**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

**Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review**

| | |
|---|---|
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| **Product Name(s):** | Karbinal ER (carbinoxamine maleate) |
| **Pediatric Labeling Approval Date:** | March 28, 2013 |
| **Application Type/Number:** | NDA 022556 |
| **Applicant/Sponsor:** | Tris Pharma Inc. |
| **OSE RCM #:** | 2016-547 |

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## EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated all postmarketing adverse event reports and drug utilization data for carbinoxamine maleate in pediatric patients.

The FDA approved carbinoxamine maleate immediate release tablets and elixir in 1953. Carbinoxamine maleate is a first generation antihistamine that exhibits anticholinergic properties. In March 1973, carbinoxamine maleate was reviewed under the Drug Efficacy Study Implementation (DESI) process and received approval for use in children 1 year of age and older for the treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, allergic skin manifestations, dermatographism, and various anaphylactic reactions.

The carbinoxamine maleate label was changed on June 9, 2006 to contraindicate the use of carbinoxamine maleate in children younger than 2 years of age because of safety concerns with cough and cold medicine use in children and with the marketing of unapproved carbinoxamine-containing products.

Karbinal ER (carbinoxamine maleate) extended-release oral suspension, the drug product that triggered this PREA evaluation, was approved by the FDA on March 28, 2013. The same DESI indications, listed above, were approved for this product in patients 2 years of age and older.

A search of the FAERS database identified 18 serious pediatric cases with all carbinoxamine maleate drug products (including Karbinal ER). There were 15 pediatric death cases, all of which occurred in children less than 1 year of age and were reported to FDA in or prior to 2007. Fourteen of the 15 pediatric death cases reported carbinoxamine/pseudoephedrine combination product use or positive pseudoephedrine levels. The remaining death case, involving a 3-month-old female with single ingredient carbinoxamine, was received in FAERS in 2007 (proximal to the labeling change date). There were three non-fatal serious cases; one lacked information for evaluation, one provided an alternative explanation, and one involved a labeled event.

Analysis of drug utilization data showed that pediatric patients aged 0-16 years old accounted for 86% (4,361 patients) out of the nationally estimated number of total patients (5,055 patients) who received a dispensed prescription for Karbinal ER from U.S. outpatient retail pharmacies from March 2013 through February 2016. Although there appears to be some use in pediatric patients younger than 2 years of age, this use cannot be validated due to the lack of access to patient medical records.

Review of postmarketing reports suggests that there are no new or unexpected pediatric safety concerns with carbinoxamine maleate at this time. DPV-I will continue monitoring of all adverse events associated with carbinoxamine maleate in pediatric patients.

# 1 INTRODUCTION

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated all postmarketing adverse event reports and drug utilization data for carbinoxamine maleate in pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

The FDA approved carbinoxamine maleate immediate release tablets and elixir in 1953. Carbinoxamine maleate is a first generation antihistamine that exhibits anticholinergic properties. In March 1973, carbinoxamine maleate was reviewed under the Drug Efficacy Study Implementation (DESI) process and received approval for use in children 1 year of age and older for the treatment of:

- Seasonal and perennial allergic rhinitis
- Vasomotor rhinitis
- Allergic conjunctivitis due to inhalant allergens and foods
- Mild, uncomplicated allergic skin manifestations of urticarial 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

In December 2005, two cases of death involving infants who received carbinoxamine-containing drug products were reported to the FDA. In response to these two death cases and growing safety concerns with cough and cold medicine use in children, a postmarketing review of carbinoxamine-containing products was performed in early 2006. The review identified 19 additional cases of death in children less than 2 years of age who received marketed unapproved carbinoxamine-containing products in the Adverse Event Reporting System (AERS). As a result of the safety review, a Federal Registry notice (effective as of June 9, 2006) announced the removal of all unapproved drug products containing carbinoxamine from the market. In addition, the labeling (for approved drug products) was revised to indicate use only in patients 2 years of age and older.[1]

Karbinal ER (carbinoxamine maleate) extended-release oral suspension, the drug product that triggered this PREA evaluation, was approved by the FDA on March 28, 2013. The same DESI indications, listed above, were approved for this product in patients 2 years of age and older.

