

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 for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2016, Fasenra 2017, Nucala 2017*). Additionally, tiotropium, long used for chronic obstructive pulmonary disease (COPD), has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2017*).
- 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. While 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.
- 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 existing 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)	-
ArmonAir RespiClick (fluticasone propionate)	-
Arnuity Ellipta (fluticasone furoate)	-
Asmanex HFA (mometasone furoate)	-
Asmanex Twisthaler (mometasone furoate)	-
Flovent Diskus (fluticasone propionate)	-
Flovent HFA (fluticasone propionate)	-
Pulmicort Flexhaler (budesonide)	-
Pulmicort Respules (budesonide)	✓
QVAR RediHaler (beclomethasone dipropionate)	-

(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)	✓ (age ≥ 12 years)
ArmonAir RespiClick (fluticasone propionate)	✓ (age ≥ 12 years)
Arnuity Ellipta (fluticasone furoate)	✓ (age ≥ 5 years)
Asmanex HFA (mometasone furoate)	✓ (age ≥ 12 years)
Asmanex Twisthaler (mometasone furoate)	✓ (age ≥ 4 years)
Flovent Diskus & Flovent HFA (fluticasone propionate)	✓ (age ≥ 4 years)
Pulmicort Flexhaler (budesonide)	✓ (age ≥ 6 years)
Pulmicort Respules (budesonide)	✓ (age 12 months to 8 years)
QVAR RediHaler (beclomethasone dipropionate)	✓ (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 2017)

- 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 FEV₁ 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 FEV₁, forced expiratory flow at 25 to 75% of forced vital capacity (FVC; i.e., forced expiratory flow [FEF]_{25 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 FEV₁, 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, FEV₁, 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 FEV₁, 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 FEV₁, 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 FEV₁, 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 FEV₁ (*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 FEV₁ for fluticasone propionate-treated patients than beclomethasone dipropionate-treated patients. At endpoint, mean FEV₁ 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 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 FEV₁ 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 FEV₁, FEF_{25 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 (FEV₁, FVC, FEF₂₅ 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 FEV₁, 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, Szeffler *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 *et al* 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 FEV₁, 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 *et al* 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 FEV₁ 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 in patients 4 to 11 years of age (Amar *et al* 2016, Hampel *et al* 2017, QVAR RediHaler prescribing information 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 FEV₁ area under the effect curve 0 to 12 weeks (AUEC_{0-12wk}), 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 FEV₁ AUEC_{0-12wk} 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 FEV₁ AUEC_{0-6wk}, 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 (*QVAR RediHaler prescribing information 2017*, *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 FEV₁ AUEC_{0-12wk}; 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 (*QVAR RediHaler prescribing information 2017*, *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	<p><u>Patients treated previously with only bronchodilators:</u> initial, 80 mcg twice daily; maximum, 160 mcg twice daily</p> <p><u>Patients treated previously with an ICS:</u> initial, 80 mcg twice daily; maximum, 320 mcg twice daily</p> <p><u>Patients treated previously with oral corticosteroids:</u> initial, 320 mcg twice daily; maximum, 320 mcg twice daily</p>	Not indicated for children < 12 years of age.
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per inhalation	Inhalation	<u>Patients ≥ 12 years of age:</u> 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: 100 or 200 mcg per actuation	Inhalation	<p><u>Patients not previously on an ICS:</u> initial, 100 mcg once daily; maximum, 200 mcg once daily</p> <p><u>Patients treated previously with an ICS:</u> Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily</p> <p>Age 5 to 11 years: 50 mcg once daily</p>	Not indicated for children < 5 years of age.
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 100 or 200 mcg per actuation	Inhalation	<p><u>Patients previously receiving a medium-dose ICS:</u> 100 mcg, 2 inhalations twice daily</p> <p><u>Patients previously receiving a high-dose ICS:</u> 200 mcg, 2 inhalations twice daily</p> <p><u>Patients currently receiving oral corticosteroids:</u> 200 mcg, 2 inhalations twice daily</p>	Not indicated for children < 12 years of age.

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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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	
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol: 40 or 80 mcg per actuation	Inhalation	<p>Patients \geq 12 years of age, not previously on an ICS: 40 to 80 mcg twice daily; maximum, 320 mcg twice daily</p> <p>Patients \geq 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</p>	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 several differences among products with respect to their available formulations, dosing, 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. Also, while most ICSs are approved for use in children, the starting age varies among products. Table 5 summarizes some of these key characteristics.

Table 5. Characteristics of ICS agents

Drug	Formulation	Advantages	Disadvantages/Limitations
Alvesco (ciclesonide)	Inhalation aerosol	-	<ul style="list-style-type: none"> Not approved in children <12 years of age Pregnancy Category C
ArmonAir RespiClick (fluticasone propionate)	Dry powder inhaler	-	<ul style="list-style-type: none"> Contraindicated with hypersensitivity to milk proteins Not studied in pregnant women
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler	<ul style="list-style-type: none"> Once daily dosing 	<ul style="list-style-type: none"> Not approved in children <12 years of age Pregnancy Category C Contraindicated with hypersensitivity to milk proteins
Asmanex HFA (mometasone furoate)	Inhalation aerosol	-	<ul style="list-style-type: none"> Not approved in children <12 years of age Not studied in pregnant women

Drug	Formulation	Advantages	Disadvantages/Limitations
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler	<ul style="list-style-type: none"> Approved in children ≥ 4 years May be given either once or twice daily 	<ul style="list-style-type: none"> Contraindicated with hypersensitivity to milk proteins Pregnancy Category C
Flovent Diskus (fluticasone propionate)	Dry powder inhaler	<ul style="list-style-type: none"> Approved in children ≥ 4 years 	<ul style="list-style-type: none"> Contraindicated with hypersensitivity to milk proteins Not studied in pregnant women
Flovent HFA (fluticasone propionate)	Inhalation aerosol	<ul style="list-style-type: none"> Approved in children ≥ 4 years 	<ul style="list-style-type: none"> Not studied in pregnant women
Pulmicort Flexhaler (budesonide)	Dry powder inhaler	<ul style="list-style-type: none"> Approved in children ≥ 6 years Pregnancy Category B 	<ul style="list-style-type: none"> Contraindicated with hypersensitivity to milk proteins
Pulmicort Respules (budesonide)	Suspension for nebulization	<ul style="list-style-type: none"> Approved in children 12 months to 8 years May be given either once or twice daily Pregnancy Category B (although not indicated in adults) Generic availability 	<ul style="list-style-type: none"> Pediatric only; not approved in ages > 8 years
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol	<ul style="list-style-type: none"> Approved in children ≥ 4 years 	<ul style="list-style-type: none"> Not studied in pregnant women

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