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1 Introduction and Background

This is clinical review of a Complete Response (CR) to a CR action taken by the Agency on October 7, 2011, for a 505(b)(2) application from Tris Pharma for Carbinoxamine Extended-Release (ER) Oral Suspension, equivalent to 4 mg of carbinoxamine maleate (CM) per 5 mL. The formulation is a sustained release formulation of carbinoxamine suspended in a drug-polistirex resin complex. The proposed Trade Name, Karbinal ER, was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

The application references both the currently available generic immediate-release Carbinoxamine Maleate 4 mg tablets (ANDA 40-442) and oral solution 4 mg/5 mL (ANDA 40-458), marketed under the brand name Palgic and manufactured by Milkart, Inc., and the no-longer-marketed immediate-release innovator products, Clistin 4 mg tablets (NDA 08-915) and 4 mg/5 mL elixir (NDA 08-955), previously marketed by McNeil. McNeil discontinued marketing the Clistin products in the 1990s, but not for safety or efficacy reasons¹. As a 505(b)(2) application, which cannot rely on a generic, the application relies on the no-longer-marketed innovator NDA product, Clistin, while using the marketed generic immediate release Palgic for bridging. This was in accord with an agreement between the Agency and Tris made at a Pre-IND meeting held on May 15, 2008.

The proposed Indications include symptomatic treatment of following conditions in patients 2 years of age and older:

- Seasonal and perennial allergic rhinitis
- 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.

The proposed Indications are the same as that for the generic immediate release product, Palgic, and are based on the Agency's DESI (Drug Efficacy Study Implementation) review of immediate-release carbinoxamine maleate products, Clistin Elixir and Tablets, under DESI 6303, and the subsequent approval of [DESI] efficacy supplements.

The development program included 2 BA/BE studies, but no clinical trials or nonclinical studies. The studies were designed to show that the relative bioavailability of the test

¹ 65 FR 18998 and 65 FR 27986

ER formulation was the same as the reference immediate release Palgic. The single dose study (M1FT08001) compared test to reference under fasted conditions and also, test to test under fed conditions. The multiple dose study (M1FT08002) compared test to reference at steady state under fasted conditions. The BA/BE studies show that the Tris Carbinoxamine Extended-Release Oral Suspension is bioequivalent to the immediate release reference, Palgic. However, late in the first review cycle, investigators from the Division of Scientific Investigations (DSI) identified significant violations to the bioavailability and bioequivalence requirements of 21 CFR 320 in bioanalytical studies conducted by (b) (4)

(b) (4) Since there was insufficient time during the review cycle to evaluate the accuracy and integrity of the data for the two studies, a CR action was taken.

In addition to the bioanalytic site issues, unresolved issues during the first review cycle included several CMC issues that could preclude approval, including an unsatisfactory establishment inspection, and some microbiological issues. Additionally, there were clinical issues with respect to the indications and age groups supported by the application that were not resolved during the first review cycle. Finally, since a CR action was to be taken, labeling negotiations were not carried out during the first cycle.

2 Review of the Submission

2.1 Bioanalytic Issues

The bioanalytic analyses for the studies were performed at (b) (4) during February and April of 2009. However, late in the first review cycle for this application, investigators from DSI identified significant violations in the bioanalytical studies conducted by (b) (4) between the dates of (b) (4) which included the studies for this application.² DSI found the following: (1) widespread falsification of dates and times in laboratory records for subject sample extractions, (2) apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations. The Office of Scientific Investigations (OSI) declined to inspect the studies as the issues with (b) (4) were well documented and the study conduct time period of these studies fell in the identified time period of potential fraud. However, the ORA field inspector did inspect the clinical site where study was conducted. Since there was insufficient time during the review cycle to evaluate the accuracy and integrity of the data for the two studies, a CR action was taken, and the Complete response letter gave Tris the options of: a) reanalysis, b) repeat the BE studies, or c) conduct new clinical studies.

Subsequently, OSI recommended the option of an independent third-party data integrity audit if the studies were conducted between March 1, 2008 to August 31, 2009. Since the two studies conducted for this application were initiated and completed in Jan to Apr of 2009 this option was applicable. OSI also provided a detailed plan as to how this could be accomplished, which was communicated to this sponsor in an Advice letter dated May 1, 2012. Tris subsequently followed this approach and had an independent audit conducted by [REDACTED] (b) (4) which concluded that the studies were at low risk for sample manipulation.

OSI then inspected the clinical site and the data for the two studies passed inspection. Their findings were summarized in a memo dated September 11, 2012, the only specific recommendation being to consider whether the data for one of the subjects who became pregnant and had a miscarriage should be excluded from the analyses. This subject was administered reference treatment on 1/3/09, test treatment (fast) on 1/17/09, and test treatment (fed) on 1/31/09. She had a positive pregnancy test on 2/3/09 when her 72 hour blood sample (last PK blood sample for this patient in the study) was collected. Subsequently, she had a miscarriage on [REDACTED] (b) (6). It was left to the review Division to decide whether the subject should be removed from PK analysis. Clinical Pharmacology discussed this and, based on the timeline of the PK evaluations, considered that the pregnancy would not affect the PK outcome.

