

Division of Pulmonary, Allergy, and Rheumatology Products

To: Pediatric Advisory Committee (PAC)

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Subject: Backgrounder for discussion at the PAC meeting, September 14, 2016

Product: Karbinal™ ER (carbinoxamine maleate) extended-release oral suspension

NDA: 22-556

Date: August 11, 2016

Executive Summary

The safety of carbinoxamine in children is being discussed at the September 14, 2016, Pediatric Advisory Committee (PAC) because of the approval of Karbinal™ ER (carbinoxamine maleate) extended-release oral suspension (NDA 22-556) on March 28, 2013. Carbinoxamine is a first generation antihistamine that was first approved in the 1950s for treatment of several allergy indications in patients 1 year of age and older. In addition, carbinoxamine was often included in unapproved combination products that were marketed specifically for treatment of coughs and colds (indications for which carbinoxamine was never approved) as well as allergic symptoms, in infants and young children. In 2006, the Agency noted a safety signal of death with the use of carbinoxamine-containing drug products in children under the age of 2 years. All of these deaths were with use of the unapproved combination products. As a consequence, several regulatory actions were taken. These included:

- 1) addition of a Contraindication for children <2 years of age and removal of the dosing information for children 1 to <2 years of age for the approved, single-ingredient, prescription carbinoxamine drug products;
- 2) removal of all of the marketed unapproved carbinoxamine-containing combination drug products from the market.

Since that time, FDA has continued surveillance of the safety issues related to carbinoxamine use in children. In the interim, several generic single-ingredient tablet and oral solution products have been approved, and Karbinal ER was approved in 2013. Safety surveillance has not found a continued safety signal as was noted prior to the 2006 actions, nor have any new safety signals been identified.

More details, including a summary of the safety issues identified in 2006, and the regulatory actions that followed, are included below. This document also summarizes an additional set of events that occurred in 2007-8, related to the marketing and use of over-the-counter (OTC) cough and cold products in young children. This latter information is included for completeness, but does not relate specifically to the safety of Karbinal ER, the subject of the PAC safety review.

Regulatory Background

Carbinoxamine, often manufactured as carbinoxamine maleate (CM), is a first generation histamine H₁ receptor blocking agent (i.e., antihistamine) of the ethanolamine class. This class exhibits antihistaminic, anticholinergic, and sedative properties.

Carbinoxamine maleate (CM) was approved and marketed as single ingredient prescription products in the early 1950s and sold by McNeil Laboratories under the brand name Clistin.¹ Clistin carried indications for treatment of various allergic conditions and the symptomatic treatment of measles in patients 1 year of age and older.

In 1962, the Food, Drug and Cosmetics Act was amended to require that all approved drugs be proven effective for their labeled indications, as well as safe. This amendment required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that were approved as safe between 1938 and 1962. To perform these reviews, FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that had been approved only for safety (i.e., drugs approved between 1938 and 1962). The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency then reviewed the reports and published its findings in Federal Register (FR) notices. FDA's administrative implementation of the NAS/NRC reports and the Agency's subsequent effectiveness decisions was called the Drug Efficacy Study Implementation or "DESI". Clistin Tablets and Elixir were found to be "effective" for the following indications in adult and pediatric patients 1 year of age and older² (other products, including Clistin Expectorant³ and Clistin RA Tablets⁴, and other indications⁵, were found to be not effective):

- 1) symptomatic treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis due to inhalant allergens and foods;
- 2) mild, uncomplicated allergic skin manifestations of urticaria and angioedema;
- 3) amelioration of the severity of allergic reactions to blood or plasma in patients with a known history of such reactions;
- 4) dermographism; and
- 5) as therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

Of note, except for the Clistin Expectorant product (which contained carbinoxamine maleate, ammonium chloride, sodium citrate, potassium guaiacolsulfonate, and benzyl alcohol), the effectiveness evaluation of carbinoxamine-containing products under DESI did not include evaluation of the effectiveness of carbinoxamine for the treatment of cough or cold symptoms,

¹ Clistin Tablets and Clistin RA Tablets (NDA 08915), Elixir (NDA 08955), and Expectorant (NDA 09248)

² DESI 6303, 38 FR 7265; March 19, 1973

³ Clistin Expectorant (NDA 09248) was found to lack substantial evidence of effectiveness, and the NDA was proposed to be withdrawn. DESI 6514, 47 FR 11973 at 11974; March 19, 1982.

⁴ Clistin RA Tablets was reclassified as lacking substantial evidence of effectiveness as a timed release dosage form. DESI 6303, 47 FR 18667; April 30, 1982.

