Safety profile of budesonide inhalation suspension in the pediatric population: worldwide experience

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Objective: To review the worldwide safety data for budesonide inhalation suspension (Pulmicort Respules) to provide a budesonide inhalation suspension pediatric tolerability profile.

Data Sources: Clinical study data were obtained from AstraZeneca safety databases used by the US Food and Drug Administration to support the approval of budesonide inhalation suspension and from postmarketing surveillance reports (January 1, 1990, through June 30, 2002).

Study Selection: Completed parallel-group studies of patients with asthma 18 years and younger.

Results: Safety data for budesonide inhalation suspension were pooled from 3 US, 12-week, randomized, double-blind, placebo-controlled studies (n = 1,018); data from their open-label extensions (n = 670) were pooled with data from a fourth US open-label study (n = 335). Data for 333 patients 18 years and younger enrolled in 5 non-US studies also were analyzed. No posterior subcapsular cataracts were reported in any study, and the frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable. There were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in 2 of 5 trials that evaluated this variable. No increased risk of adverse events was apparent from postmarketing reports.

Conclusions: Short- and long-term treatment with budesonide inhalation suspension, using a wide range of doses, is safe and well tolerated in children with asthma.


INTRODUCTION
Inhaled corticosteroids (ICSs) are effective in controlling airway inflammation and are considered the preferred therapy for children with persistent asthma.1–3 Treatment with ICSs controls symptoms, reduces exacerbations, improves lung function, and decreases hospitalization rates.4–7 Despite evidence supporting the efficacy of ICS therapy in pediatric patients, underuse of ICSs in the United States has been documented.8,9 Challenges in medication delivery10,11 and concerns about safety may contribute to the underuse of ICSs.5,8

Nebulizers require little coordination from the patient and no voluntary control of respiration, thereby allowing the child to breathe at his or her own rhythm.12 Both the National Heart, Lung, and Blood Institute asthma treatment guidelines3 and the American Academy of Allergy, Asthma and Immunology pediatric practice guidelines2 recommend nebulization as an option for the delivery of ICSs, cromolyn, and short-acting β2-agonists, especially in children younger than 2 years. In the United States, budesonide inhalation suspension (Pulmicort Respules; AstraZeneca LP, Wilmington, DE) is the only Food and Drug Administration (FDA)–approved ICS available for delivery by nebulization and the only ICS indicated for the management of asthma in children aged 12 months to 8 years.13,14

The severity and frequency of adverse events associated with ICS therapy depend on a wide range of variables (eg, mode of administration, concurrent medications, and age-specific factors).15 National asthma guidelines, however, suggest that the potential risks of ICS therapy are well balanced by the benefits.2,3 Until recently, there was a paucity of published age-specific safety data to guide practicing physicians in the use of ICSs in children, particularly those younger than 4 years.16 Few double-blind, placebo-controlled clinical studies have evaluated the safety and efficacy of different ICSs administered to pediatric patients via pressurized metered-dose inhaler with a spacer.

Studies assessing the efficacy and tolerability of budesonide inhalation suspension treatment for asthma have been conducted worldwide in children as young as 5 months. Furthermore, it is estimated that as of June 30, 2002, there
have been more than 314.1 million treatment days of postmarketing experience with budesonide inhalation suspension worldwide (data on file, AstraZeneca LP). This report reviews the safety profile of nebulized budesonide inhalation suspension therapy in children, including those younger than 4 years, based on worldwide clinical experience and postmarketing surveillance reports. Safety is reviewed in the context of adverse events commonly associated with ICS therapy.

MATERIALS AND METHODS

Data Sources
Clinical study data were obtained from AstraZeneca safety databases that included data from US and non-US studies (completed and ongoing) on patients of all ages using budesonide inhalation suspension for various indications. These studies were used by the US FDA to support the approval of budesonide inhalation suspension.

Postmarketing adverse event reports following the first worldwide approval of budesonide inhalation suspension (January 1, 1990, through June 30, 2002) also contributed to the safety databases and included spontaneous reports. These reports represent postmarketing safety data received by AstraZeneca (data on file, AstraZeneca LP) and case reports in the literature, as well as National Adverse Drug Reaction Advisory Committee reports, which represent reports provided by national health authorities to AstraZeneca and the FDA.