In summary, the bioanalytic data are now considered acceptable for consideration. Since the results demonstrated bioequivalence between test and reference, the studies support Approval of this application.

2.2 CMC Issues

The recommendation from ONDQA is Approval. In the first cycle, the recommended action from the CMC perspective was a Complete Response, pending resolution of several deficiencies and clarifications related to specifications, manufacturing process, control of leachables, updated stability data, and control of PSD for the final drug product. These issues have been resolved, and the drug substance and drug product manufacturing and testing sites have been inspected.

2.3 Microbiology Issues

The recommended action from Microbiology is Approval. In the first review cycle the recommendations was a Complete Response pending resolution of deficiencies related to (a) development of test method and specifications to include the absence of Burkholderia Cepacia complex organisms and (b) preservative effectiveness testing on three batches of drug product. These issues have now been addressed.

2.4 Clinical Issues and Risk/Benefit Assessment

2.4.1 Results of BA/BE studies

The two relative bioavailability studies support Approval of this application. The studies compared the proposed carbinoxamine extended release oral suspension (Test) with a Reference carbinoxamine maleate oral solution (Palgic, manufactured by Mikart) in healthy adults. The studies were a single dose study (Study MIFT08001) that evaluated the food effect on the Test product, and a multiple dose study (Study MIFT08002) that compared the Test and Reference products at steady state under fasted conditions. The results show that the Test product is bioequivalent with the Reference product after both single dose and multiple dose administration under fasted conditions and that food has no effect on the Test product. The results are depicted in the graphs below (Figure 1 and Figure 2) copied from Dr. Doddapaneni’s first cycle CDTL review.

Figure 1. Plasma Concentration-Time Profile and Summary Analysis for M1FT08001.

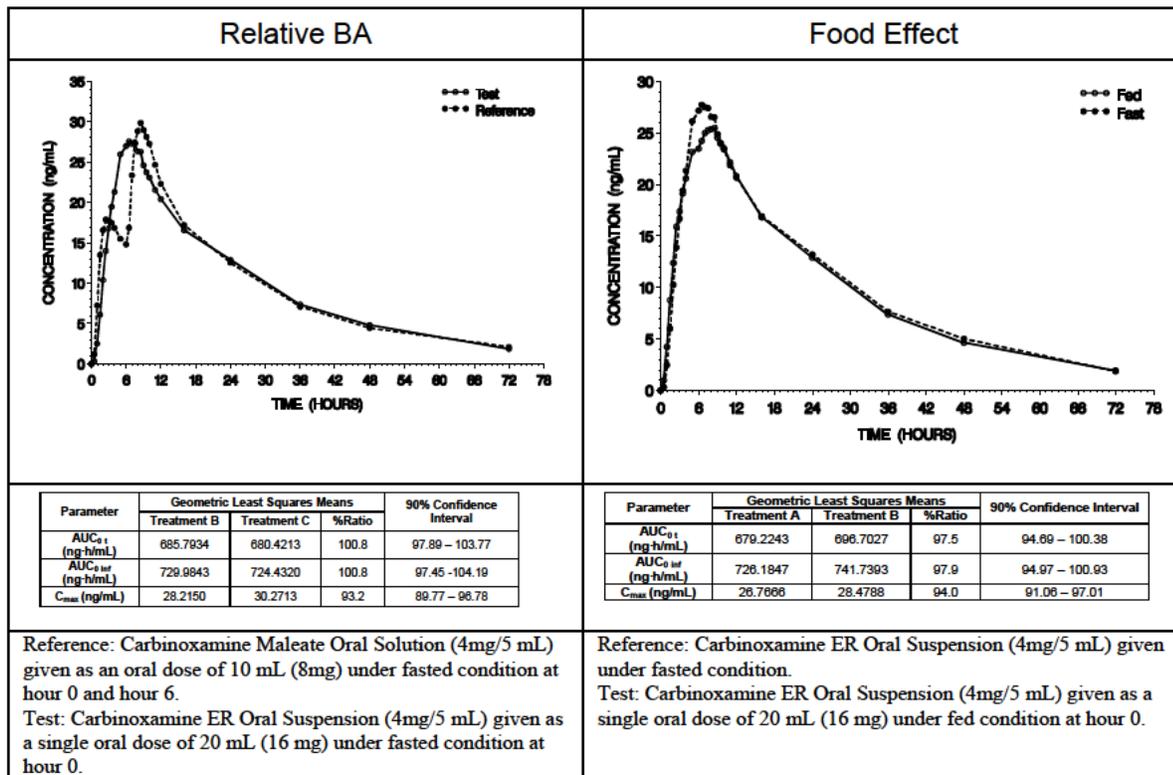
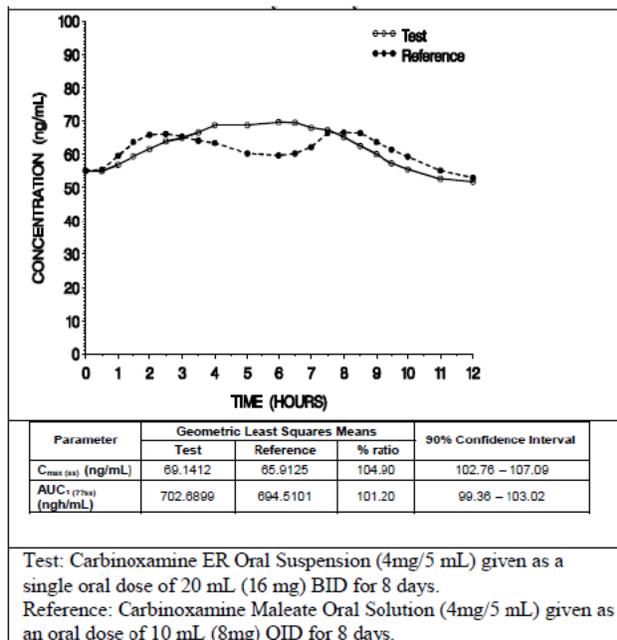


