Position of the AAAAI and ACAAI
With Endorsement of the AAP
FDA NDAC Meeting On The Switch From Prescription To Over-the-counter (OTC) Of
Triamcinolone Acetonide Nasal Spray
July 31, 2013

David P. Skoner, MD
Director, Division of Allergy, Asthma & Immunology, Department of Medicine,
Allegheny General Hospital, Pittsburgh, Pennsylvania.
Professor of Medicine, Temple University.
Professor of Pediatrics, West Virginia University.
Introduction
Safety Concerns About INS OTC Switch

• Inhaled and intranasal corticosteroids (ICS and INS) are guideline-recommended, first-line therapies for asthma and allergic rhinitis, respectively.(1,2)

• There are significant risks in adults and children, summarized in a previous 2006 position statement of the Joint Task Force of the American Academy of Allergy, Asthma & Immunology and American College of Allergy, Asthma & Immunology.(3)

• Since then, additional new evidence has emerged from studies in children that further strengthens the arguments put forth in the position statement.

The Fate of Intranasal Steroids

Nasal Inhaler

Passage Across the Nasal Mucosa

Swallowed Fraction

Absorption Across the Nose

Nose and Posterior Pharynx

Absorption From the Gut

Active Drug From the Gut

“First Pass” Inactivation

GI Tract

Liver

Systemic Circulation

Potential impact on growth
Growth Suppression Is a Well Developed Model to Study Systemic Side Effects of ICS/INCS

ICS/INCS

Blood

Growth

Skin
Osteoporosis
Adrenal

Neuropsychiatric
Glaucma/Cataracts
Metabolic

US FDA MEETING JULY 1998
Intranasal Beclomethasone (BDP)

Mean Change in Standing Height From Baseline for All Patients

Mean Change From Baseline (cm)

BDP
Placebo

Month

1 2 4 6 8 10 12

* P<0.05
† P<0.01

## Intranasal Beclomethasone (BDP):
### Summary

<table>
<thead>
<tr>
<th>Percentile ≤</th>
<th>Placebo (%</th>
<th>Beclomethasone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3</td>
<td>4%</td>
<td>22%</td>
</tr>
<tr>
<td>≤ 10</td>
<td>13%</td>
<td>31%</td>
</tr>
<tr>
<td>≤ 25</td>
<td>23%</td>
<td>43%</td>
</tr>
<tr>
<td>≤ 50</td>
<td>35%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Joint PADAC/MEDAC meeting, July 30-31, 1998
Class Labeling – Intranasal Corticosteroids

PRECAUTIONS:

General: Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use section).

Pediatric Use: Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown.
2001 FDA Guidelines for Evaluation of the Effects of Inhaled Corticosteroids on Growth

Population

- Pre-pubertal
- Mild, persistent asthma*
- Comparable baseline demographics

Study design

- Primary: Regression analysis of growth velocity
  - Total length of 95% CI ≤0.5 cm
- Secondary: Shift analysis in growth velocity percentile; analysis of growth velocity percentiles; growth velocity during follow-up

Analysis

- At least 1 year treatment period
- Untreated control group
- Baseline growth velocity data (at least 16 weeks)
- Follow-up period (at least 8 weeks)
- Repeat stadiometer measurements
- Cortisol measurements
- Pulmonary function tests

Ciclesonide Growth Results: No Detectable Impact on Growth

Mean Change (± SE) in Stadiometer Height (cm) From Baseline

Month of Study

-6 -3 - .5 0 1 2 3 4 6 8 10 12 14

Run-in Period Double-blind Treatment Period Follow-up Period

Start of double-blind treatment period

End of double-blind treatment period

Placebo (n=221)
CIC 40 µg/day* (n=221)
CIC 160 µg/day (n=219)

FDA: Conclusions cannot be drawn from this study because compliance could not be assured (Pediatrics. 2008;122(1):213; author reply 14.)

