 mg total daily dose Children 12 months to 8 years of age treated previously with an ICS: initial, 0.5 mg total daily dose administered either once daily or divided into two doses; maximum, 1 mg total daily dose Children 12 months to 8 years of age treated previously with an oral corticosteroid: initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	Not indicated in adults.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol: 40 or 80 mcg per actuation	Inhalation	Patients ≥ 12 years of age, not previously on an ICS: 40 to 80 mcg twice daily; maximum, 320 mcg twice daily Patients ≥ 12 years of age, previously treated with an ICS: initial, 40, 80, 160, or 320 mcg twice daily (dependent on prior asthma therapy and asthma severity); maximum, 320 mcg twice daily	Children 4 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily

See the current prescribing information for full details.

CONCLUSION

- ICS agents are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of ICS agents as long-term controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for initiating therapy in children and adults with persistent asthma. It is important to note that the current consensus guidelines do not give preference to one ICS over another (*GINA 2018, NHLBI 2007*).
- Although individual head-to-head clinical trials have demonstrated some differences among ICS agents on certain endpoints, results have not conclusively demonstrated one agent to be significantly more effective than another in the management of asthma. Contraindications, warnings/precautions, and adverse effects are also similar among products.
- There are differences among products with respect to their available formulations, dosing schedule, and use in the pediatric population. Notably, some products are available as dry powder formulations, while others are available as inhalation aerosols. Most ICSs are dosed twice daily; however, Arnuity Ellipta is administered once daily. Asmanex Twisthaler and Pulmicort Respules may be administered either once or twice daily.
  - The appropriate choice of an ICS agent for an individual patient may depend on ease of use of the ICS device, dosing schedule, and contraindications such as hypersensitivity to milk proteins.
  - The inhaler device is an important component of treatment, and the patient's response, preference, and ability to use the inhaler device should be considered in product selection.

REFERENCES

- Alvesco [package insert], Zug, Switzerland: Covis Pharma; March 2018.
- Amar NJ, Moss MH, Kerwin EM, et al. Safety and efficacy of beclomethasone dipropionate delivered by breath-actuated or metered-dose inhaler for persistent asthma. *Allergy Asthma Proc*. 2016;37(5):359-69. doi: 10.2500/aap.2016.37.3983.
- Amar NJ, Shekar T, Varnell TA, et al. Mometasone furoate (MF) improves lung function in pediatric asthma: A double-blind, randomized controlled dose-ranging trial of MF metered-dose inhaler. *Pediatr Pulmonol*. 2017;52(3):310-318.
- ArmonAir RespiClick [package insert], Frazer, PA: Teva Respiratory, LLC; March 2018.
- Arnuity Ellipta [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2018.
- Asmanex HFA [package insert], Whitehouse Station, NJ: Merck & Co., Inc.; March 2018.
- Asmanex Twisthaler [package insert], Whitehouse Station, NJ: Merck Sharp & Dohme Corp; March 2018.
- Baker JW, Mellon M, Wald J, et al. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics*. 1999 Feb;103(2):414-21.
- Bernstein DI, Gillespie M, Song S, et al. Safety, efficacy, and dose response of fluticasone propionate delivered via the novel MDPI in patients with severe asthma: a randomized, controlled, dose-ranging study. *J Asthma.* 2017;54(6):559-569.
- Bleecker ER, Lotvall J, O'Byrne PM, et al. Fluticasone furoate-vilanterol 100-25 mcg compared with fluticasone furoate 100 mcg in asthma: a randomized trial. *J Allergy Clin Immunol Pract*. 2014;2:553-561.
- Bousquet J, D'Urzo A, Hebert J, et al. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler®. *Eur Respir J*. 2000;16:808-16.
- Busse W, Raphael GD, Galant S, et al. Low-dose fluticasone propionate compared to montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2001 Mar;107(3):461-8.
- Cinqair [package insert], Frazer, PA: Teva; March 2016.
- Corren J, Berkowitz R, Murray JJ, et al. Comparison of once-daily mometasone furoate vs once-daily budesonide in patients with moderate persistent asthma. *Int J Clin Pract*. 2003;57(7):567-72.

- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 16, 2018.
- Dupixent [package insert], Bridgewater, NJ: Sanofi-aventis U.S. LLC; October 2018.
- Fasenra [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017.
- FDA Drug Shortages - Flunisolide (Aerospan) Inhalation Aerosol. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Flunisolide+%28Aerospan%29+Inhalation+Aerosol&st=d&tab=tabs-2. Accessed November 16, 2018.
- Ferguson AC, Spier S, Manjra A, et al. Efficacy and safety of high-dose inhaled steroids in children with asthma: A comparison of fluticasone propionate with budesonide. *J Pediatr*. 1999;134(4):422-7.
- Ferguson AC, Van Bever HP, Teper AM, et al. A comparison of the relative growth velocities with budesonide and fluticasone propionate in children with asthma. *Respiratory Medicine.* 2007;101:118-29.
- Fish JE, Karpel JP, Craig TJ, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. *J Allergy Clin Immunol*. 2000;106:852-60.
- Fitzgerald D, Van Asperen P, Mellis C, et al. Fluticasone propionate 750 µg/day vs beclomethasone dipropionate 1500 µg/day: comparison of efficacy and adrenal function in pediatric asthma. *Thorax.* 1998;53(8):656-61.
- Flovent Diskus [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2017.
- Flovent HFA [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2017.
- Garcia ML, Wahn U, Gilles L, et al. Montelukast compared to fluticasone for control of asthma among six to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatrics.* 2005 Aug;116(2):360-9.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2018. Available from: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed November 16, 2018.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://goldcopd.org/gold-reports/. 2019 update. Accessed November 16, 2018.
- Hampel FC Jr, Carr W, Gillespie M, Small CJ. Evaluation of beclomethasone dipropionate (80 and 160 micrograms/day) delivered via a breath-actuated inhaler for persistent asthma. *Allergy Asthma Proc*. 2017;38(6):419-430. doi: 10.2500/aap.2017.38.4089.
- Harnest U, Price D, Howes T, Sussman G. Comparison of mometasone furoate dry powder inhaler and fluticasone propionate dry powder inhaler in patients with moderate to severe persistent asthma requiring high-dose inhaled corticosteroid therapy: findings from a non inferiority trial. *J Asthma.* 2008;45:215-20.
- Karpel JP, Nayak A, Lumry W, et al. Inhaled mometasone furoate reduces oral prednisone usage and improves lung function in severe persistent asthma. *Respir Med*. 2007;101:628-637.
- Kerwin EM, Gillespie M, Song S, et al. Randomized, dose-ranging study of a fluticasone propionate multidose dry powder inhaler in adolescents and adults with uncontrolled asthma not previously treated with inhaled corticosteroids. *J Asthma.* 2017;54(1):89-98.
- Kramer S, Rottier BL, Scholten RJPM, et al. Ciclesonide versus other inhaled corticosteroids for chronic asthma in children. *Cochrane Database of Systematic Reviews.* 2013, Issue 2. Art. No.: CD010352. doi: 10.1002/14651858.CD010352.
- Lotvall J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 µg once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomized trial. *Respir Med*. 2014;108:41-49.
- Mansfield L, Yiu G, Sakov A, et al. A 6-month safety and efficacy study of fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers in persistent asthma. *Allergy Asthma Proc*. 2017;38(4):264-276.
- Meltzer E, Korenblat P, Weinstein S, et al. Efficacy and safety evaluation of ciclesonide in mild to moderate persistent asthma previously treated with inhaled corticosteroids. *Allergy & Asthma Proceedings*. 2009;30(3):293-303.
- Meltzer EO, Kuna P, Nolte H, et al. Mometasone furoate/formoterol reduces asthma deteriorations and improves lung function. *Eur Respir J*. 2012;39:279-289.
- Nathan RA, Nayak AS, Graft DF, et al. Mometasone furoate: efficacy and safety in moderate asthma compared to beclomethasone dipropionate. Ann *Allergy Asthma Immunol.* 2001;86:203-10.
- Nathan RA, Nolte H, Pearlman DS, et al. Twenty-six-week efficacy and safety study of mometasone furoate/formoterol 200/10 microg combination treatment in patients with persistent asthma previously receiving medium-dose inhaled corticosteroids. *Allergy Asthma Proc*. 2010;31(4):269-279.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed November 16, 2018.
- National Heart, Lung, and Blood Institute. What is Asthma? August 2014. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. Accessed November 16, 2018.
- Nelson HS, Busse WW, deBoisblanc BP, et al. Fluticasone propionate powder: Oral corticosteroid-sparing effect and improved lung function and quality of life in patients with severe chronic asthma. *J Allergy Clin Immunol*. 1999;103(2 pt 1):267-75.
- Nucala [package insert], Research Triangle Park, NC: GlaxoSmithKline; December 2017.
- O'Byrne PM, Bleecker ER, Bateman ED, et al. Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma. *Eur Respir J*. 2014;43:773-782.
- O'Connor B, Bonnaud G, Haahtela T, et al. Dose-ranging study of mometasone furoate dry powder inhaler in the treatment of moderate persistent asthma using fluticasone propionate as an active comparator. *Ann Allergy Asthma Immunol.* 2001;86:397-404.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2018. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed November 16, 2018.
- Ostrom NK, Raphael G, Tillinghast J, et al. Randomized trial to assess the efficacy and safety of beclomethasone dipropionate breath-actuated inhaler in patients with asthma. *Allergy Asthma Proc*. 2018;39:117-126. doi: 10.2500/aap.2018.39.4115.
- Pulmicort Flexhaler [package insert], Wilmington, DE: AstraZeneca; October 2016.
- Pulmicort Respules [package insert], Wilmington, DE: AstraZeneca; November 2016.
- QVAR RediHaler [package insert], Frazer, PA: Teva Respiratory, LLC; June 2018.