Figure 2. Plasma Concentration-Time Profile and Summary Analysis for M1FT08002.



2.4.2 Indications

The Indications sought for this extended-release product are the same as for the immediate-release generic reference product, which are based on the original DESI (Drug Efficacy Study Implementation) indications for the no-longer-marketed innovator immediate-release NDA product, Clistin Tablets and Elixir (DESI 6303). While the Clistin products are no longer marketed, they were not removed from the market due to safety concerns.³

In my first cycle review I recommended limiting the indications to patients with seasonal and perennial allergic rhinitis (SAR and PAR) ≥ 17 years of age. This recommendation was made based on my review of the studies submitted to the DESI review panels to support carbinoxamine maleate within the framework of today's scientific and regulatory standards and based on current, published clinical practice parameters. I concluded that the risk/benefit assessment for this drug product only supports the indications of SAR and PAR in patients 17 years of age and older. From a scientific perspective, this recommendation stands.

However,

(b) (5)

³ On January 26, 1993, the R.W Johnson Pharmaceutical Research Institute notified FDA in writing that Clistin 4 mg immediate release tablets were no longer being marketed under NDA 8-915 and requested the withdrawal of that application. The FDA complied and announced that NDA was withdrawn in an FR notice dated March 2, 1994 (59 FR 9989). Subsequently, the FDA responded to a citizen petition from Sage Pharmaceuticals, dated January 22, 1998 (Docket No. 98P-0062/CP1), that the NDA had not been withdrawn for sale for reasons of safety or effectiveness (63 FR 27986, May 21, 1998).

(b) (5)

the regulatory requirements do not allow implementation of my recommendations. Since this extended-release product is bioequivalent to two doses of the immediate-release product, all of the DESI indications and age groups from the immediate-release product will port directly to this product.

To understand the differences between the scientific recommendations and the regulatory requirements, details of the background follow.

2.4.2.1 The DESI Process: Effectiveness and Indications

Carbinoxamine maleate is a first-generation histamine H₁-receptor blocking agent (antihistamine) of the ethanolamine class. This antihistamine class also includes diphenhydramine, an OTC drug. This class exhibits antihistaminic, anticholinergic, and sedative properties. The NDAs for Clistin date to the 1950s, with the NDA for Clistin 4 mg Tablets and Clistin R-A 8 and 12 mg Tablets (NDA 8-915) approved on June 22, 1953, the NDA for Clistin Elixir 4 mg/5mL (NDA 8-955) approved on June 23, 1953, and the NDA for Clistin Expectorant (NDA 9-248) approved on February 5, 1954⁴. Another combination of carbinoxamine with phenylephrine and acetaminophen, Clistin-D, was also marketed but may never have been the subject of a New Drug Application (NDA).

