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 (eg, mast cells and eosinophils) and mediators (eg, 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 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (*Centers for Disease Control and Prevention 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- 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 Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007, Global Initiative for Asthma [GINA] 2021*).
  - Control medications include:
    - Corticosteroids (ICSs, or oral corticosteroids for severe exacerbations)
    - Long-acting β-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting β-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - Anticholinergics (ie, 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 2020, Dupixent 2021, Fasenra 2021, Nucala 2020*) or with oral corticosteroid dependent asthma (*Dupixent prescribing information 2021*). Additionally, tiotropium, long used for chronic obstructive pulmonary disease (COPD), is FDA-approved for the maintenance treatment of asthma (*Spiriva Respimat prescribing information 2020*).
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2021 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. The preferred track for Step 1 and Step 2 therapy in adults and adolescents is low dose combination ICS-formoterol as needed. (*GINA 2021*).
- LABAs should not be used as monotherapy for the management of asthma due to an increased risk for serious adverse events including death; however, they are part of combination ICS-formoterol therapy and can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2021, NHLBI 2007*).
- The preferred reliever medication recommended by GINA is low dose ICS-formoterol. SABA-only treatment is not recommended for the treatment of asthma in adults or adolescents. Children can be managed with as needed SABA or ICS-formoterol. (*GINA 2021*).

- 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 but are not recommended. An additional controller option is LTRAs. Add-on options for severe asthma include tiotropium, low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
- 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] 2021*).
- Of note, QVAR RediHaler, a breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva Pharmaceuticals, was approved by the FDA in August 2017 and was launched in February 2018, replacing the previous QVAR product (*Teva Pharmaceuticals 2018*). Additionally, in January 2018, Mylan informed the FDA of the discontinuation of Aerospan (flunisolide) due to business reasons (*FDA Drug Shortages Web site*). ArmonAir RespiClick (fluticasone propionate) was also discontinued in 2018.
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alvesco (ciclesonide) inhalation aerosol	-
ArmonAir Digihaler (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) suspension for nebulization	✔
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

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 Digihaler (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 ≥ 5 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) suspension for nebulization	✔ (age 12 months to 8 years)
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	✔ (age ≥ 4 years)

(*Prescribing information: Alvesco 2020, ArmonAir Digihaler 2020, Arnuity Ellipta 2020, Asmanex HFA 2020, Asmanex Twisthaler 2021, Flovent Diskus 2020, Flovent HFA 2021, Pulmicort Flexhaler 2019, Pulmicort Respules 2019, QVAR RediHaler 2021*)

- 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 forced expiratory volume (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% ($FEF_{25\ to\ 75\%}$) of forced vital capacity (FVC), 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 2019 Cochrane review that included the 2007 study by Ferguson et al in addition to 5 other studies also concluded that fluticasone may have a less suppressive effect on growth when compared to budesonide. When pooling data from 2 studies, the mean difference in change in height over a period from 20 weeks to 1 year was 0.97 cm (95% confidence interval [CI], 0.62 to 1.32); however, there was no significant difference in linear growth velocity with comparing the 2 agents (mean difference, 0.39 cm/year; 95% CI, -0.94 to 1.73) (*Axelsson et al 2019*).

