

Efficacy and Safety of Inhaled Corticosteroids in Infants and Young Children with Persistent Asthma

by William E. Berger

Background: Inhaled corticosteroids (ICSs) are recommended as the preferred controller treatment for all severities of persistent asthma in children aged 5 years and younger.

Methods/Data base: A review of published efficacy and safety data for ICS use in infants and children younger than 5 years was based on relevant articles identified from MEDLINE and reference lists of review articles.

Results: Extensive clinical data for nebulized budesonide inhalation suspension in children aged 6 months to 8 years and more limited data for budesonide and fluticasone administered via pressurized metered-dose inhaler or dry-powder inhaler demonstrate that ICS therapy is both effective and safe for the treatment of persistent asthma in infants and young children.

Conclusion: Published studies, especially for nebulized budesonide suspension, support the preferred use of ICSs in infants and young children with persistent asthma. As the only ICS available in the United States for nebulization, this ICS, in particular, may be well suited for infants and children unable to use conventional ICS delivery devices.

Keywords: inhaled corticosteroids, treatment efficacy, nebulized budesonide inhalation suspension, young children

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Introduction

The efficacy and safety of inhaled corticosteroids (ICSs) are well documented in children with asthma who are older than 4 years; however, relatively few studies have evaluated ICS use in

patients younger than 4 years. A reluctance to prescribe ICSs for young children in the United States (the prescribing rate is half that of other countries) likely reflects this limited data and lingering concerns about the safety of ICSs in pediatric patients with asthma. These concerns were addressed in the 2002 National Asthma Education and Prevention Program (NAEPP) update of asthma treatment guidelines [1], which incorporated the findings of 2 studies comparing ICSs with placebo in preschool-aged children [1]. This review encompasses additional studies of ICS use reported in the literature that have included infants and children younger than 5 years.

ICS Delivery to Young Children with Asthma

A variety of devices are available for the delivery of inhaled asthma medications to children (see Table 1) [2]. Choosing the appropriate device is key to providing maximal treatment benefit. Conventional ICS delivery devices (i.e., pressurized metered-dose inhalers (pMDIs) and dry-powder inhalers (DPIs)) may be inappropriate for some children. For those children who have difficulty in coordinating pMDI actuation with inspiration, the use of a spacer can help; however, coordination is still required for optimal delivery. The use of a DPI can be a disadvantage for those children who are unable to generate sufficient inspiratory flow. Although DPIs can be used by 4-year-old children, delivery via DPI is more reliable in children older than 5 years [2].

Of the available delivery device options, only nebulizers do not require coordination of actuation with inspiration or a high inspiratory flow rate for optimal medication delivery. Greater ease of ICS delivery via nebulization may improve asthma management in infants and some young children. For those children who are unable to use a mouthpiece effectively, the use of a face mask with a nebulizer (or pMDI plus spacer) may be of added

TABLE 1
AVAILABLE DELIVERY DEVICES FOR INHALED ASTHMA MEDICATIONS

| Delivery Device | Medication | Recommended Age for Use | Remarks |
|----------------------------|---|---|--|
| Metered-dose inhaler (MDI) | Anticholinergics β_2 -adrenergic agonists Corticosteroids Cromolyn sodium Nedocromil sodium | > 5 years (< 5 years with spacer/holding chamber and face mask for some children) | The child may have difficulty triggering a puff while inhaling. Use with a spacer/holding chamber helps. |
| Breath-actuated MDI | β_2 -adrenergic agonists | > 5 years | The child may not be able to generate the necessary inspiratory flow. Device does not require use of a holding chamber or spacer. |
| Dry-powder inhaler (DPI) | β_2 -adrenergic agonists Corticosteroids | > 5 years (can be used in 4 year olds, but delivery is more consistent > 5) | Some devices deliver drug more effectively than an MDI. Some devices may not work in children with low inspiratory volumes. |
| Nebulizer | Anticholinergics β_2 -adrenergic agonists Corticosteroids Cromolyn sodium | Patients of any age who cannot use an MDI with spacer/holding chamber or with face mask | Useful in infants and very young children, and any child with a moderate to severe asthma episode although MDI with spacer/holding chamber may be as effective. Delivery method of choice for cromolyn sodium. |

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benefit. To date, no clinical studies have been conducted to compare ICS delivery to the lungs when administered by nebulizer or pMDI plus spacer in pediatric patients with asthma.