The Kefauver-Harris Amendment of 1962 required evaluation of the effectiveness of all drugs that had been approved by the NDA process (based on safety) between 1938 and October 10, 1962. As a pre-1962 drug moiety, the Clistin family of products was subject to the DESI evaluation of effectiveness, which was performed by panels from the National Academy of Sciences – National Research Council, Drug Efficacy Study Group. The panels evaluated groups of drugs within the setting of a pharmacologic drug class and gave ‘drug class’ indications. Clistin Tablets, R-A Tabs, Elixir, and Expectorant were evaluated within DESI 6303. Two panels evaluated these products, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II. The Agency then reviewed the Panels’ recommendations and published its findings in various Federal Register notices. The determination was made that the immediate-release, single-ingredient carbinoxamine maleate products, marketed as Clistin Tablets and Elixir, were effective for the symptomatic treatment of the following conditions (DESI 6303, 38 FR 7265, March 19, 1973):

- Seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR)

⁴ In a notice published in the Federal Register on March 19, 1982 (47 FR 11973), FDA revoked a temporary exemption for this combination product that allowed the product to be marketed beyond the time limit scheduled for the implementation of the Drug Efficacy Study. The product was thereby reclassified as lacking substantial evidence of effectiveness and offered an opportunity for a hearing. As no new data was submitted, the FDA announced withdrawal of marketing approval in the Federal Register on May 18, 1982 (47 FR 21301).

- 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.

Although the innovator product, Clistin, is no longer marketed, the NDA holder did not withdraw the immediate-release products from the market due to safety concerns.^{5,6} As a result, when the current immediate-release reference listed drug, i.e., Palgic Oral Solution, was approved as a generic to Clistin in 2003, the indications were the same as the indications allowed the originator [Clistin] under the DESI review process.

While the two marketed extended-release products, Clistin RA 8 and 12 mg, were initially classified as probably effective under DESI (26 FR 9339, May 22, 1971) they were later reclassified as “lacking substantial evidence of effectiveness” because of a lack of the required *in vivo* bioavailability data linking the extended-release and the immediate-release products (47 FR 18667, April 30, 1982). The applicant was offered an opportunity for a hearing, but because no data was submitted, the FDA announced withdrawal of marketing approval in the Federal Register on July 29, 1983 (48 FR 34514).

The Division was not aware of the withdrawal of marketing approval of the extended-release Clistin product during the first review cycle. Nevertheless, during the first cycle review, the Division considered it reasonable to examine the data that formed the basis of the Agency’s previous DESI effectiveness designation for the immediate-release carbinoxamine maleate, including the adequacy of the studies used to support each of the DESI indications based on today’s scientific and regulatory standards, and with consideration given to the relevance of each of the DESI indications to today’s current practice standards. At that time, I reviewed all of the original clinical study publications that were available to and were reviewed by the two DESI panels to support DESI determination for carbinoxamine maleate. My review of the data found no scientific support for the current DESI indications for carbinoxamine maleate beyond seasonal and perennial allergic rhinitis. The findings are summarized below.

The DESI process evaluated the effectiveness of a drug, with each indication theoretically required to be supported by adequate and well-controlled clinical trials. Nevertheless, it is quite clear that as the determinations were made both the Panels and

5 See in-text reference #2.

6 On April 5, 1985, FDA announced that NDA 8-955 was withdrawn (50 FR 13661), after McNeil Pharmaceutical notified FDA in writing that Clistin Elixir 4 mg / 5 mL was no longer being marketed under NDA 8-955 and requested the withdrawal of that application. Subsequently, the FDA responded to a citizen petition from Milkart Inc., dated October 8, 1999 (Docket No. 99P-48482/CP1), that the NDA had not been withdrawn for sale for reasons of safety or effectiveness (65 FR 18988, April 10, 2000).

the Agency took into consideration what was known about other drugs in the same or similar pharmacologic classes, as the DESI reviews were performed in the context of the review of a grouping of drugs within the same pharmacologic class (for DESI 6303, antihistamines and antihistamine combinations), and the indications allowed by the Agency were not only the same for all of the members of the class but they were also more extensive than those reviewed by the DESI Panels. For example, the Panel on Drugs Used in Allergy examined Clistin for the following indications: SAR and PAR, urticaria, and adjunctive therapy in asthma, and the Panel on Drugs Used in Dermatology II examined Clistin for symptomatic relief of allergic disorders such as pruritic skin conditions and for the symptomatic relief of allergic disorders such as urticaria. The reason why the Panels did not review all of the indications is not documented, nor is the reason why the Agency allowed additional indications than the data for a given drug. However, a broad and similar set of indications was allowed for the group of prescription antihistamines that were reviewed under DESI 6303, including carbinoxamine maleate, chlorpheniramine maleate, cyproheptadine hydrochloride, promethazine hydrochloride, diphenhydramine hydrochloride, and tripeleminamine hydrochloride, among others (36 FR 11758, June 18, 1971 and 38 FR 7265, March 19, 1973) [*Note:* This is not a complete list]. Diphenhydramine is in the pharmacologic class of ethanolamine antihistamines as carbinoxamine, whereas others are not.

This indication grouping is understandable, given the prevailing medical view at the time that indications could be based to a large extent on the pharmacologic class of a drug. However, in the interim, review standards have changed. Based on current review standards, the relative effect of a candidate drug within a pharmacologic class would be screened and evaluated based on its effect on each potential receptor, and clinical trial data would be required to support each proposed indication. Therefore, the DESI process is disturbing when viewed in light of current regulatory standards and review practices, because it means that while the scientific evidence to support carbinoxamine maleate was considered, deficiencies in that evidence were overlooked in that there appears to have been no scientific evidence (i.e., clinical trial data) to support some of the indications that were granted to carbinoxamine maleate under DESI.