⁵ All of the carbinoxamine products were found to lack substantial evidence of effectiveness for the prevention and symptomatic relief of measles. DESI 6303, 36 FR 9339; May 22, 1971.

either as a single ingredient product or as part of a combination with other drug products, such as decongestants or cough suppressants.

After publication of the DESI effectiveness findings, holders of new drug applications (NDAs) that had been “deemed approved” (i.e., applications which became effective on the basis of safety prior to October 10, 1962) were required to submit an efficacy supplement to the NDA, following which a product was considered a “new drug” once the new labeling was agreed upon and the supplement was approved.

It is important to note that the DESI reviews did not include an evaluation of safety or the dosage of drugs, because safety was considered as having been established in the original new drug application. Specifically, the Agency did not require any dosing or pharmacokinetic information for the carbinoxamine products as part of the DESI process. Also of note, the original approval of these applications in the 1950s (based on safety) predated an understanding of the need for obtaining safety evaluations of antihistamines in specific populations as part of a marketing application, including effects on QT interval, safety in pediatric populations, and safety in subjects with hepatic or renal impairment. Further, retrospective review of the carbinoxamine applications reveals that pediatric dosing recommendations appear to have been extrapolated from adult dosing based on body weight (i.e. mg/kg) rather than having been based on specific pharmacokinetic and safety data in these populations.

In the 1980s and 1990s, the marketing applications for Clistin Tablets and Elixir were withdrawn, but not because of efficacy or safety concerns.⁶ In 2003, generic marketing applications from Milkart, Inc., for single-ingredient carbinoxamine maleate tablets and solution were approved.⁷ The applications and approval relied on the Agency’s previous findings of efficacy and safety for the Clistin products. PamLab, L.L.C. licenses and markets these products under the trade name Palgic[®] 4 mg Tablets and 4 mg/5 mL Oral Solution. With approval, the prescription labeling and indications from the previous Clistin products were transferred to the new products and these products were listed in the Orange Book⁸ as the reference drug products.

Marketed Unapproved Carbinoxamine Products

Prior to 2006, carbinoxamine was often marketed by prescription in combination with other active ingredients, such as decongestants or antitussives in tablet, syrup, and drop formulations and sold under many trade names.⁹ Many of these combinations were specifically targeted for the treatment of colds and cough in infants and young children below 1 year of age despite the fact that this was an indication and age range for which none of the ingredients had been evaluated. Most combinations included pseudoephedrine (PSE), with or without dextromethorphan, although some were later reformulated to replace PSE with phenylephrine.

It is important to note that pseudoephedrine, dextromethorphan, and phenylephrine are allowed to be marketed as part of over-the-counter cough and cold drug products under the final monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) Drug

⁶ 50 FR 13661; April 5, 1985, and 59 FR 9989; March 2, 1994

⁷ ANDA 40442 and ANDA 40458, respectively

⁸ The Orange Book is the FDA listing of all products that have been approved under section 505 of the Federal Food, Drug, and Cosmetic Act, as required under 21 U.S.C. 360(j).

⁹ Examples include: Andehist, Carboxefed, Carbaxafed, Carbodec, Carbofed, Cardec, Histex, Pseudo-Car, Rondec, Sildec, and Tussafed

Products.¹⁰ The CCABA monograph establishes the active ingredients, permitted combinations, labeling, and dosages of immediate release OTC cough and cold products, including combinations of antihistamines, decongestants, antitussives, and expectorants. The monograph provides permitted dosages for these active ingredients for patients starting at either 2 years (decongestants, expectorants, some antitussives) or 6 years (antihistamines, some antitussives) of age and older, depending upon the ingredient. For those ingredients that do not have OTC dosages for patients 2-6 years of age, the monograph states to the label the product as “Consult a Doctor” for patients less than 6 years of age, in which case professional labeling, including suggested dosages for patients 2-6 years of age, are provided for physicians at the end of the monograph (21 CFR 341.90). Note that under the monograph, permitted combinations do not allow combination with any non-monographed ingredients, such as carbinoxamine, nor does the monograph allow for use of these active ingredients under the age of 2 years.

As of April 1, 2006, a total of 26 manufacturers had listed with FDA a total of 120 prescription drug products containing carbinoxamine. All of these products were unapproved products, and many were in the form of oral drops (with built-in droppers). Other unapproved and unlisted carbinoxamine products were also on the market.

Marketing applications for drug products include data to support safety and efficacy for the desired indication and age range. Applications also contain drug product quality, pharmacodynamic, pharmacokinetic, drug-drug interaction, and dose-response data. Quality data include chemistry, manufacturing and control (CMC) information regarding good manufacturing practices (GMP), stability, and excipients. Without this critical information, the quality, safety, and efficacy of unapproved drug products cannot be assured.