Efficacy of Nebulized ICSs in Young Children

Nebulized formulations of beclomethasone dipropionate, budesonide, and fluticasone propionate have been developed for asthma treatment; however, only nebulized budesonide inhalation suspension (BIS; Pulmicort Respules[®], AstraZeneca LP, Wilmington, DE, USA) is available for use in the United States. BIS is approved by the US Food and Drug Administration for the treatment of asthma in children aged 12 months to 8 years. The efficacy and safety of nebulized fluticasone propionate inhalation suspension (Flixotide[®], Nebules[®], GlaxoSmithKline, Research Triangle Park, NC, USA) have been assessed over the short term only in those pediatric asthma patients older than 4 years suffering from acute asthma exacerbations [3, 4].

Beclomethasone Dipropionate

Studies of nebulized beclomethasone in infants and young children are limited, and results have been inconsistent [5–9]. In

a small, double-blind, crossover study conducted in children aged 24 months to 5 years with moderately severe asthma, parents of 8 children who completed the study felt that their child's asthma was better controlled with nebulized beclomethasone (150 μ g daily), whereas the parents of 5 children thought that placebo provided greater asthma control. Analysis of daily diaries maintained by the parents supported these views [5]. Breakthrough medication use and the number of children requiring oral corticosteroids were similar in children treated with beclomethasone and placebo [5]. In a second study that failed to demonstrate clear benefit of nebulized beclomethasone in preschool-aged children (mean age 3.6 years) with severe asthma, differences in reported symptoms between patients receiving beclomethasone and placebo were significant only for wheeze [6].

In contrast to these studies, more recent studies have demonstrated clear efficacy of nebulized beclomethasone in pediatric patients with asthma [7–9]. In a randomized, parallel-group, open-label study, 130 children aged 6 months to 6 years with severe persistent asthma were randomized to receive beclomethasone dipropionate suspension for nebulization (Clenil A[®], Chiesi Farmaceutici SpA, Parma, Italy) 800 μ g daily or BIS 750 μ g daily, plus oral ketotifen for 12 weeks [7]. In this trial, both agents significantly reduced exacerbations, nights with wheeze, and days of oral corticosteroid use [7]. Similar results were observed in another comparative trial of these agents that

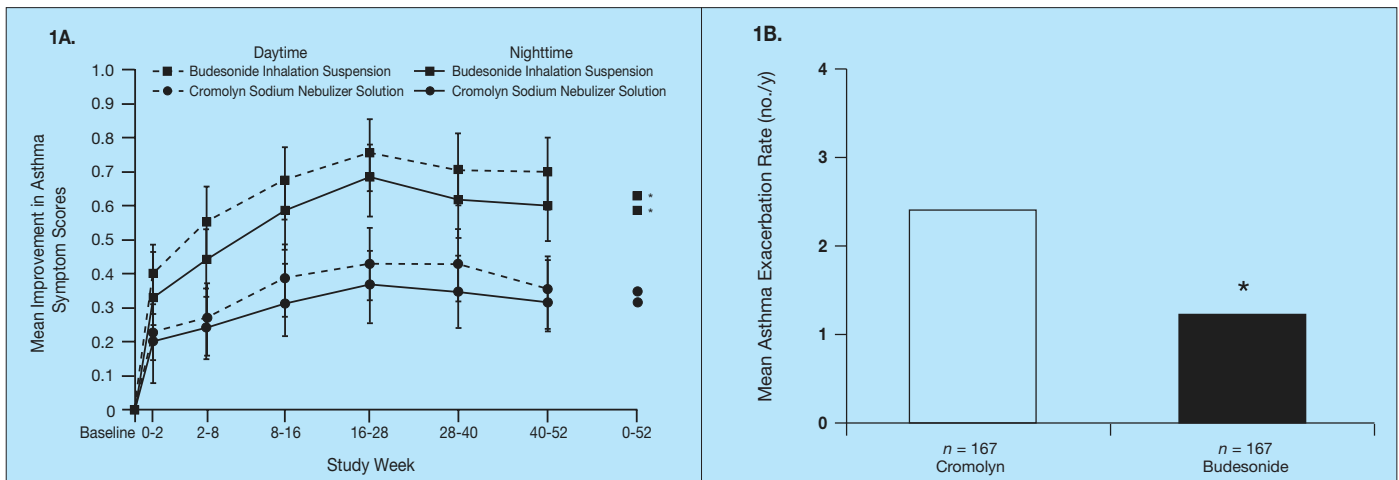


Figure 1. Comparison of budesonide inhalation suspension vs. cromolyn sodium nebulizer solution based on (A) mean improvements from baseline in asthma symptom scores from week 0 to 52 and (B) mean rate of asthma exacerbations over 52 weeks. * $p < .001$ for budesonide versus cromolyn. (Part A reproduced with permission from [16]. Part B reproduced with permission from [50].)