The DESI Panels findings are reproduced in Appendix 1 of this review, and data that the Panels reviewed are discussed below.

Four published studies served as the basis of the Panels' recommendations. Two of the four studies were placebo-controlled, of which one used a parallel (Beale) and one used a crossover (MacLaren) design. Combined, three of the four studies give support for the most common indication studied, namely allergic rhinitis, including both SAR and PAR. The results from these studies are considered sufficient to support the indications of SAR and PAR.

Three studies provide some support for the indication of the treatment of urticaria. However, only one of the trials was placebo-controlled and two were open-label, the number of patients treated [28] was small, and the results are somewhat conflicting. Therefore, the body of evidence for the treatment of urticaria would not be considered adequate by today's standards.

My review of these studies revealed that there were insufficient data to support other DESI indications for carbinoxamine maleate. For each of the other indications, either no patients were studied, or the numbers of patients included in studies were too small, or the trial design was not adequate, to make a reasonable conclusion about either the efficacy or safety of carbinoxamine maleate for treatment of that condition.

Additionally, I reviewed all of the practice parameters for treatment of allergic conditions published by accepted authorities, such as the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council on Allergy, Asthma and Immunology, and others. My review found no specific support in the practice parameters for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. The primary source of practice parameters comes from the Joint Council on Allergy, Asthma and Immunology, which represents both the AAAAI and ACAAI, and has created a Joint Task Force to establish and publish practice parameters. First generation antihistamines may be considered for a wide range of indications, although (with the exception of allergic rhinitis, and OTC use under the OTC monograph) their use is infrequent and often as second line or adjunctive therapy, with second generation antihistamines preferred because of concerns for unwanted side effects of sedation, anti-cholinergic effects, and performance impairment with older antihistamines.

My review found no safety concerns about carbinoxamine maleate beyond those already known and labeled, and none that would support limiting the indications in adults. The side effects reported in the clinical pharmacology studies conducted for this application are consistent with the labeling in the current PI for the immediate-release product. Therefore, the adequacy of current Adverse Reactions section is supported, with the exception that borderline elevations in uric acid, noted in the multiple-dose PK study conducted to support this application should be added to the Adverse Reactions section of the PI.

In sum, the proposed indications for this extended-release product are based on the indications for the immediate-release carbinoxamine maleate product that was found to be effective under DESI. Whereas the previous extended-release carbinoxamine maleate product was found to be ineffective under DESI, this was due to the fact that no bioavailability studies had been performed to match systemic exposure between the extended-release and the immediate-release products. This application supplies the necessary BA/BE link between the proposed extended-release suspension (Karbinal ER) and the immediate-release reference product (Palgic).

As a result, while the risk/benefit assessment for this drug product only supports the indications of seasonal and perennial allergic rhinitis (SAR and PAR) based on today's scientific [and regulatory] standards, the proposed extended-release product is bioequivalent to [2 doses of] the immediate-release product. Because, short of rule-making, there is no regulatory basis to change or modify the indications for the immediate-release product that were allowed under the DESI process (regardless of how lacking in support the indications are from a scientific perspective) unless there is a safety concern, this product will gain all of the indications as has the immediate-release product.

2.4.2 Pediatric Considerations: Age groups supported and PREA

This application triggers PREA because the extended-release dosage form is a new dosage form. The applicant has requested approval of this extended-release suspension for use in children 2 years of age and older, including all of the DESI Indications discussed above, and waivers for the following:

1. Pediatric studies birth to <2 years of age because carbinoxamine is contraindicated in children under 2 years of age, and
2. Pediatric bioequivalence studies in children 2 to <18 years of age.

With regard to the first request, a waiver of studies in children under 2 years of age is appropriate, since carbinoxamine is contraindicated in this age group because of the safety concern of deaths in children less than 2 years of age who are exposed to carbinoxamine-containing products.

With regard to the second request, per guidance, the BA/BE studies were performed in healthy adults, and it is considered that the results of these studies are applicable to the adolescents and children 2 to <18 years of age. Therefore, a waiver of BA/BE studies in children 2 to <18 years of age would be appropriate but is irrelevant.

With regard to the request for Approval in patients 2 years of age and older, with submission of satisfactory evidence to support bioavailability and bioequivalence, all of the DESI indications and age groups transfer from the immediate-release product to the extended-release product unless there were a safety issue that precludes this.