Study Selection
Only studies completed at the time of manuscript preparation were included. Studies must have included patients 18 years and younger with asthma; studies of other indications or conducted exclusively in adults were excluded from the analysis. Parallel-group studies were selected from the non-US studies to facilitate pooling of adverse events, whereas US studies could also include those with a crossover design. Pharmacokinetic studies and studies of compassionate use programs were excluded.

Outcomes
Safety databases were evaluated for adverse events commonly associated with corticosteroid use. Adverse events were stratified by drug (ie, budesonide, placebo, and reference drug) in the US and non-US studies. In US studies, the incidence and type of common adverse events, effect on growth, and clinical laboratory findings were evaluated. In non-US studies, adverse events were evaluated as a percentage of the total reported adverse events. Because of differences in adverse event reporting, US and non-US study data were not pooled. Postmarketing surveillance reports of adverse events were tabulated regardless of suspected causal relationship or severity.

RESULTS

Clinical Studies
Short- and long-term clinical studies of budesonide inhalation suspension were included in the analysis (Table 1). Short-term US safety data for budesonide inhalation suspension were obtained from 3 randomized, 12-week, double-blind, placebo-controlled, multicenter studies involving 1,018 patients aged 6 months to 8 years with persistent asthma treated once or twice daily with budesonide inhalation suspension (0.25–2.0 mg/d).17–19 Long-term safety data were obtained from 670 children who received budesonide inhalation suspension or conventional asthma therapy (including oral and inhaled β2-agonists, oral methylxanthines, cromolyn sodium, or other ICSs) during the 52-week open-label extensions of these 3 studies20–22 and from 335 patients aged 2 to 6 years who participated in a 52-week study comparing asthma-related health outcomes with budesonide inhalation suspension vs cromolyn sodium nebulizer solution.7 Growth data are presented separately for each of these 4 open-label trials. However, a previously published pooled analysis of growth data from the 3 pivotal open-label trials also is reviewed.21

Data from 5 non-US parallel-group studies involving 333 pediatric patients treated with budesonide inhalation suspension or reference drug were also analyzed for safety (Table 1): 4 studies included only children with moderate-to-severe persistent asthma and 1 study included adults and adolescents with acute asthma. The double-blind trial by Ilangovan et al23 evaluated the oral corticosteroid-sparing effects of budesonide, 1 mg twice daily, vs placebo for more than 8 weeks in children with severe persistent asthma. The trial by Wennergren et al24 was a single-blind, 18-week study that evaluated the minimum effective dose of budesonide needed for maintenance treatment of moderate-to-severe persistent childhood asthma. An unpublished trial included children who participated in the 52-week open-label extension of the previous dose-finding study. The trial by Nikander et al25 was a randomized, double-blind, 24-week investigation of treatment compliance with budesonide administered twice daily to children younger than 6 years with severe prednisolone-dependent asthma. Another unpublished trial compared the short-term efficacy of budesonide with that of placebo and oral prednisolone (60 mg) in adults and adolescents with acute asthma. Evaluable data for two 18-year-old patients from this study of acute asthma are reported herein.

Outcomes

Growth and bone metabolism. The effects of budesonide inhalation suspension on growth demonstrated in the 3 pivotal US open-label extension studies have been reviewed in detail elsewhere.20,21 Briefly, in the open-label extensions of the studies by Baker et al19 and Shapiro et al,19 no significant differences were observed between the budesonide and conventional asthma therapy groups in changes in growth velocities or height SD scores. In the 52-week open-label extension of the study by Kemp et al17 there was a small but statistically significant decrease in growth velocity (−0.8 cm/y; P = .002) and height SD score (−0.19; P = .003) with budesonide (mean daily dose, 0.52–0.54 mg) compared with conventional asthma therapy.21 However, in pooled analyses of data from children who completed the three 52-week
open-label extensions of the US pivotal studies, no significant difference in growth velocity was observed in those who received budesonide (n = 871) vs conventional asthma therapy (n = 261). Mean growth velocity was 6.64 ± 2.28 and 6.45 ± 2.52 cm/y in the budesonide and conventional asthma therapy groups, respectively. Standard median heights and skeletal age, which were evaluated in 2 of the studies, also were similar in children who received budesonide vs conventional asthma therapy.

Although not designed as a prospective growth study, the open-label trial of budesonide inhalation suspension vs cromolyn yielded results similar to those of the study by Kemp et al., with children who received cromolyn having a significantly greater mean change in height vs those who received budesonide (7.55 vs 6.69 cm/y). The mean daily dose of budesonide inhalation suspension ranged from 0.54 mg (weeks 0–8) to 0.61 mg (weeks 40–52). In the 1 non-US study that evaluated growth, children given budesonide showed a growth velocity during the 18-week study similar to that during the run-in period and in accordance with Swedish reference values for height.