No clinical trials were performed for the approval of Karbinal ER (carbinoxamine maleate). It was approved based on two relative bioavailability studies to demonstrate bioequivalence of the test and reference products and previous DESI findings of efficacy and safety of carbinoxamine maleate in patients 2 years of age and older.

## 1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The current Karbinal ER (carbinoxamine maleate) product labeling provides the following information excerpted from the pertinent sections (update 28-Mar-2013).[2] Note that the use of Karbinal ER is contraindicated in children younger than 2 years of age.

**Contraindications**

- Children younger than 2 years of age
- Nursing mothers
- Patients with known hypersensitivity to the drug or any of the inactive ingredients
- Monoamine oxidase inhibitors (MAOI)

**Warnings and Precautions**

- Activities requiring mental alertness: Avoid engaging in hazardous tasks requiring complete mental alertness such as driving or operating machinery.
- Anticholinergic actions: Use with caution in patients with increased intraocular pressure, narrow angle glaucoma, hyperthyroidism, cardiovascular disease, hypertension, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction, pyloroduodenal obstruction.
- Contains sodium metabisulfite, a sulfite that may cause anaphylaxis including life-threatening or less severe asthmatic episodes in susceptible individuals.

**Adverse Reactions**

The most frequent adverse reactions include: sedation, sleepiness, dizziness, disturbed coordination, epigastric distress and thickening of bronchial secretions.

The following adverse reactions, listed by body system, have been identified in case reports and during the use of carbinoxamine in observational studies.

- Body as a Whole: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.
- Cardiovascular: Hypotension, headache, palpitations, tachycardia, extrasystoles.
- Central Nervous System: Fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.
- Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, constipation.
- Hematologic: Hemolytic anemia, thrombocytopenia, agranulocytosis.
- Laboratory: Increase in uric acid levels.
- Respiratory: Tightness of chest and wheezing, nasal stuffiness.
- Urogenital: Urinary frequency, difficult urination, urinary retention, early menses.

**Drug Interactions**

- Use of Karbinal ER is contraindicated in patients who are taking monoamine oxidase inhibitors (MAOIs) which prolog and intensify the anticholinergic (drying) effects of antihistamines.
- Avoid use of Karbinal ER with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.) due to additive effects.

**Use in Specific Populations**

- Pregnancy Category C. Animal reproductive studies have not been conducted with carbinoxamine maleate. It is also not known whether Karbinal ER can cause fetal harm when administered to a pregnant woman and can affect reproductive capacity. Karbinal ER should be given to a pregnant woman only if clearly needed.

- Nursing Mothers: Because of the risk of mortality in infants given carbinoxamine-containing drugs, use of Karbinal ER is contraindicated in nursing mothers.
- 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.

# 2 DRUG UTILIZATION DATA

## 2.1 METHODS AND MATERIALS

We used proprietary drug utilization databases available to the Agency to conduct the analyses in this review. **Appendix A** includes detailed descriptions of the databases.

### 2.1.1 Determining Settings of Care

***The IMS Health, IMS National Sales Perspectives™ database*** was used to determine the settings of care by which Karbinal (carbinoxamine) ER is distributed from manufacturers from March 1, 2013 through February 29, 2016 in aggregate. Sales distribution data showed that approximately 98% of Karbinal ER bottles were sold to retail pharmacies; 2% was sold to non-retail settings; and <1% was sold to mail order/specialty pharmacies.[3] Based on these sales data, we examined the drug utilization patterns for Karbinal ER in outpatient retail pharmacies.

### 2.1.2 Data Sources Used

***The IMS, Total Patient Tracker™ (TPT) database*** was used to obtain the nationally estimated number of patients who received a dispensed prescription for Karbinal ER through U.S. outpatient retail pharmacies, stratified by patient age (0-1, 2-16, 17 years and older) from March 1, 2013 through February 29, 2016 in aggregate. We used the labeling approval date (March 2013) of Karbinal ER through February 2016 (data availability) to examine the drug utilization pattern.

## 2.2 RESULTS

### 2.2.1 Unique Number of Patients

Table 2.2.1 shows in aggregate the nationally estimated number of patients with a dispensed prescription for Karbinal ER suspension from U.S. outpatient retail pharmacies from March 2013 through February 2016.