The pediatric issues for this application were discussed with the Pediatric Review Committee (PeRC) during the first review cycle on August 31, 2011. PeRC agreed with the waiver for children under 2 years of age. At that time, the Division was considering



As a result, there is a significant discrepancy between the scientific supports for this application and what the regulations currently require. The standards for efficacy and safety in force at the time of approval of the originator and throughout the DESI process were less than ideal with regard to providing sufficient data in children, and are not at the level of today's standards. PREA requires that all applications include a pediatric assessment in all relevant age ranges containing data to: "1) assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and 2) support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective." While extrapolation of efficacy from older age groups is possible when the

course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, safety and dosing can never be extrapolated. Nevertheless, the Agency's previous findings of safety and efficacy in the pediatric age groups allow approval of the products.

One safety issue has been noted for carbinoxamine maleate that did allow for modification of the indications for the immediate-release product. Originally, the immediate-release Clistin products had DESI indications and dosing recommendations for children 1 year of age and older, although pediatric dosing recommendations were never provided for the extended-release Clistin products (see Table 1).

Table 1. Clistin dosing recommendation table

A large rectangular area of the document is redacted with a solid grey fill. In the top right corner of this redacted area, the text "(b) (4)" is printed in a small font.

The lower age bound for the immediate-release products was changed from 1 to 2 years of age in 2006, because of a new safety finding of deaths in children under 2 years of age who were administered a carbinoxamine-containing product.⁷ At the same time, because of the safety risk, the existing ANDA holder (Milkart) agreed to add a contraindication for use in children younger than 2 years of age. As a result, the immediate release formulations now carry Indications and dosing recommendations for use in children 2 years of age and older.

As part of my review, I reviewed the study report publications submitted to DESI. My review revealed that only the specific indications of seasonal and perennial allergic rhinitis were studied sufficiently to support efficacy and safety in adults, and none were sufficient to support efficacy or safety for any indications in pediatric patients. Although pediatric dosing recommendations were provided for the immediate-release Clistin tablets and elixir, I was unable to find any PK data in children to support the original dosing recommendations. Further, none of the DESI study publications included pediatric PK data, and in searches of the published literature I was unable to find any pediatric PK or safety data for carbinoxamine maleate.

Without PK data, it is most likely that the pediatric dosing schema for carbinoxamine maleate was arrived at via an *ad hoc* process that proportioned the pediatric dose from the adult dose. This was an accepted procedure for choosing the pediatric dose of OTC

⁷ On June 9, 2006, the Agency published a notice in the Federal Register [71 FR 33462] stating that the Agency intended to take action against marketed unapproved carbinoxamine-containing products. This notice was published at the same time that the Guidance for Staff and Industry - Compliance Policy Guide for Marketed Unapproved Products - was finalized. The action against the marketed unapproved carbinoxamine-containing products was taken primarily because of a new safety finding of 21 deaths in children under 2 years of age who were administered a carbinoxamine-containing product.

and Rx cough, cold, allergy, bronchodilator, and asthmatic [CCABA] drugs at the time that carbinoxamine maleate was developed in the early 1950s and eventually incorporated into the OTC CCABA Monograph in 1976.⁸ Typically, this procedure involved halving the adult dose of drugs for patients in the 6-11 year age range and quartering the adult dose for patients in the 2-5 year age range, although it was not always followed exactly, and in the case of carbinoxamine maleate the pediatric dosing schema does not exactly match the proportional $\frac{1}{2}$ and $\frac{1}{4}$ adult dose. Nevertheless, there is no information to support that anything other than an *ad hoc* process was employed for the original dose selection of carbinoxamine maleate in children.

The adequacy of the *ad hoc* dose selection schema has since been raised by the Agency⁹ and discussed at an Advisory Committee meeting¹⁰, with the result that this dosing schema is no longer acceptable for dose selection and PK data are now required to support selection of the appropriate pediatric dose.^{11,12,13,14} (b) (5)

However, the lack of PK and safety data does reflect on the appropriate dose to support the safety and dosing of an extended-release carbinoxamine maleate product in children.

By extension, one could construe that safety issue of mortality in children under 2 years of age may potentially also relate to safety in the age group of pediatric patients 2-5 years of age when an extended-release product is used. Extended-release products, including suspensions, are typically reserved for use in children 6 or 12 years of age and older, depending upon the product, with immediate release products typically used below these ages. This is the case for many symptomatic use products, including

8 Advanced Notice of Proposed Rulemaking [Monograph] for OTC Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Products; 41 FR 38333, September 9, 1976.

9 Pediatric Dosing Information for Over-the-Counter Human Drugs; Intent and Request for Information; 53 FR 23183, June 20, 1988.

10 The Nonprescription Drugs Advisory Committee meeting, held on January 13, 1995, discussed pediatric dosing for children under 12 years of age.

11 Advanced Notice of Proposed Rulemaking; Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; 62 FR 43900, August 15, 1997.

12 Draft Guidance for Industry: General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products, November 1998; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072114.pdf>, Accessed 7/13/2011.

13 Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population, December 2000; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073143.pdf>, Accessed 7/13/2011.