Safety Issues with Carbinoxamine Use in Infants and Young Children: 2005-6

In December of 2005, two cases of deaths in infants being administered carbinoxamine-containing drug products were reported by the coroner in Kane County, Illinois. Although neither of these deaths appeared to be due to carbinoxamine overdose, extremely high levels of PSE were reported in both infants. FDA became involved to ensure that the drug products involved in the cases were not super-potent. The cases also sparked a post-marketing assessment of the safety of carbinoxamine-containing drug products by the Agency. The safety review was performed during the first half of 2006.

For the period between 1983 and early 2006¹¹, a total of 22 unique reports of deaths were found associated with the use of carbinoxamine-containing products, 21 of which were in children under 2 years of age. All of the cases involved use of a marketed unapproved combination product containing CM, PSE and/or dextromethorphan. Most deaths were sudden and unexplained, with nine reported as either sudden infant death syndrome (SIDS) or possible SIDS, and seven as possible accidental overdoses due to medication errors. Only seven of the 22 cases reported elevated or toxic blood levels of carbinoxamine, PSE (or both), with or without other drugs. As a result, a causative relationship between exposure to carbinoxamine and death could

¹⁰ 21 CFR Part 341

¹¹ 19 of the cases were found in the FDA’s Adverse Event Reporting System (AERS), and 2 cases were reported by the coroner in Kane County, Illinois. The AERS database, now called FAERS, extends back to 1969 (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm>). However, the earliest reported death at any age is in 1983.

not be established, because in most of those reports other active ingredients or other factors could have been responsible for the death. However, because children in this age range are considered to be a vulnerable population, the Agency was concerned about the risks of serious and life-threatening adverse outcomes associated with the use of these combination drug products, which were being promoted for off-label use in this age group for treatment of colds and coughs.

As noted above, at that time the only FDA approved carbinoxamine-containing products were the single ingredient generic Palgic products marketed by Mikart, all the other carbinoxamine-containing products being marketed unapproved products. To address these safety concerns, Milkart agreed to submit supplements for Palgic Tablets and Oral Solution to add a Contraindication for use in patients under 2 years of age and to remove the dosing and administration information for this age group. The Palgic labeling supplements were approved on June 7, 2006.¹²

Compliance Policy Guide and Carbinoxamine-Containing Products: 2006

Two days later, on June 9, 2006, FDA published in the Federal Register (FR) a Compliance Policy Guide (CPG) for Marketed Unapproved Drugs, describing how the Agency intended to exercise its enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing, and encouraging companies currently manufacturing drugs without FDA approval to comply with the drug approval process to ensure the safety and efficacy of their marketed products.¹³

At the same time as it issued the CPG, the Agency published an FR notice summarizing the safety findings from the Agency's safety review of carbinoxamine-containing products, and announcing its intention to take enforcement action against all unapproved products that contain carbinoxamine.¹⁴ The notice stated that manufacturers wishing to market a carbinoxamine product must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA). Any firm manufacturing a carbinoxamine-containing product that was labeled for use in children less than 2 years of age or marketed as drops for oral administration would be subject to enforcement action on or after July 10, 2006, and any firm manufacturing any other unapproved carbinoxamine-containing product would be subject to enforcement action on or after September 7, 2006. The effect was a more or less immediate elimination of these products from the marketplace.

Events Related to the Use of OTC Monographed Cough and Cold Products in Young Children: 2007-8

During 2007 and 2008, a number of events occurred that had the effect of limiting use of all over-the-counter (OTC) cough and cold products in children less than 4 years of age. While not specifically related to the safety of carbinoxamine, a brief summary of these events is included to place the regulatory steps the Agency took for the carbinoxamine-containing products into context.

¹² ANDA 40442, S-003 and ANDA 40458, S-005.

¹³ 71 FR 33466, June 9, 2006

¹⁴ 71 FR 33462, June 9, 2006

On March 1, 2007, the Agency received a Citizen Petition¹⁵ from Dr. Joshua Scharfstein and pediatric colleagues, requesting that the FDA amend the final monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic (CCABA) Drug Products to state that the OTC antitussives, expectorants, nasal decongestants, and combinations are not safe and effective and should not be used in children less than 6 years of age due to lack of evidence to demonstrate safety and efficacy of these products in this age group. In addition, the petitioners requested that the Agency notify manufacturers of products whose labeling uses terms as “infant” or “baby” or displays images of children under the age of 6, that such marketing is not supported by scientific evidence and that manufacturers will be subject to enforcement action.