**Table 2.2.1**

**Nationally estimated number of patients with a dispensed prescription for Karbinal ER (carbinoxamine) suspension, stratified by patient age*, from U.S. outpatient retail pharmacies, from March 2013 through February 2016 in aggregate**

| | 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
File: TPT 2016-547 Karbinal ER BPCA April-2016.xlsx

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

# 3 POSTMARKET ADVERSE EVENT REPORTS

## 3.1 METHODS AND MATERIALS

### 3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

**Table 3.1.1 FAERS Search Strategy**

| | |
|---|---|
| Date of Search | April 18, 2016 |
| Time Period of Search | January 12, 2006* - February 29, 2016 |
| Search Type | FBIS Profile Report |
| Product Name(s) | Active ingredient: carbinoxamine, carbinoxamine maleate<br>Product name: Karbinal ER, Karbinal |
| Search Parameters | All ages, all outcomes, worldwide |

* Cut-off date of latest DPV review on carbinoxamine maleate postmarket safety

## 3.2 RESULTS

### 3.2.1 Total Number of FAERS Reports by Age

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

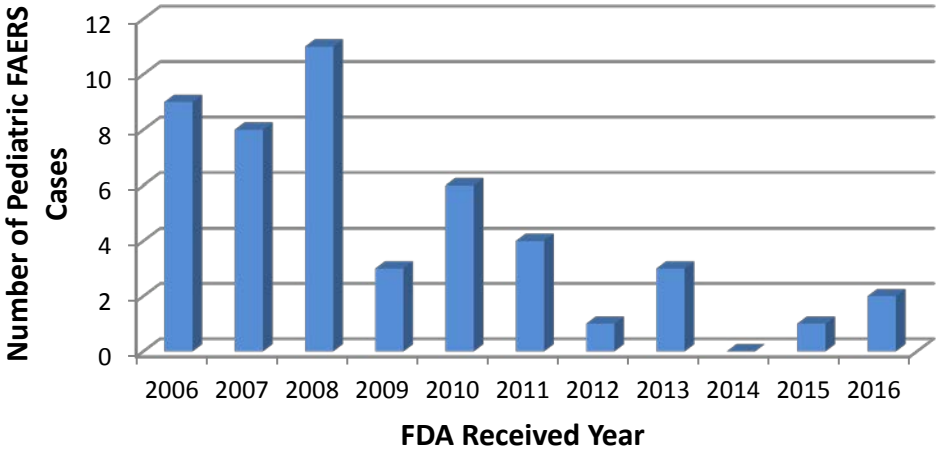
| | All reports (US) | Serious† (US) | Death‡ (US) |
|---|---|---|---|
| **Adults (≥ 17 years)** | 19 (7) | 15 (3) | 1 (0) |
| **Pediatrics (0 - <17 years)** | 48 (47) | 46 (45) | 43 (43) |

* 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.

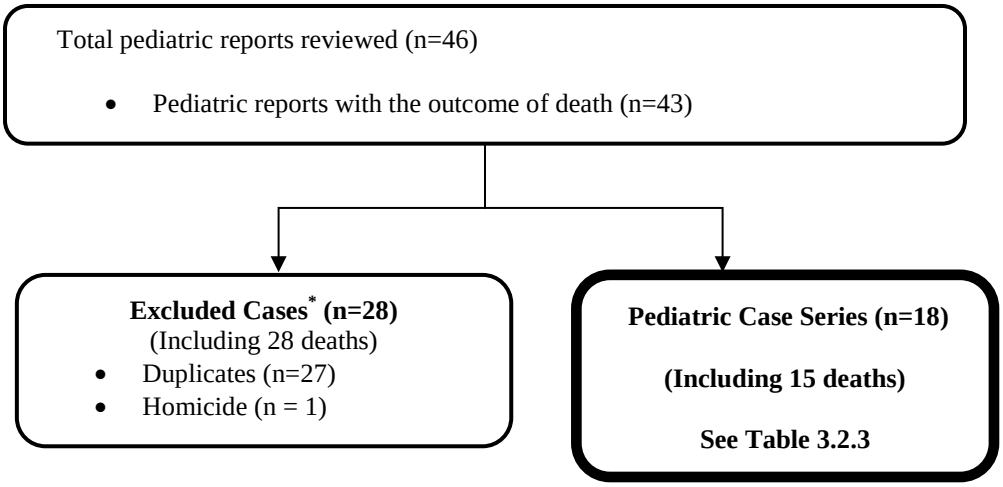
**Figure 3.2.1 All Pediatric Reports for carbinoxamine maleate, by year of FDA receipt January 12, 2006 to February 29, 2016 (n=48)**




### 3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 46 serious pediatric reports with carbinoxamine maleate (See Table 3.2.1). See **Figure 3.2.2** below for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

**Figure 3.2.2 Selection of Serious Pediatric Cases with Carbinoxamine Maleate**




* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above

### 3.2.3 Characteristics of Pediatric Case Series

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the pediatric case series.