Varicella

Varicella infection was infrequent in children receiving placebo (2%) or budesonide inhalation suspension (<1%) in the 3 US double-blind studies, and data combined from the 4 US open-label studies revealed a comparable incidence of varicella in children receiving budesonide (5.2%) and reference drug (4.2%). In the non-US studies, varicella accounted for only a small percentage of total adverse events reported in children receiving budesonide (1.3%) or reference drug.

Table 1. US and Non-US Studies of Budesonide Inhalation Suspension for Asthma

<table>
<thead>
<tr>
<th>Study population</th>
<th>Age range</th>
<th>Study drug</th>
<th>Assessable patients, n</th>
<th>Discontinued patients, n</th>
<th>Extension study drug</th>
<th>Assessable patients, n</th>
<th>Discontinued patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>US studies</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mild-to-moderate persistent asthma17</td>
<td>6 mo to 8 y</td>
<td>BUD, 0.25–1 mg/d</td>
<td>267</td>
<td>50</td>
<td>BUD</td>
<td>182</td>
<td>25</td>
</tr>
<tr>
<td>Mild-to-moderate persistent asthma18</td>
<td>6 mo to 8 y</td>
<td>Placebo nebulization</td>
<td>92</td>
<td>26</td>
<td>CAT</td>
<td>90</td>
<td>29</td>
</tr>
<tr>
<td>ICS-dependent asthma19</td>
<td>4 to 8 y</td>
<td>BUD, 0.5–2 mg/d</td>
<td>134</td>
<td>20</td>
<td>BUD</td>
<td>61</td>
<td>8</td>
</tr>
<tr>
<td>Persistent asthma20</td>
<td>2 to 8 y</td>
<td>Placebo nebulization</td>
<td>44</td>
<td>19</td>
<td>CAT</td>
<td>30</td>
<td>4</td>
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<tr>
<td>Non-US studies</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Severe OCS-dependent asthma21</td>
<td>9 to 60 mo</td>
<td>BUD, 2 mg/d</td>
<td>18</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent asthma22†</td>
<td>5 to 47 mo</td>
<td>Placebo nebulization</td>
<td>19</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent asthma22†</td>
<td>2 to 4 y</td>
<td>BUD, 0.5 and 2 mg/d, titrated to MED24</td>
<td>102</td>
<td>14</td>
<td>Individual BUD dose</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>Persistent asthma22†</td>
<td>7 to 71 mo</td>
<td>BUD, 0.2 mg, for 2–12 wk + BUD, 0.05 mg, to 24 wk</td>
<td>115</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute asthma‡</td>
<td>16 to 88 y</td>
<td>BUD, 2 × 4 mg, in the acute phase (4 h)</td>
<td>28</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo nebulization in the acute phase</td>
<td>31</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral prednisolone, 60 mg, in the acute phase</td>
<td>29</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BUD, budesonide inhalation suspension; CAT, conventional asthma therapy; CN, cromolyn sodium nebulizer solution; ICS, inhaled corticosteroid; MED, minimum effective dose; OCS, oral corticosteroid.

* Only studies including patients 18 years and younger are listed in the table.
† Single-blind study. The open-label follow-up results to the study by Wennergren et al24 are unpublished; data on file, AstraZeneca.
‡ Unpublished study of acute asthma; data on file, AstraZeneca. Two patients 18 years and younger were included in the pediatric safety analyses; both patients were in the 30-mg prednisolone reference group. Patients received budesonide Turbohaler for 3 or 4 weeks after the acute phase.
§ Twenty-four children who initially received budesonide were using placebo at study end.
¶ Data on file, AstraZeneca.
Furthermore, only 2 incidences of varicella infection have been reported in postmarketing surveillance for budesonide inhalation suspension through June 2002.