14 Pediatric Research Equity Act of 2003 (Public Law 108-155); S650, December 3, 2003; available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf>, Accessed 7/13/2011

antihistamine and antihistamine combination products. One reason is that the dosage form for many extended-release products is a tablet or capsule that does not lend itself to use in the younger age ranges, such as 2-5 years of age. However, another is the potential safety issue of adverse events with use of an extended-release product in young children that may be prolonged compared to adverse events with use of an immediate-release product containing the same active moiety. As a result, the present postmarketing safety data that limit the use of carbinoxamine in children less than 2 years of age raise the concern that there may also be a safety risk in children 2-5 years of age when an extended-release product is used instead of an immediate-release product. However, there is no way to assess this risk without clinical trials, and pediatric studies cannot be required under PREA unless there is a safety risk. Hence, this presents a scientific and regulatory dilemma that cannot be easily resolved.

In summary, the sponsor has requested a waiver of pediatric studies in patients 0-2 years of age and approval for use in patients 2-17 years of age. While this is acceptable from a regulatory perspective, from a scientific perspective the risk/benefit assessment for this extended-release product does not support approval of the requested pediatric age range of 2-17 years of age. There are no PK data in children to support the dosing, and dosing for the immediate-release products is based on *ad hoc* dose selection schema that has since been considered inadequate by the Agency. Therefore, application of the immediate-release product's dosing schema to this extended-release product is not scientifically consistent with current review standards. This view is consistent with recommendations provided by a recent joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee held on October 18-19, 2007, to discuss the efficacy and safety of over-the-counter (OTC) CCABA medications in children, at which the issues of efficacy, safety, and dosing of the OTC drugs were discussed. At that meeting, the Advisory Committee recommended that clinical trials be performed for all OTC CCABA medications, with the exception being that for OTC antihistamines for SAR and PAR the Agency argued, and the AC accepted, that there are sufficient data available to accept the indications without the need for efficacy studies if PK and safety data are available.¹⁵

While the Agency may require pediatric studies under PREA to support all the indications considered appropriate for the pediatric age range when data are lacking to support efficacy, safety, or dosing, the Agency's previous findings of safety and effectiveness preclude use of this mechanism without a known safety risk. Since the immediate-release products are already approved for use in children 2 years of age and older and this extended-release product is bioequivalent to [2 doses of] the immediate-release product, efficacy and safety for use in this age group is supported.

15 Summary Minutes and Transcript of the Joint Nonprescription Drugs and Pediatric Advisory Committees meeting, October 18-19, 2007; <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#NonprescriptionDrugs>, Accessed 7/13/2011.

2.5 Consults

2.5.1 Proprietary Name

During the first review cycle, the proposed proprietary name, Karbinal ER, was found to be acceptable from both a promotional and safety perspective by the Division of Medication Error Prevention and Analysis (DMEPA), and Tris was notified of this conclusion on November 16, 2011.

The proposed proprietary name was re-reviewed upon submission of the Complete Response, and on January 3, 2013, DMEPA notified Tris that the proposed proprietary name is acceptable. DMEPA will still need to re-review the proposed proprietary name within 90 days prior to approval of the application.

2.5.2 Other Consults

Labeling consults are being obtained from the Office of Surveillance and Epidemiology (OSE) and the Office of Prescription Drug Promotion (OPDP).

3 Recommendations

3.1 Regulatory Action

Although I have serious scientific reservations about the risk/benefit of this product for the indications and age groups requested, there is no regulatory basis upon which I can make a recommendation other than for an Approval action for this product.

3.2 Postmarket Risk Evaluation and Mitigation Strategies

None

3.3 Postmarket Requirements and Commitments

None.

3.4 Labeling

Labeling negotiations were not carried out during the first cycle review period, but will be carried out during this cycle after completion of this review [labeling IR sent on February 22, 2013]. A summary of the significant issues being addressed during labeling is provided below:

1. This application represents the first PLR labeling for a carbinoxamine product. Therefore, the labeling will necessarily differ from other (immediate-release) carbinoxamine maleate products in this respect.
2. The contraindication for children under 2 years of age will be maintained. Additionally, since the extent of infant exposure while breast-feeding is unknown, the product will be contraindicated for use in breast-feeding women.
3. Since the Warnings section lists warnings hierarchically by importance, the warning with regard to activities requiring mental alertness needs to be elevated, as this is a key warning for use of this drug.
4. The potential for increased exposure with concomitant alcohol use can be handled by appropriate labeling, which is already present in the labeling.
5. (b) (4) that is being proposed by the applicant.

4 Comments to Applicant

None

Appendix 1. DESI 6303 files for carbinoxamine maleate

CLISTIN
NDA 8955
LOG 1847

Panel on Drugs Used in Allergy

INDICATIONS

I. Seasonal and perennial allergic rhinitis.

EVALUATION: Probably effective.

COMMENTS: None.