# Summary of Effects of INS on Childhood Growth

## Pre-FDA Guidance; Post-FDA Guidance

<table>
<thead>
<tr>
<th>INS</th>
<th>Dose studied/maximum indicated</th>
<th>Number of subjects Active/placebo</th>
<th>Growth rate</th>
<th>Findings (Effects on growth)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP</td>
<td>168/336</td>
<td>45/35</td>
<td>-1.45 cm/yr</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>BUD</td>
<td>64/128</td>
<td>110/58</td>
<td>-0.25 cm/yr</td>
<td>Not significant</td>
</tr>
<tr>
<td>FP</td>
<td>200 (max)</td>
<td>44/39</td>
<td>-0.14 cm/yr</td>
<td>Not significant</td>
</tr>
<tr>
<td>MF</td>
<td>100 (max)</td>
<td>42/44</td>
<td>PL&gt;Mom</td>
<td>Not significant</td>
</tr>
<tr>
<td>TAA</td>
<td>110/220</td>
<td>133/134</td>
<td>-0.45 cm/yr</td>
<td>P=0.0096</td>
</tr>
<tr>
<td>FF</td>
<td>110 (max)</td>
<td>217/218</td>
<td>-0.27 cm/yr</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Why should we conclude that FP, MF and BUD do not affect growth when the studies were not designed in accordance with FDA guidance and compliance could not be assured?
Does Use of the ICS Budesonide in Childhood Affect Final Adult Height? It Depends on When You Read NEJM!

It doesn’t!

It does (low dose!)


Better scientific quality (NIH-Funded) → Detect effects
Effect of Combined ICS/INCS Administration on Growth – NO DATA!

CONSIDER SAFETY
What Can Go Wrong When ICS/INS Use is Improperly Monitored or Unmonitored?

➢ HISTORY
  ➢ 6.5 year old female presented to a physician for runny nose, nasal congestion and cough. Allergic to tree and grass pollen, mold and house dust mite. Spirometry suggestive of asthma.

➢ DIAGNOSES
  - Allergic rhinitis.
  - Asthma (cough-variant).

➢ TREATMENT
  - Flovent 110µg 2 puffs bid without mouth rinsing
  - Nasonex 50µg 2 sprays per nostril qd

➢ CLINICAL COURSE
  - Symptoms were completely controlled, no albuterol use.
  - No guideline-recommended step-down in doses
  - 18 months into treatment, developed an infection and nearly died of hypotension while on vacation
BMI (height/weight) Changes
Changing Physical Features (Start Therapy December 2009)

October 2009, 2 months before

February 2010, 2 months
Changing Physical Features
(Start Therapy December 2009)

April 2010, 4 months
November 2010, 11 months
April 2011, 16 months
What is the diagnosis?

- Absent serum cortisol and ACTH and urine cortisol
- Diagnosis: Iatrogenic Cushing’s Syndrome
- Treatment: Gradual corticosteroid withdrawal and full recovery of adrenal function
- Osteopenia and 3 major bone fractures resulting from minor trauma
- Direct quotes from her mother to you: “Truly unbelievable if this drug makes it over the counter!!” & “my child will need to be on growth hormone shots every day until she goes through puberty as a result of her growth suppression that never corrected itself.”
- The life-threatening adrenal (and growth) suppression that occurred as a result of improper monitoring in this case will certainly occur if INS/ICS use is unmonitored.
Summary

Safety Concerns About INS OTC Switch

• There are significant risks of ICS and INS in adults and children, summarized in a previous 2006 position statement.
• Additional new evidence from studies in children further strengthens the arguments put forth in the position statement.
• The decision to switch INS to OTC status will undoubtedly and unnecessarily cause growth and adrenal suppression in a large number of children.
• Dose adjustments and the correct monitoring and management of local and systemic adverse effects can only be done in a healthcare setting.
• With these considerations, we recommend that INS NOT be approved for over-the-counter usage.