Pediatric Focused Safety Review: Karbinal ER™ (carbinoxamine maleate) Pediatric Advisory Committee Meeting September 14, 2016

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Outline

- Background Information
- Regulatory History
- Relevant Labeling
- Drug Use Trends
- Safety
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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 ^: (DESI 6514, 47 FR 11973),

@: https://www.federalregister.gov/articles/2006/06/09/E6-9033/carbinoxamine-products-enforcement-action-dates

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- 1980s and 1990s: Marketing applications for Clistin tablets and elixir were withdrawn (not because of efficacy or safety concerns).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

^Guidance for FDA Staff and Industry Marketed Unapproved Drugs —Compliance Policy Guide; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf

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

	March 1, 2013 - February 29, 2016, aggregated	
	Patient Count (N)	Share (%)
Karbinal ER Suspension Total Patients	**5,055**	**100.0%**
0-16 (age in years)	**4,361**	**86.3%**
0 - 1 years	447	10.2%
2-16 years	3,929	90.1%
17+ years	**659**	**13.0%**
Unspecified age	**42**	**<1%**

Source: IMS, Vector One : Total Patient Tracker. March 2013-February 2016. Extracted April 2016
Note: unique patient counts may not be added due to possibility of double counting those patients aging during the study

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)

	All reports (US)	Serious† (US)	Death‡ (US)
Adults (≥ 17 years)	19 (7)	15 (3)	1 (0)
Pediatrics (0 - <17 years)	48 (47)	46 (45)	43 (43)

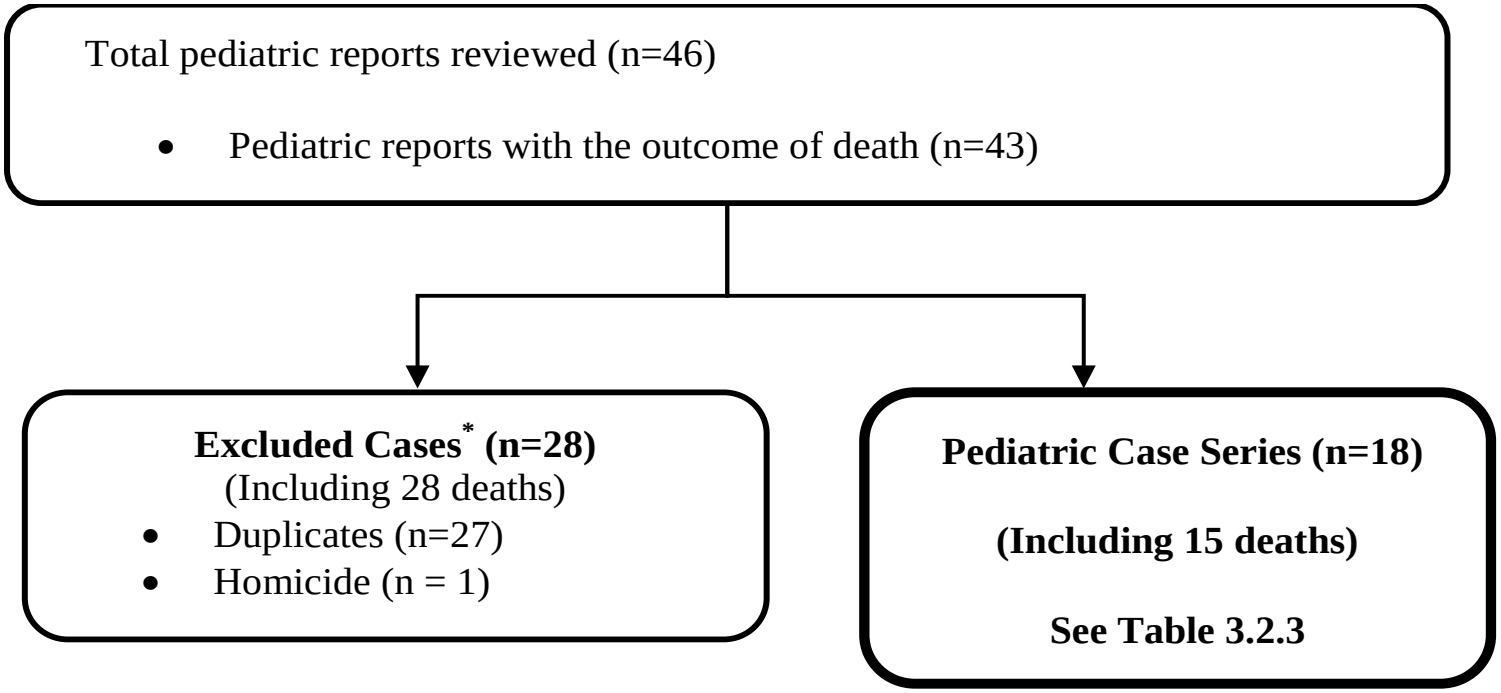
* May include duplicates and transplacental exposures; reports have not been assessed for causality

† 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



* These cases were reviewed and excluded from the case series for the reasons listed.

Characteristics of Pediatric FAERS Cases: Carbinoxamine Maleate (n=18)

Age	0 - < 1 month	0
	1 month - <2 years	16
	2- < 6 years	1
	6- <12 years	1
	12- < 17 years	0
Serious Outcome*	Death	15
	Life-threatening	1
	Hospitalized	2
	Disability	0
	Congenital anomaly	0
	Other serious	5
Carbinoxamine-Containing Products	Carbinoxamine/Pseudoephedrine (Carbaxefed)	7
	Not reported (but positive pseudoephedrine levels)	7
	Extended-release carbinoxamine maleate (Karbinal ER)	2
	Carbinoxamine maleate (Palgic)	1
	Foreign multi-ingredient carbinoxamine product (Paburon)	1

* 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.

*FDA Safety Communication: http://www.fda.gov/Drugs/DrugSafety/ucm363041.htm

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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