DOCUMENTATION:

1. Beal, H.D., F.F.A. Rawling, and K.D. Figley. Clistin maleate: a clinical appraisal of a new antihistaminic. J. Allerg. 25:521-524, 1954.
2. Garat, B.R., C.R. Landa, O.F. Rossi Richeri, and R.O. Tracchia. Clinical, chemical and pharmacologic relationships of antihistamines. J. Allerg. 27:57-62, 1956.
3. Johnson, H.J., Jr. Clinical evaluation of a new antihistaminic: clistin maleate. Am. Pract. Dig. Treat. 5:862-863, 1954.
4. MacLaren, W.R., W.C. Bruff, B.C. Eisenberg, H. Weiner, and W.H. Martin. A clinical comparison of carbinoxamine maleate, tripeleennamine hydrochloride, and bromodiphenhydramine hydrochloride in treating allergic symptoms. Ann. Allerg. 13:307-312, 1955.

II. Urticaria.

EVALUATION: Probably effective.

COMMENTS: None.

DOCUMENTATION:

1. Beal, H.D., F.F.A. Rawling, and K.D. Figley. Clistin maleate: a clinical appraisal of a new antihistaminic. J. Allerg. 2:521-524, 1954.
2. Garat, B.R., C.R. Landa, O.F. Rossi Richeri, and R.O. Tracchia. Clinical, chemical and pharmacologic relationships of antihistamines. J. Allerg. 27:57-62, 1956.
3. Johnson, H.J., Jr. Clinical evaluation of a new antihistaminic: clistin maleate. Am. Pract. Dig. Treat. 5:862-863, 1954.

III. Adjunctive therapy in asthma.

EVALUATION: Possibly effective.

COMMENTS: The use of antihistamines in the treatment or prophylaxis of asthma is unwarranted in the vast majority of cases. These agents may be useful in asthmatic children, some of whom may respond favorably. This response may be due to the sedative side effects of antihistamines. Antihistamines generally fail to improve the condition

of asthmatic adults. In fact, there is some theoretical and clinical argument that these agents are contraindicated. Some asthmatics become more difficult to manage after treatment with antihistamines, possibly due to the drying effect of these drugs on respiratory secretions.

DOCUMENTATION: Same as for Indication II.

GENERAL COMMENTS

"Usually low incidence of side effects" is a relative statement that could be misleading. For example, in the paper by MacLaren (cited on Page 1) Clistin produced fewer side effects than Pyribenzamine or Ambodryl, but it is noteworthy that there was a 26% incidence of side effects associated with its use in the study, compared with 9% from a placebo.

Approved by Adolph Rostenberg
Chairman

CLISTIN ELIXIR
NDA 8955
LOG 1847

Panel on Drugs Used in Dermatology II

INDICATIONS

- I. For the symptomatic relief of allergic disorders such as pruritic skin conditions.

EVALUATION: Possibly effective.

COMMENTS: There is little evidence regarding the clinical effectiveness of systemic antihistamines in reducing these cutaneous reactions or their associated pruritus. While these products may produce sedation in some patients, they may produce no sedative effect or excitation in others. Thus, the Panel feels that the role of the product in the treatment of these conditions needs further evaluation so that its therapeutic value can be adequately ascertained.

Furthermore, the product has no prophylactic value against these various conditions and has no effect on the primary lesion.

DOCUMENTATION:

1. Beale, H.D., F.F. Rawling, and K.D. Figley. Clistin maleate; clinical appraisal of a new antihistaminic. J. Allerg. 25: 521-524, 1954.
2. Garat, B.R., C.R. Landa, O.F.R. Richeri, and R.O. Tracchia. Clinical, chemical, and pharmacologic relationships of antihistamines; study of new synthetic antihistaminic, carbinoxamine maleate (clistin maleate). J. Allerg. 27:57-62, 1956.
3. Johnson, H.J., Jr. Clinical evaluation of a new antihistaminic: clistin maleate. Amer. Practit. 5:862-863, 1954.
4. MacLaren, W.R., W.C. Bruff, B.C. Eisenberg, H. Weiner, and W.H. Martin. A clinical comparison of carbinoxamine maleate, tripelenamine hydrochloride, and bromodiphenhydramine hydrochloride in treating allergic symptoms. Ann. Allerg. 13:307-312, 1955.

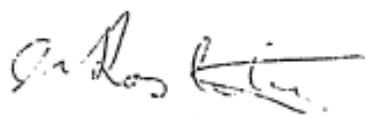
- II. For the symptomatic relief of allergic disorders such as urticaria.

EVALUATION: Effective.

COMMENTS: This product is an effective form of treatment in mild and uncomplicated cases of these types of allergic cutaneous reactions.

DOCUMENTATION: Same as for Indication I.

Signature


Adolph Rostenberg, M.D., Chairman
Dermatology Panel II

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
02/25/2013

THERESA M MICHELE
02/25/2013