enrolled 127 children aged 6 to 14 years with mild to moderate persistent asthma [8]. Comparable efficacy of beclomethasone administered via nebulization or MDI (1,600 vs. 800 $\mu\text{g}/\text{day}$, respectively) was demonstrated in children aged 6 to 16 years with moderate to severe exacerbations of asthma [9].

Budesonide

US and non-US clinical trials have demonstrated efficacy of nebulized budesonide for the treatment of asthma in infants and young children [10–16]. The efficacy of inhaled budesonide in young children was first evaluated outside of the United States. Overall, children with moderate to severe asthma (aged 6 months to 5 years) who received inhaled budesonide demonstrated improved daytime and nighttime symptom scores, fewer asthma exacerbations, and decreased need for additional asthma medications, including oral corticosteroids [10–12].

In the United States, three large, randomized, double-blind, placebo-controlled, parallel group studies enrolling a total of 1,017 children as young as 6 months, evaluated the efficacy and safety of BIS for the treatment of mild to moderate persistent asthma [13–15]. Two studies included patients with a history of ICS use [13,14], whereas the third study enrolled patients dependent on daily ICSs [15]. Oral corticosteroids or other ICSs were not permitted during these studies, which included a baseline screening period, followed by 12 weeks of double-blind treatment with BIS or placebo.

Kemp and colleagues [13] evaluated BIS efficacy vs. placebo in 359 patients aged 6 months to 8 years with mild persistent asthma that was poorly controlled with bronchodilators or non-corticosteroid anti-inflammatory medications. Patients were randomized to receive BIS 0.25, 0.5, or 1 mg once daily or placebo for 12 weeks. Compared with placebo, BIS significantly ($p < .05$) improved daytime and nighttime asthma symptom scores and decreased daily bronchodilator use. The 0.5 mg and 1 mg doses of BIS also provided significant ($p < .05$) im-

provement in forced expiratory volume in 1 s (FEV_1) vs. placebo in the subgroup of patients able to perform pulmonary function tests.

The second US pivotal study assessed the efficacy and safety of BIS administered once or twice daily in 480 children aged 6 months to 8 years with moderate persistent asthma, one third of whom were maintained on ICSs before study enrollment [14]. Statistically significant ($p \leq .01$) improvements from baseline in nighttime asthma symptom scores were observed for patients receiving BIS 0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily in the morning. Similar improvements were observed in daytime asthma symptom scores.

Shapiro and colleagues [15] compared the efficacy and safety of BIS 0.25, 0.5, or 1 mg administered twice daily vs. placebo in 178 children aged 4 to 8 years with ICS-dependent asthma. Children receiving BIS demonstrated a 30% to 40% reduction in asthma symptom scores and a > 50% reduction in the number of days that reliever medication was required ($p \leq .03$) compared with placebo [15]. The 0.25-mg twice-daily BIS dose provided more variable effects compared with higher BIS doses. For this reason, BIS therapy should be initiated at higher daily doses, with subsequent step-down in dose, whenever possible.

Finally, in a 52-week, randomized, open-label comparator trial, 335 children aged 2 to 6 years with persistent asthma requiring ≥ 1 long-term control medication received either BIS 0.5 mg daily or cromolyn sodium nebulizer solution 20 mg 4 times daily for 8 weeks [16]. After the initial 8-week treatment period, study drug doses could be adjusted as needed, by the investigator. Improvements in asthma symptoms were observed within 2 weeks of randomization and were maintained throughout the study (see Figure 1A). Compared with nebulized cromolyn, BIS treatment significantly ($p \leq .001$) decreased the yearly rate of asthma exacerbations (see Figure 1B). Patients receiving BIS had a mean exacerbation rate of 1.23 ± 1.99 exacerbations per year compared with 2.41 ± 6.13 for patients receiv-

ing cromolyn. Moreover, the times to first exacerbation and to first use of additional long-term controller medication were significantly ($p < .001$) longer for children receiving BIS compared with cromolyn. Patients receiving BIS also had a lower requirement for breakthrough medication and oral corticosteroid use, and had fewer urgent care visits than those receiving cromolyn. Reductions in breakthrough medication use, emergency department use, and hospitalizations also were reported in the 52-week, open-label extension studies of 2 of the BIS pivotal trials in which asthma health care services were assessed [17, 18].