**Respiratory Tract Infection**

Viral infection was reported in only 3% and 4% of children receiving placebo and budesonide inhalation suspension, respectively, in the 3 US double-blind studies. In pooled data from the 4 US open-label studies, viral infection was reported in fewer children receiving budesonide vs reference therapy (9.8% vs 13.5%). Although respiratory tract infection, sinusitis, and otitis media were among the most common adverse events in the double-blind and open-label phases of the 3 pivotal US studies, the rates of these adverse events were similar among patients treated with budesonide inhalation suspension, placebo, and conventional asthma therapy. For example, the 1-year incidence of otitis media in the US open-label studies was approximately 24% in both the budesonide and reference treatment groups. Respiratory tract infection was reported in approximately 55% of children with asthma in both groups. Among children enrolled in the non-US studies, rates of respiratory tract infection were the same in the budesonide and reference treatment groups (19.5%). Rates of otitis media also were similar in children in the budesonide inhalation suspension and reference treatment groups (7.0% and 5.9%, respectively).

**Ocular Events**

In the present analysis, databases from US and non-US studies were searched for reports of cataract, glaucoma, conjunctivitis, intraocular pressure, and lenticular opacity in children (Tables 2 and 3). Although not evaluated with specific ophthalmologic examinations, there were no adverse event reports of subcapsular or lenticular cataracts in the 3 budesonide inhalation suspension US pivotal studies, their 52-week open-label extensions, or the 5 non-US parallel-group studies. Furthermore, there were no reports of cataracts, glaucoma, intraocular pressure, or lenticular opacity among children in the fourth US open-label study. In this study, conjunctivitis was reported in 6% and 4% of children receiving budesonide and cromolyn sodium, respectively. Only 3 reports of cataract were recorded in postmarketing surveillance of budesonide inhalation suspension through June 2002 (patient ages: 9 months, 24 months, and 14 years). Confounding factors, including prematurity and a history of congenital cataracts, were present in 2 cases.

**Oral Candidiasis**

Proactive evaluation of oropharyngeal fungal cultures from children enrolled in the 3 pivotal double-blind trials demonstrated no differences in fungal culture growth between the budesonide and placebo groups at weeks 0 and 12. Positive fungal culture findings were expected among infants in the placebo group because yeast is found in the normal oral flora of infants and children. At week 12, 49% and 46% of children treated with budesonide and placebo, respectively, had fungal growth. Only 3 patients in the budesonide group, all of whom received total daily budesonide doses of 1 mg or greater, experienced clinically relevant oral fungal infections that were considered to be possibly or probably related to budesonide treatment. These infections were of mild intensity. In the pivotal studies, moniliasis was reported in 4% of children receiving budesonide inhalation suspension compared with 2% of those receiving placebo.

Pooled analysis of the 52-week open-label extension studies of the 3 pivotal trials demonstrated no differences in fungal culture findings between budesonide and reference therapy at week 52. Oropharyngeal and nasal fungal cultures were not proactively evaluated in the fourth US open-label study. In these 4 studies, overall, moniliasis, which included cases of candidiasis regardless of site, occurred in 5% and 2% of children given budesonide and reference drug, respectively. In non-US studies, moniliasis accounted for 2.9% of adverse events in children receiving budesonide and 2.8% of adverse events in children receiving reference drug.

**Table 2. Ocular Adverse Events in US Studies**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Double-blind, n (%)</th>
<th>Open label, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUD (n = 786)</td>
<td>Placebo (n = 231)</td>
</tr>
<tr>
<td>Cataract</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lenticular opacity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>11 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Eye itching</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Abbreviations: BUD, budesonide inhalation suspension; CAT, conventional asthma therapy.

**Table 3. Ocular Adverse Events in Non-US Studies**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>BUD†</th>
<th>Reference drug†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>Eye burning</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: BUD, budesonide inhalation suspension; CAT, conventional asthma therapy.

* Most patients in the non-US trials received treatment with budesonide inhalation suspension vs reference therapy.
† Numbers of adverse events reported for patients 18 years and younger; patients may have reported the same adverse event more than once.
Of 5 cases of moniliasis reported during the postmarketing experience, only 1 report noted suspected causality to budesonide inhalation suspension treatment.

**Dysphonia**

Dysphonia was reported infrequently (<3%) in the 3 US double-blind and open-label studies of budesonide inhalation suspension and occurred in only 1 patient from each treatment group in the 52-week open-label comparator trial conducted with cromolyn. In non-US studies, reports of dysphonia among patients treated with budesonide and reference drug numbered 32 and 8, respectively. Only 1 case of dysphonia and 3 cases of hoarseness were reported during the postmarketing experience with budesonide inhalation suspension.