- 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 $FEF_{25\ to\ 75\%}$, 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, $FEF_{25\ to\ 75\%}$, 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 4 studies of ciclesonide versus 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 LTRA, 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 QVAR RediHaler were evaluated in 1858 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 versus 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 RediHaler 80 mcg and 160 mcg as compared to placebo (difference of least square means [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 versus 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 versus 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 versus placebo, although the differences were not significant. Overall, the safety profiles of QVAR and QVAR RediHaler were comparable (*Amar et al 2016*).
  - A 6-week randomized, double-blind, parallel-group, placebo-controlled trial compared QVAR RediHaler 160 mcg and 320 mcg twice daily versus 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 versus 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 versus placebo, with similar results demonstrated with QVAR 160 mcg treatment (*Ostrom et al 2018*).
  - A 12-week randomized, double-blind, parallel-group, placebo-controlled trial in pediatric patients compared QVAR RediHaler 40 mcg and 80 mcg twice daily versus 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 versus 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*).
- The FDA approval of ArmonAir Digihaler was based on trials of the fluticasone propionate (ArmonAir RespiClick) dry powder inhaler. The safety and efficacy of ArmonAir RespiClick was evaluated in 2130 patients with asthma, including two 12-week Phase 3 confirmatory trials (*ArmonAir Digihaler prescribing information 2020*).
  - The first 12-week Phase 3 trial (N = 647) was a randomized, double-blind, placebo-controlled trial in patients > 12 years of age previously treated with low-dose or medium-dose ICS or ICS/LABA combinations. Patients were randomized to 1 of 5 different groups: placebo, fluticasone propionate 50 mcg, fluticasone propionate 100 mcg, fluticasone propionate/salmeterol 50/12.5 mcg, or fluticasone propionate/salmeterol 100/12.5 mcg. Each treatment was administered twice daily. The efficacy of all active treatment groups was superior to placebo in terms of change from baseline in trough FEV_1 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after the dose (FEV_1 $AUEC_{0\text{–}12h}$). Change from baseline in trough morning PEF was greater with fluticasone propionate 100 mcg versus placebo, but a significant difference was not seen for fluticasone propionate 50 mcg versus placebo. Change from baseline in total daily asthma symptom scores was greater for all active treatment groups versus placebo (*Raphael et al 2018*).
  - The second 12-week Phase 3 trial (N = 728) was a randomized, double-blind, placebo-controlled trial in patients > 12 years of age previously treated with an ICS ± LABA. Patients were randomized to 1 of 5 different groups: placebo, fluticasone propionate 100 mcg, fluticasone propionate 200 mcg, fluticasone propionate/salmeterol 100/12.5 mcg, or fluticasone propionate/salmeterol 200/12.5 mcg. Each treatment was administered twice daily. All active treatment groups were superior to placebo in terms of change from baseline in trough FEV_1 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after the dose (FEV_1 $AUEC_{0\text{–}12h}$). Daily asthma symptoms scores and trough morning PEF were also improved for all active treatment groups versus placebo (*Sher 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, LTRAs, 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.

- A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS/LABA therapy with a SABA as needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS/LABA therapy.

- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
  - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (*Chipps et al 2019, GINA 2021*). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

SAFETY SUMMARY

- ICS agents are generally contraindicated in patients with hypersensitivity to components of the product. ArmonAir Digihaler, 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, dysmenorrhea, dysphonia, ear infections, epistaxis, fever, gastrointestinal discomfort, gastroenteritis, headache, increased asthma symptoms, musculoskeletal pain, nasal congestion, nasopharyngitis/pharyngitis, nausea and vomiting, oral candidiasis, otitis media, pharyngolaryngeal pain, rash, sinusitis, throat irritation, and upper respiratory infection.
- Asmanex HFA and Twisthaler, ArmonAir Digihaler, Arnuity Ellipta, Flovent Diskus and HFA, and Pulmicort Flexhaler and Respules carry warnings regarding coadministration with strong inhibitors of cytochrome P450 3A4 (eg, ketoconazole, itraconazole, nefazodone); coadministration with these agents may increase systemic corticosteroid exposure.

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 Digihaler (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per actuation	Inhalation	Patients not previously on an ICS, with less severe asthma: initial, 55 mcg twice daily; maximum, 232 mcg twice daily Patients with greater asthma severity: initial, 113 to 232 mcg twice daily; maximum, 232 mcg twice daily Patients switching from another ICS: Starting dose should be based on previous asthma drug therapy and disease severity, either 55, 113, or 232 mcg twice daily For patients who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Not indicated in children < 12 years of age. The ArmonAir Digihaler is a digital dry powder device with built-in sensors to detect when it is used and to measure inspiratory flow. It is designed to be used with a companion mobile app.
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	Age 5 to 11 years: 50 mcg once daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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 For patients ≥ 12 years of age who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 50, 100, or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg, 2 inhalations twice daily; maximum 200 mcg, 2 inhalations twice daily Patients treated previously with oral corticosteroids: 200 mcg, 2 inhalations twice daily For patients ≥ 12 years of age who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 5 to 11 years of age: 50 mcg, 2 inhalations twice daily
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 Patients treated previously with oral corticosteroids: initial, 440 mcg twice daily; maximum, 880 mcg per day For patients ≥ 12 years of age 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, 110 mcg once daily in the evening; maximum, 110 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	Children 4 to 11 years of age: initial, 50 mcg twice daily; maximum, 100 mcg twice daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			dosages may provide additional control.	
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 For patients who do not respond adequately to the starting dose after 1 to 2 weeks, higher dosages may provide additional control.	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 2 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 2 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.
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	Children 4 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			twice daily (dependent on prior asthma therapy and asthma severity); maximum, 320 mcg twice daily For patients who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	

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 controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for therapy in children and adults with asthma to prevent exacerbation and control symptoms. The 2021 GINA Global Strategy for Asthma Management and Prevention report recommends initial treatment based on a patient's presenting symptoms. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed. Step-wise adjustments to the ICS dose are recommended based on control of asthma symptoms.
- 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. ArmonAir Digihaler offers built-in sensors and connects with a companion mobile application that allows tracking and information on usage and inspiratory flow rates.
  - 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.

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