**Table 3.2.3 Characteristics of Pediatric Case Series with 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 |
| Sex | Male | 10 |
| | Female | 6 |
| | Unknown | 2 |
| Country | United States | 17 |
| | Foreign | 1 |
| 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 | 1 |

| Table 3.2.3 Characteristics of Pediatric Case Series with Carbinoxamine Maleate (N=18) |
|---|
| (Paburon) |
| * 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. |

### 3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=15)

DPV-I identified 15 fatal pediatric cases with carbinoxamine maleate in FAERS from January 16, 2006 through February 29, 2016. The fatal cases are summarized below:

- All of the fatal pediatric cases involved children less than 1 year of age (there was one case that did not report the age but the patient was described as "baby").
- All of the fatal pediatric cases were reported to FDA in 2007 or prior to 2007.
- Pseudoephedrine was concomitantly reported in 14 of the 15 cases; Carbaxefed (carbinoxamine/pseudoephedrine, N = 7), positive pseudoephedrine levels (N = 7)
- The remaining case involving carbinoxamine maleate as a single ingredient is described below:

**FAERS Case #6408110, Death, Direct, US, 2007:** A 3-month-old female was provided a physician's sample of carbinoxamine maleate 4mg/5ml oral solution (Palgic) with instructions to administer 0.5ml every 6 hours for an upper respiratory infection. She received a total of three doses over the time span of 15 hours (at 4:30 pm, 10:30 pm and 7:30 am the following morning). She was noted to be lethargic by her grandmother at 7:30 am and 9:00 am. The child was found to be unresponsive at 11:00 am and could not be resuscitated.

*Reviewer comment: This is a death case in which carbinoxamine maleate was administered despite the contraindication for use in children younger than 2 years of age. There is a paucity of additional clinical information to properly assess this case.*

### 3.4 SUMMARY OF NON-FATAL SERIOUS PEDIATRIC ADVERSE EVENT CASES (N=3)

There were three non-fatal serious pediatric cases reported in FAERS from January 16, 2006 through February 29, 2016. The three cases are summarized below:

**FAERS Case #11914356, US, 2016:** A 6-year-old male experienced increased nosebleeds while taking Karbinal ER.

*Reviewer comment: Carbinoxamine maleate is a first generation antihistamine that exhibits anticholinergic properties. Dryness of the nose is a labeled adverse event in the product labeling and can lead to nosebleeds in children.*[4]

**FAERS Case #12039119, Direct US, 2016:** A 1.5-year-old male was taking 2.5ml of Karbinal ER every 12 hours as needed for allergies. A daycare worker reported witnessing two episodes

of “eyes rolling back” and suspected a seizure. Three days later, the patient fell down the stairs and was taken to see his physician. Neither the physician nor the parents witnessed any seizure activity.

*Reviewer comment: This product labeling for carbinoxamine maleate contraindicates use in children younger than 2 years of age. The adverse event of seizure was not medically confirmed and lacked additional details for evaluation.*

**FAERS Case #7064703, Foreign, 2009:** This is a literature report[5] involving a 10-year-old female who developed extended toxic epidermal necrolysis (TEN) from Stevens Johnson syndrome (SJS) with associated leucopenia. The patient was previously in good health and took acetaminophen and a commercially available cold medicine containing carbinoxamine maleate (Paburon) for a high fever. The next day, she developed erythematous eruption on her face, trunk and extremities. She was diagnosed with acute tonsillitis at a local hospital. Her bullous eruptions progressed and the patient was admitted to the hospital with suspicion of SJS. TEN was subsequently diagnosed on the basis of clinical conditions and laboratory data. The patient was successfully treated with IV cyclosporine A, methylprednisolone and granulocyte-colony stimulating factor (G-CSF) and discharged home from the hospital without any sequelae.