**Skin-Related Adverse Events**

In the US double-blind and open-label studies of budesonide inhalation suspension, there was no increased incidence of bruising or skin thinning. Bruising or skin thinning was not evaluated in children in the non-US studies. In postmarketing surveillance data, only 1 case was reported. Reports of rash were lower with budesonide inhalation suspension therapy vs placebo therapy in the US double-blind studies (2.4% vs 3.4%). A higher frequency of skin rash, however, was reported for children receiving budesonide vs reference drug in the pooled analysis of data from the 4 US open-label studies (7% vs 5%). In the non-US parallel-group studies of budesonide inhalation suspension, skin disorders, which included facial skin irritation, accounted for 3.8% of adverse events in children treated with budesonide compared with 3.3% in children treated with reference drug. As of June 2002, 25 skin-related adverse events (eg, facial rash and dermatitis) had been documented through postmarketing surveillance.

**Hypothalamic-Pituitary-Adrenal Axis Suppression**

The effects of budesonide inhalation suspension on hypothalamic-pituitary-adrenal (HPA) axis function in children who participated in the US pivotal studies have been described previously. Briefly, the pooled analysis of the studies ported for children receiving budesonide vs reference drug in the double-blind and open-label studies of budesonide inhalation suspension, 24 although the ranges of values for patients in each group were similar. Three weeks after randomization, only 4 patients receiving 0.5 mg/d and 10 receiving 2 mg/d of budesonide had levels below reference values after corrections for short courses of beclomethasone. Of 77 patients who participated in the follow-up study, 15 had plasma cortisol values below the reference range and 14 had values above this range. These findings were confounded by difficulties in sample collection and concomitant oral corticosteroid use.

Adrenal insufficiency was not reported in any of the US or non-US studies; however, 2 cases of adrenal insufficiency in children receiving budesonide inhalation suspension have been detected during postmarketing surveillance. These cases suggest rare instances in which children may be more sensitive to the HPA axis effects of budesonide.

**Passive Exposure and Pregnancy**

Female caregivers who assist children with the administration of ICSs may be concerned about the potential risk of ICS exposure during pregnancy. For budesonide inhalation suspension, postmarketing surveillance has revealed no congenital fetal malformations attributable to passive exposure.

**DISCUSSION**

Substantial data from short- and long-term studies and postmarketing reports provide evidence that budesonide inhalation suspension is safe and well tolerated in the pediatric population. A low frequency of systemic and localized adverse events was reported in both US and non-US trials.

Several randomized, placebo-controlled studies of ICS therapy have reported decreased growth velocity of approximately 0.8 to 1.5 cm/y in children with asthma treated with ICSs for 6 months to 1 year. Of the 5 US and non-US studies that evaluated growth, only 2 reported a slight decrease in growth velocity (<1 cm/y) with budesonide treatment. Furthermore, a pooled analysis from the 3 pivotal open-label extension studies demonstrated no significant differences in growth velocity, standard median height, or skeletal age in the budesonide inhalation suspension and conventional asthma therapy groups.

Results of the randomized study by the Childhood Asthma Management Program Research Group comparing budesonide administered via dry-powder inhaler (Turbuhaler; AstraZeneca LP, Wilmington, DE), nedocromil, and placebo for more than 4 to 6 years demonstrated an effect of inhaled budesonide (400 μg/d) on growth velocity that was transient and evident mostly within the first year. Results of a more recent 3-year study of inhaled budesonide (200 or 400 μg/d...
plus usual asthma medications) in patients with recent-onset, mildly persistent asthma demonstrated reduced growth velocity during the entire 3-year treatment period but similarly demonstrated a diminished effect on growth over time. Finally, Agertoft and Pedersen reported the results of a study that examined the effect of long-term budesonide treatment on the attainment of predicted adult height in children with asthma. In this study, 142 patients received a mean budesonide dose of 412 μg/d for a mean of 9.2 years. No differences were seen in the attainment of final adult height among children who received budesonide, patients with asthma in the control group, and healthy siblings.

Although the effect of budesonide inhalation suspension on bone mineral density was not evaluated in the US and non-US studies, findings of similar bone mineral density in children with asthma treated with inhaled budesonide for an average of more than 4 years further support budesonide safety in terms of bone metabolism. A meta-analysis of ICS effects on bone in adult patients with asthma and chronic obstructive pulmonary disease demonstrated decreases in bone mineral density and in some bone markers; the effects of budesonide were smaller compared with those of other ICSs evaluated. In summary, among the available ICSs, budesonide has the most extensive long-term data regarding growth. Budesonide inhalation suspension, in particular, provides a therapeutic option that is likely to be safer than systemically administered corticosteroids (eg, oral liquid) for infants and young children.