Administration of BIS

In each of the US pivotal studies, medication was delivered using a PARI LC-Jet Plus Nebulizer with a PARI-Master compressor (PARI Respiratory Equipment, Inc., Richmond, VA, USA). BIS is approved for use in any jet nebulizer. Currently available ultrasonic nebulizers are not recommended for the delivery of BIS because, in general, these nebulizers cannot effectively aerosolize drugs in suspension [19]. When using a jet nebulizer for BIS delivery, the use of a face mask or mouthpiece results in similar efficacy [20–22]; however, in children who are able to use a mouthpiece properly, compromised delivery from an improperly fitted face mask and reduced lung deposition as a consequence of nasal breathing may be avoided.

A recent *in vitro* study suggests that BIS can be mixed with other common nebulizable asthma medications to simplify asthma treatment regimens. The study by McKenzie and Cruz-Rivera [23] demonstrated chemical compatibility and stability of BIS admixtures containing levalbuterol hydrochloride, albuterol sulfate, ipratropium bromide, and cromolyn sodium. The authors noted that results of this study should not be extrapolated to budesonide solutions compounded by individual pharmacies.

Efficacy of ICSs Administered via MDI or DPI

Fluticasone Propionate

Most pediatric studies of fluticasone propionate administered via MDI or DPI have included children as young as 4 years with mild to severe persistent asthma [24–29]. Two reports include children as young as 12 months with recurrent asthma symptoms or wheeze [30,31].

In 166 children aged 4 to 12 years with severe persistent asthma, fluticasone 400 µg per day administered via DPI (Flovent Diskus[®], GlaxoSmithKline, Research Triangle Park, NC, USA) demonstrated improvement in morning peak expiratory flow (PEF) from a baseline of 236 ± 72 L/min to 271 ± 82 L/min after 20 weeks of treatment [24]. Asthma control based on daytime and nighttime symptoms and the need for breakthrough medication was comparable in the group of children receiving fluticasone and a group of 167 children receiving budesonide

800 µg per day via DPI (Pulmicort Turbuhaler[®], AstraZeneca LP, Wilmington, DE, USA) [24]. Although improvement in PEF was greater among children receiving fluticasone ($p = .027$), a second study demonstrated similar improvement in PEF among 229 children aged 4 to 13 years with mild to moderate persistent asthma after 8 weeks of treatment with either fluticasone Diskhaler[®] (GlaxoSmithKline, Research Triangle Park, NC, USA) 400 µg per day or budesonide Turbuhaler[™] 400 µg per day [25].

The efficacy of once- vs. twice-daily administration of Flovent Diskus[®] was evaluated in 242 patients aged 4 to 11 years by LaForce and colleagues [27]. In the 12-week, double-blind, placebo-controlled trial and its 52-week open-label extension, patients receiving fluticasone 100 µg twice daily and 200 µg once daily demonstrated significant improvement in percent predicted FEV₁ ($p \leq .005$); however, improvement was significantly greater at the end of the double-blind phase with twice- vs. once-daily dosing ($p = .045$). Significant improvements vs. placebo in morning PEF ($p \leq .005$) and nighttime awakenings ($p < .001$) were demonstrated only in those patients receiving twice-daily dosing. A report by the US Food and Drug Administration comparing the efficacy of once- vs. twice-daily dosing of fluticasone included 2 pediatric asthma studies and determined that twice-daily dosing with fluticasone was consistently more effective than once-daily administration of the same dose [32].