*Reviewer comment: There was a temporal association between the time of acetaminophen and Paburon ingestion and the onset of the disease, indicating possible drug-induced TEN. Because both acetaminophen and Paburon were taken together, it is difficult to determine which one was the offending drug. TEN is a labeled event with acetaminophen-containing products but is not labeled in the carbinoxamine maleate label.*

## 4 DISCUSSION

Pediatric patients aged 0-16 years old accounted for 86% of total patients who received a dispensed prescription for Karbinal ER from U.S. outpatient retail pharmacies. Although there appears to be some use in pediatric patients younger than 2 years of age, this use cannot be validated, because of the lack of access to patient medical records.

Of the 18 FAERS reports reviewed in pediatric patients, there were no new or unexpected safety signals identified. There were 15 pediatric death cases, all of which occurred in children less than 1 year of age and were reported to FDA in or prior to 2007. Fourteen of the 15 pediatric death cases reported positive pseudoephedrine levels or carbinoxamine/pseudoephedrine combination product use. The remaining death case, involving a 3-month-old female with single ingredient carbinoxamine, was received in FAERS in 2007 (proximal to the contraindication labeling change date in June 2006). Although analysis of utilization data appears to suggest off-label use, all of the fatal pediatric cases in children less than 1 year of age were reported to FDA before or proximal to the labeling change. There were three non-fatal serious cases; one lacked information for evaluation, one provided an alternative explanation, and one involved a labeled event.

## 5 CONCLUSION

Review of postmarketing reports suggests that there are no pediatric safety concerns with carbinoxamine maleate at this time.

## 6 RECOMMENDATIONS

DPV-I will continue monitoring of all adverse events associated with carbinoxamine maleate in pediatric patients.

## 7 REFERENCES

1. Starke P, Seymour S. Backgrounder for discussion at the PAC meeting for Karbinal ER. August 11, 2016. DARRTS Reference ID: 3970920.

2. Karbinal ER (carbinoxamine maleate) [package insert]. Monmouth Junction, NJ: Tris Pharma; March 2013.

3. IMS Health, National Sales Perspectives™. March 2013 through February 2016. Data extracted March 2016.

4. Messner A. Epidemiology and etiology of epistaxis in children. In: UpToDate, Wiley J (Ed), UpToDate, Waltham, MA. (Accessed on May 31, 2016.)

5. Aihara Y, Ito R, Ito S, et al. Toxic epidermal necrolysis in a child successfully treated with cyclosporine A and methylprednisolone. Pediatrics International. 2007; 49: 659-662.

# 8 APPENDICES

## 8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings**.**

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. Based on sales data from March 2013 through February 2016, Karbinal ER was primarily distributed to U.S. outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

**IMS Vector One®: Total Patient Tracker (TPT)**

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

The patient estimates focus on only outpatient retail pharmacies; therefore, they may not be representative of utilization in other settings of care such as mail-order/specialty and non-retail settings.

## 8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

**FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

### 8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=18)

| FAERS Case # | FAERS Version # | Manufacturer Control # |
|---|---|---|
| 11914356 | 1 | US-TRIS PHARMA, INC.-1046458 |
| 12039119 | 1 | Direct report |
| 5965952 | 1 | Direct report |
| 6004862 | 1 | 8015078 |
| 6034716 | 1 | US-JNJFOC-20060404960 |
| 6180352 | 1 | Direct report |
| 6264616 | 1 | US-JNJFOC-20070302387 |
| 6302491 | 2 | 2007314451 |
| 6302494 | 2 | 2007314446 |
| 6304301 | 1 | C-07-0011 |
| 6408110 | 1 | Direct report |
| 6439609 | 8 | US-JNJFOC-20071001791 |
| 6732707 | 1 | US-AVENTIS-200814339EU |
| 6802634 | 1 | US-JNJCH-2008053255 |
| 7064703 | 1 | GXKR2009JP07721 |
| 8533737 | 1 | US-JNJFOC-20080502845 |
| 9027859 | 2 | US-RANBAXY-2007US-05435 |
| 9502519 | 1 | US-RANBAXY-2013US-72881 |

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