Although ICSs given at recommended doses do not generally suppress adrenal function in children, some children may be more susceptible to the HPA axis effects of these agents. Furthermore, specific ICSs may have a more potent effect on the HPA axis when used at high doses. An effect of budesonide inhalation suspension on biochemical markers of HPA axis suppression has not been consistently demonstrated in US studies. Differences detected in the non-US study that evaluated plasma cortisol were confounded by difficulties in sample collection and concomitant oral corticosteroid use. Similar to the US studies, no apparent HPA axis function suppression resulted from active treatment. These findings, along with only rare cases of adrenal insufficiency reported in postmarketing surveillance and in the literature for children receiving inhaled budesonide, demonstrate that budesonide inhalation suspension may be administered to children with minimal risk of adverse HPA axis effects.

Unlike systemic corticosteroid treatment, there is no evidence that treatment with ICSs at recommended doses is immunosuppressive. In the US and non-US studies, the incidence of varicella infection was similar and low among children receiving budesonide inhalation suspension and placebo or reference drug. Rates of viral and respiratory tract infections, sinusitis, and otitis media also were similar among patients treated with budesonide, placebo, and reference drug. Rates of oropharyngeal candidiasis were also low among children treated with budesonide inhalation suspension.

In addition to potential systemic events, concern exists among health care providers regarding localized adverse events with ICS therapy, especially in patients with poor inhaler technique. The present analysis supports the safety of budesonide inhalation suspension in terms of ocular effects in children, with findings of no subcapsular or lenticular cataracts in US or non-US studies and only 3 postmarketing surveillance reports of cataract despite more than 314.1 million treatment days with budesonide inhalation suspension worldwide. Studies focusing on extended treatment with other formulations of inhaled budesonide in children have likewise detected no increased risk of posterior subcapsular cataract formation. Photographic evaluation of 1,909 eyes in 955 children enrolled in the Childhood Asthma Management Program study revealed a questionable posterior subcapsular cataract (<0.5 mm) in only 1 child in the budesonide group. In addition to inhaled budesonide, this child had received a total of 13 months of beclomethasone treatment and 38 days of oral prednisone administration during the trial, as well as an intranasal corticosteroid. Although these data support the safety of budesonide use in children, a slightly increased risk of ocular effects with cumulative high-dose ICS use cannot be ruled out, especially in adult patients. In the study by Garbe et al, ICS use for more than 3 years and high-dose ICS treatment (>1 mg/d) for more than 2 years were associated with an increased risk of cataract extraction in elderly patients.

Regarding localized oral effects of ICS therapy, dysphonia was reported infrequently in US and non-US studies and postmarketing surveillance for budesonide inhalation suspension. Similar to the findings reported herein, a case-control study of children with asthma receiving long-term (mean, 4.5 years) inhaled budesonide therapy (mean dose, 504 μg/d) vs age-matched asthmatic controls demonstrated no statistically significant differences in hoarseness between the 2 groups (20% vs 21%). In summary, the potential for budesonide inhalation suspension therapy to cause localized adverse events is low.

Finally, there have been no reports of adverse events in pregnant caregivers exposed to nebulized budesonide inhalation suspension while assisting with administration of therapy to a child. Furthermore, compared with the general population, no increase in the rate of congenital malformations was observed among 2,534 Swedish infants whose mothers used inhaled budesonide for asthma in early pregnancy (3.6% vs 3.6%). These data have led to an upgrade of the labeling for budesonide Turbuhaler (in December 2001) and budesonide inhalation suspension (in January 2003) from a pregnancy category C rating to a B rating by the FDA. Budesonide is currently the only ICS with a category B rating. Overall, the limited amount of drug to which a caregiver is exposed, coupled with data from the Swedish medical birth registries for budesonide Turbuhaler, suggests that passive exposure to budesonide during pregnancy would not be associated with an increased risk of congenital adverse events.
CONCLUSION
Short- and long-term treatment with budesonide inhalation suspension, using a wide range of doses, is well tolerated for persistent childhood asthma. Budesonide inhalation suspension is an important therapeutic option for young children and infants with persistent asthma. Comparable pediatric data are not available for any other ICS, and budesonide inhalation suspension is the ICS that is FDA approved for use in children younger than 5 years.

REFERENCES
30. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric


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