In children aged 12 to 47 months with recurrent asthma symptoms or wheeze, pooled data from 2 double-blind, placebo-controlled, parallel-group studies demonstrated a significant ($p = .002$) increase in days and nights without symptoms, vs. placebo, in patients treated with fluticasone 200 µg per day via pMDI with spacer [31]. Greater asthma control with fluticasone 100 µg administered twice daily via MDI with spacer was likewise demonstrated vs. cromolyn sodium in children aged 12 to 47 months with recurrent wheeze [30].

Budesonide

The efficacy of budesonide Turbuhaler[™] has been demonstrated in pediatric patients aged 5 to 18 years with mild to severe persistent asthma [33–36]. Although placebo-controlled trials with children younger than 5 years have not been published, a randomized, double-dummy trial compared the efficacy of budesonide administered via MDI with spacer vs. Turbuhaler[™] in 126 children aged 4 to 15 years with persistent asthma [37]. Asthma control was maintained with an approximate 50% lower mean dose of budesonide delivered via Turbuhaler[™] vs. MDI plus spacer [37].

The effectiveness of budesonide 200 µg administered twice daily via MDI with spacer and face mask was evaluated in a study of 40 children aged 1 to 3 years with severe persistent asthma. Titration up to a maximum daily dose of 800 µg was allowed [38]. Compared with placebo, nighttime breakthrough bronchodilator use decreased significantly ($p < .05$) with budesonide. Moreover, the proportion of symptom-free days was significantly ($p < .0001$) greater with budesonide vs. placebo (54% vs. 31%, respectively). A second randomized, placebo-controlled study of the effectiveness of budesonide via MDI with

spacer in children aged 2 to 5 years with persistent asthma similarly demonstrated a significant ($p = .03$) increase in the percentage of symptom-free days over 8 weeks of treatment with budesonide vs. placebo, and a significantly ($p = .01$) lower percentage of days with exacerbations of asthma (4.9% vs. 19.4% for placebo) [39]. Equipotency of budesonide 800 μg administered twice daily via MDI with spacer and nebulized budesonide 1 and 4 mg administered twice daily has been established in a dose-response study in adult patients with moderately severe, unstable asthma [40]; however, dose-response studies have not yet compared the relative efficacy of ICS delivery devices in pediatric patients with asthma.

Long-Term Safety of ICSs

In a recent systematic review of the literature, the American College of Chest Physicians, the American Academy of Allergy, Asthma and Immunology, and the American College of Allergy, Asthma and Immunology, determined that the benefits of ICS treatment outweigh the potential for adverse effects in adults and children with asthma [41]. Furthermore, based on evidence from clinical trials that followed children for as long as 6 years, the NAEPP concluded that recommended doses of ICSs do not have “long-term, clinically significant, or irreversible effects” on linear growth, bone mineral density, ocular toxicity, or adrenal function [1].

A limited number of long-term (≥ 1 year) ICS safety trials have included preschool-aged children. The safety of BIS was evaluated in 4 trials that included children younger than 4 years. Three trials of fluticasone administered via DPI have included children 4 years and older.

BIS treatment was well tolerated in the 52-week open-label extensions of the 3 BIS pivotal trials. The open-label extensions were conducted in 670 children (mean age 5 years; range 8 months to 9 years) who were randomized to receive budesonide or conventional asthma therapy (CT) after 12 weeks of double-blind, placebo-controlled treatment. The overall incidence and severity of adverse events in these trials, when adjusted for study duration, were similar between the budesonide and CT groups. Respiratory infection, the most frequently reported adverse event, occurred in 58% of children receiving BIS and 49% of children receiving CT [42]. No adrenal suppression was evident based on data from the subset of children who provided basal ($n = 189$) and corticotropin-stimulated ($n = 180$) cortisol samples [43]. Finally, no significant differences in growth velocity or standard median height between treatments were demonstrated in a pooled analysis of these 3 extensions [44]. Similar safety findings were demonstrated in an open-label trial of BIS vs. cromolyn sodium nebulizer solution that enrolled children aged 2 to 6 years with mild to moderate persistent asthma [16]. The tolerability of budesonide was comparable to that of cromolyn, with no significant differences in the frequency or type of reported adverse events between treatments. As in the

52-week extensions of the BIS pivotal studies, respiratory infection was the most frequently reported adverse event. Adrenal function was not suppressed in either treatment group [16]. Likewise, no suppression of adrenal function was evident in a longer-term safety study conducted in 15 children aged 2 to 7 years with severe asthma receiving a 200- μg daily dose of inhaled budesonide for 3 to 5 years [45]. Although mean increases in height among the 153 children who completed 1 year of treatment with BIS were lower than among the 129 children who completed 1 year of treatment with cromolyn (6.69 vs. 7.77 cm; $p < .001$) [16], growth velocity may be delayed with ICSs. Longer-term studies with inhaled budesonide [33, 46] show that growth effects with budesonide are small, nonprogressive, and may be reversible in older children [1].