- Raphael G, Yiu G, Sakov A, et al. Randomized, double-blind trial evaluating the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol delivered via multidose dry powder inhalers in patients with persistent asthma aged 12 years and older. *J Asthma.* 2017;Aug 1:1-11.
- Raphael GD, Lanier RQ, Baker J, et al. A comparison of multiple doses of fluticasone propionate and beclomethasone dipropionate in subjects with persistent asthma. *J Allergy Clin Immunol*. 1999;103(5):796-803.
- Rowe BH, Bota GW, Fabris L, et al. Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department. *JAMA*. 1999;281(22):2119-26.
- Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the inhaled steroid treatment as regular therapy in early asthma (START) study. Ann *Allergy Asthma Immunol.* 2005;94(1):48-54.
- Sher LD, Yiu G, Sakov A, et al. Fluticasone propionate and fluticasone propionate/salmeterol multidose dry powder inhalers compared with placebo for persistent asthma. *Allergy Asthma Proc*. 2017;38(5):343-353.
- Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of three controller regimens for mild-moderate persistent childhood asthma: the pediatric asthma controller trial. *J Allergy Clin Immunol*. 2007 Jan;119(1):64-72.
- Spiriva Respimat [package insert], Ridgefield, CT: Boehringer Ingelheim; May 2018.
- Szefler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005 Feb;115(2):233-42.
- Teva Announces U.S. Launch of QVAR® RediHaler™ (Beclomethasone Dipropionate HFA) Inhalation Aerosol. Teva Pharmaceuticals website. http://www.tevapharm.com/news/teva_announces_u_s_launch_of_qvar_redihaler_beclomethasone_dipropionate_hfa_inhalation_aerosol_02_18.aspx. Published February 16, 2018. Accessed November 16, 2018.
- Vandewalker M, Hickey L, Small CJ. Efficacy and safety of beclomethasone dipropionate breath-actuated or metered-dose inhaler in pediatric patients with asthma. *Allergy Asthma Proc*. 2017;38(5):354-364. doi: 10.2500/aap.2017.38.4078.
- Wardlaw A, Larivee P, Eller J, et al. Efficacy and safety of mometasone furoate dry powder inhaler vs fluticasone propionate metered-dose inhaler in asthma subjects previously using fluticasone propionate. *Ann Allergy Asthma Immunol.* 2004;93:49-55.
- Yang D, Wang J, Bunjhoo H, et al. Comparison of the efficacy and safety of mometasone furoate to other inhaled steroids for asthma: a meta-analysis. *Asian Pac J Allergy Immunol*. 2012;31:26-35.
- Zeiger RS, Szefler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol*. 2006 Jan;117(1):45-52.

Publication Date: January 3, 2019