Pediatric Focused Safety Review: Karbinal ER™ (carbinoxamine maleate)
Pediatric Advisory Committee Meeting
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Outline

• Background Information
• Regulatory History
• Relevant Labeling
• Drug Use Trends
• Safety
• Summary
Background Drug Information
Karbinal ER™ (carbinoxamine maleate)

- **Drug**: Karbinal ER™ (carbinoxamine maleate)*
- **Formulation**: Extended release oral suspension
- **Sponsor**: Tris Pharma, INC
- **Original Market Approval**: March 28, 2013
- **Therapeutic Category**: H1 histamine receptor antagonist
- **Postmarketing Requirements**: None

*CM=carbinoxamine, carbinoxamine maleate
K-ER=Karbinal ER®
Karbinal ER™ (carbinoxamine maleate)

Indications

• Seasonal and perennial allergic rhinitis (SAR/PAR)
• Vasomotor rhinitis
• Allergic conjunctivitis due to inhalant allergens and foods
• Mild, uncomplicated allergic skin manifestations of urticaria and angioedema
• Dermatographism
• As therapy for anaphylactic reactions *adjunctive* to epinephrine and other standard measures after the acute manifestations have been controlled
• Amelioration of the severity of allergic reactions to blood or plasma
Regulatory History: carbinoxamine maleate*,^,@

- **1950s:** Clistin first approved as a single active ingredient CM product for treatment of allergy indications in patients 1 year of age and older.

- **1960s:** CM, alone or in combination with other active ingredients, was subsequently marketed for a variety of unapproved indications, including for treatment of “colds and coughs” (indications for which carbinoxamine was never approved) as well as allergic symptoms, in infants and young children.

*:* [http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-9033.htm](http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-9033.htm)  
^: (DESI 6514, 47 FR 11973),  
Regulatory History: carbinoxamine maleate (cont’d)

• 1980s and 1990s: Marketing applications for Clistin tablets and elixir were withdrawn (not because of efficacy or safety concerns).

• 2003: Generic marketing applications for single-ingredient CM tablets and solution were approved based on the Agency’s previous findings of efficacy and safety from Clistin.

• 2005-2006: FDA noted a safety signal of death with the use of CM-containing drug products in children under the age of 2 years (a summary of a FDA assessments and actions is on the next two slides).
Carbinoxamine Maleate
Safety Review and Actions (2006)*

• 1983-2006: 21 deaths in children younger than 2 years.

• A relationship of the deaths to CM was not established.
  – Most, or all, deaths were associated with use of unapproved combination products containing CM with pseudoephedrine (PSE).

*https://www.federalregister.gov/articles/2006/06/09/E6-9033/carbinoxamine-products-enforcement-action-dates#h-12
Carbinoxamine Maleate Safety Review and Actions (2006), cont’d*

- Actions for approved, single active ingredient CM products
  - Contraindication for use in children less than 2 years of age
  - Removal of the dosing information for children 1 to less than 2 years

- Actions for all unapproved CM containing products
  - Removal from the marketing.^

*https://www.federalregister.gov/articles/2006/06/09/E6-9033/carbinoxamine-products-enforcement-action-dates#h-12

Karbinal ER™ (carbinoxamine maleate)  
Basis of Approval

• The safety and efficacy of Karbinal ER in patients 2 years and older is based on demonstration of bioequivalence to the immediate release reference product (Labeling sections 6, 12.3 and 14.1).

• PREA studies for patients less than 2 years were waived because there is evidence strongly suggesting that the drug product would be unsafe in this pediatric group.
Relevant Labeling*
Karbinal ER™ (carbinoxamine maleate)

2 DOSAGE AND ADMINISTRATION

4 CONTRAINDICATIONS

4.1: Children younger than 2 years
4.2 Nursing mothers because of risk of mortality in infants given CM-containing products

5 WARNINGS AND PRECAUTIONS

5.1: Pediatric Mortality
5.5 Dosing (i.e., use accurate measuring device; teaspoons not accurate)

* Complete labeling supplied in background materials.
Relevant Labeling, cont’d
Karbinal ER® (carbinoxamine maleate)

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use

“Deaths have been reported in children younger than 2 years of age who were taking carbinoxamine containing drug products. Therefore, Karbinal ER is contraindicated in children younger than 2 years of age and in nursing mothers. Carbinoxamine may diminish mental alertness or produce sedation in children. Paradoxical reactions with excitation are more likely in younger children.”
Drug Utilization Data: Karbinal ER

Nationally estimated number of pediatric patients with a dispensed prescription for karbinal ER suspension from U.S. outpatient retail pharmacies