Growth effects of fluticasone were evaluated in 60 children aged 4 to 10 years who were included in 1 of the 3 long-term pediatric fluticasone trials. In a 1-year open-label trial of children with mild asthma, no significant differences in height velocity adjusted for age and sex were observed for children who received cromolyn sodium 20 mg 4 times daily ($n = 26$) and fluticasone 50 μg twice daily via Diskhaler[®] ($n = 34$) [47]. This study also demonstrated no difference in 24-hour urinary free cortisol between the treatment groups at 12 months.

The effects of fluticasone on adrenal function also were evaluated in a second open-label trial in which children aged 4 to 11 years received fluticasone 200 μg via DPI administered once daily or in divided doses twice daily for 1 year [27]. Although no clinically relevant changes from baseline in mean morning plasma cortisol concentrations occurred, 9 patients experienced abnormal cortisol concentrations, defined as a cortisol level less than 4 $\mu\text{g}/\text{dL}$, at their last study visit. Four of these patients had received concomitant oral prednisone. Overall, fluticasone was well tolerated in this trial, with reports of drug-related adverse events occurring in 4% to 6% of patients in each group. It should be noted, however, that fluticasone has been associated with a markedly greater number of cases of adrenal crisis compared with other ICSs [48]. According to a UK survey reported by Todd and colleagues, most adults and children identified with adrenal crisis (91%) in the survey had received fluticasone as their ICS controller medication [48]. The fact that most cases of adrenal crisis occurred in patients receiving fluticasone (≥ 500 μg daily) was unexpected considering the infrequent prescribing of fluticasone in the United Kingdom. The authors suggested caution in prescribing fluticasone at daily doses > 400 μg for children.

Growth and adrenal function were not evaluated in the third long-term fluticasone trial. This open-label study evaluated the safety of fluticasone 50 or 100 μg twice daily via Diskhaler[®] in 257 children aged 4 to 17 years with moderately severe asthma [49]. As in the BIS trials, upper respiratory tract infection was among the most commonly reported adverse events, second only to “asthma and related events.” Overall, fluticasone was well tolerated, with adverse events considered possibly, likely, or certainly related to study medication (e.g., asthma-related event, hoarseness, oral candidiasis, cough, throat problems) occurring in 10% of patients.

Conclusions

The role of ICS use in adults and older children is firmly established in the literature, however, there are relatively few published studies addressing efficacy and safety of most ICS formulations in infants and children younger than 5 years. Numerous ICS formulations are available for treating asthma in children. The choice of delivery device (i.e., pMDI, DPI, or nebulizer) is key to providing optimal treatment benefit and will depend on the variable abilities of pediatric patients who require their use. Nebulizer therapy can provide an effective approach to ICS delivery for infants and very young children who lack the ability to properly use pMDIs and DPIs. Among ICSs developed for nebulization, BIS is available in the United States and approved for use in children as young as 12 months. The efficacy and safety of BIS have been extensively evaluated in the pediatric population. Clinical studies enrolling > 1,000 patients as young as 6 months have demonstrated clear efficacy and safety of this ICS formulation in infants and young children with a range of asthma severities. Although less extensive, data also demonstrate that administration of ICSs via pMDI or DPI benefit young children with asthma who have the coordination and physical capabilities to use these delivery devices. Long-term studies demonstrating safety of ICS use in children point to the greater risk of uncontrolled asthma in this population.

The NAEPP now recommends ICSs as the preferred treatment for the long-term control of persistent asthma, including mild persistent asthma, in children \leq 5 years of age. For those children aged 4 and 5 years, non-nebulized ICS formulations may be effective and appropriate. As the only nebulizable ICS available in the United States, and the only ICS approved by the FDA for children as young as 12 months, BIS is an important first-line anti-inflammatory agent for the treatment and maintenance of persistent asthma in children 4 years and younger, as well as in older children who cannot appropriately use other ICS delivery devices.

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