In response to the Citizen Petition, FDA convened a joint Nonprescription and Pediatric Advisory Committee meeting on October 18-19, 2007. Leading up to the meeting, several events occurred that are significant.

In their briefing document for the meeting, the Consumer Health Care Products Association (CHPA), a trade association that represents the major drug companies that market OTC cough and cold products, recommended that the labels for these products be changed to explicitly state "Do Not Use" in children under 2 years of age. In response, on October 3, 2007, Representative Henry Waxman, Chairman of the House Committee on Oversight and Government Reform, sent a letter to CHPA, requesting that CHPA provide a description of the actions that the association intended to take to ensure that its member companies cease marketing pediatric formulations for use in infants and children under 2 years of age. CHPA responded with a Dear Healthcare Professional Letter announcing a voluntary withdrawal of OTC cough/cold products that refer to “infants”, including elimination of all advertisements as well as pictures of infants on the labels of their products. Thus, in the weeks preceding the Advisory Committee meeting, the marketing of cough and cold products for use in children less than 2 years of age effectively was eliminated.

Among other things, the Advisory Committee recommended that more efficacy and safety data are needed, stating that the available published studies were too few in number, the sample sizes were too small and underpowered, and the outcome assessments were not appropriate. The committee overwhelmingly voted against extrapolation of efficacy from older patients, including adults, to younger children. They recommended that the Agency obtain additional efficacy and safety data, starting with data for each of the individual ingredients in pediatric patients.¹⁶

In January of 2008, the FDA issued an advisory strongly recommending that over-the-counter cough and cold medications not be given to infants and children under two years of age because of the risk of life-threatening side effects. The American Academy of Pediatrics (AAP) immediately published a statement supporting this recommendation and urging parents to seek safer ways to soothe infants and young children suffering from colds and coughs.¹⁷ Previously, the AAP had published and reaffirmed a 1997 policy statement discouraging the use of codeine- and dextromethorphan-containing cough remedies in children.¹⁸

¹⁵ The Citizen Petition may be found at: <http://www.fda.gov/ohrms/dockets/dockets/07p0074/07p0074.htm>

¹⁶ Meeting materials and minutes may be found at: <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs>

¹⁷ Available at: http://www.generaterecords.net/PicGallery/AAP_CC.pdf

¹⁸ AAP Policy Statements, Pediatrics, February 2007, 119(2); 405

In October of 2008, CHPA announced a voluntary change in the labeling of their OTC cough and cold products to state that these products should not be used in children under age 4 years. They also added wording to certain antihistamine labels to say that the products should not be used for sedation.

As a result of these events, use of all OTC cough and cold products in children under 4 years of age has significantly decreased, and emergency department visits for cough and cold medication adverse drug events has declined nationally.¹⁹

Regulatory and Safety History of Carbinoxamine after 2006

Since 2006, several generic single-ingredient carbinoxamine tablet and oral solution products have been approved. The applications for each referenced the Agency's previous findings of efficacy and safety for Palgic. As generics, these products incorporate the same labeling as Palgic, including the labeling updates from 2006.

An extended-release, single-ingredient carbinoxamine product, Karbinal™ ER (carbinoxamine maleate) extended-release oral suspension, was approved on March 28, 2013. The approval of this product is the reason that the safety of carbinoxamine is now being discussed at the PAC. Karbinal ER suspension contains carbinoxamine complexed with polistirex, equivalent to 4 mg carbinoxamine maleate. The development program relied entirely on pharmacokinetic studies in adults that established bioequivalence between the proposed extended-release product and an approved immediate-release carbinoxamine product, thereby supporting the efficacy and safety of the extended release product for all age ranges approved for the immediate-release reference product. Consistent with the Contraindication for use in patients less than 2 years of age, a waiver under PREA was granted for this age group, and the product was approved for use in patients 2 years of age and older with the same indications as granted under DESI.

Since the 2006 regulatory actions, the Agency has continued surveillance of the safety issues related to carbinoxamine use in children. It should also be noted that, immediately after the 2006 FR notices, the Agency received a number of safety reports about deaths in children who had received carbinoxamine-containing products. The Agency believes that these reports were directly stimulated by the actions it had taken, and do not represent an additional safety signal because, beyond 2007 there have been no additional reports of death in children who have received carbinoxamine-containing drug products, nor have any new safety signals with the use of the approved single-ingredient carbinoxamine products been noted.

¹⁹ Hampton LM, et al. Cough and Cold Medication Adverse Events After Market Withdrawal and Labeling Revision. *Pediatrics*, 2013, 132(6); 1047-54.