<table>
<thead>
<tr>
<th></th>
<th>March 1, 2013 - February 29, 2016, aggregated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Count (N)</td>
</tr>
<tr>
<td>Karbinal ER Suspension</td>
<td>5,055</td>
</tr>
<tr>
<td>Total Patients</td>
<td></td>
</tr>
<tr>
<td>0-16 (age in years)</td>
<td>4,361</td>
</tr>
<tr>
<td>0 - 1 years</td>
<td>447</td>
</tr>
<tr>
<td>2-16 years</td>
<td>3,929</td>
</tr>
<tr>
<td>17+ years</td>
<td>659</td>
</tr>
<tr>
<td>Unspecified age</td>
<td>42</td>
</tr>
</tbody>
</table>

Note: unique patient counts may not be added due to possibility of double counting those patients aging during the study

www.fda.gov
Total Number of FAERS Reports: Carbinoxamine Maleate
January 12, 2006^ - February 29, 2016

Table 3.2.1 Total Adult and pediatric FAERS reports* from January 12, 2006 to February 29, 2016 with carbinoxamine maleate (including Karbinal ER)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>All reports (US)</th>
<th>Serious † (US)</th>
<th>Death ‡ (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 years)</td>
<td>19 (7)</td>
<td>15 (3)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Pediatrics (0 - &lt;17 years)</td>
<td>48 (47)</td>
<td>46 (45)</td>
<td>43 (43)</td>
</tr>
</tbody>
</table>

* May include duplicates and transplacental exposures; reports have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ One additional report of pediatric death was identified among reports not reporting an age.

^ Cut-off date of prior DPV carbinoxamine maleate safety review
Pediatric Case Selection of Serious Pediatric Cases with Carbinoxamine Maleate

Total pediatric reports reviewed (n=46)
- Pediatric reports with the outcome of death (n=43)

Excluded Cases* (n=28) (Including 28 deaths)
- Duplicates (n=27)
- Homicide (n = 1)

Pediatric Case Series (n=18) (Including 15 deaths)
See Table 3.2.3

* These cases were reviewed and excluded from the case series for the reasons listed.
# Characteristics of Pediatric FAERS Cases: Carbinoxamine Maleate (n=18)

<table>
<thead>
<tr>
<th>Age</th>
<th>0 - &lt; 1 month</th>
<th>1 month - &lt;2 years</th>
<th>2- &lt; 6 years</th>
<th>6- &lt;12 years</th>
<th>12- &lt; 17 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome*</td>
<td>Death</td>
<td>Life-threatening</td>
<td>Hospitalized</td>
<td>Disability</td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carboxamine-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Containing</td>
<td>Carbinoxamine/Pseudoephedrine (Carbaxefed)</td>
<td>Not reported (but positive pseudoephedrine levels)</td>
<td>Extended-release carbinoxamine maleate (Karbinal ER)</td>
<td>Carbinoxamine maleate (Palgic)</td>
<td>Foreign multi-ingredient carbinoxamine product (Paburon)</td>
</tr>
<tr>
<td>Products</td>
<td>7</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. Reports may have more than one outcome.
Pediatric Death Cases (n=15)  
Carbinoxamine maleate

• No new deaths not already accounted for in the 2006 safety review. All cases in the current review were reported to FDA in 2007 or earlier.

• All were in children less than 1 year of age (one case did not report the age but the patient was described as “baby”).

• PSE was concomitantly reported or detected in 14/15 reports
  – carbinoxamine/pseudoephedrine, N = 7
  – positive pseudoephedrine levels, N = 7

• Death with single active ingredient CM product: A 3 month old female with an ‘upper respiratory tract infection’ was found to be lethargic and unresponsive 2 to 4 hours after her third dose (4 mg/5 mL solution, “0.5 mL every 6 hours” over ~15 hours). Resuscitation failed. No additional clinical information available.
Non-Fatal Pediatric Cases (n=3)  
Carbinoxamine maleate

- A 10 year old female experienced “toxic epidermal necrolysis (TEN) from Stevens-Johnson syndrome (SJS)” with “leucopenia”. She was receiving acetaminophen and a CM product not available in the US (unable to determine if single agent or combination product) for fever and tonsillitis. She was treated with cyclosporin A, methylprednisolone, and granulocyte-colony stimulating factor and recovered.
  - Acetaminophen is linked to TEN which could contributed to other clinical findings*

- Undocumented “seizure” reported in a 1.5 year old receiving “2.5 mL of Karbinal ER every 12 hours”.
  - No additional clinical information and Karbinal ER is labeled for convulsions.

- **Nosebleed(s)** in a 6 year old.
  - CM has anticholinergic properties which can produce local effects such as dryness of the nose, which is labeled and which can contribute to nosebleeds.

Summary of Safety Review
Karbinal ER™ (carbinoxamine maleate)

• This concludes the pediatric focused safety review of FAERS reports.

• No newly occurring deaths since the safety related regulatory activities of 2005-2006, including no deaths with Karbinal ER®.

• No new safety signals were identified.

• FDA recommends continued ongoing safety monitoring.

• Does the committee agree?
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