

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-556Orig1s000**

**MEDICAL REVIEW(S)**



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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 reasons<sup>1</sup>. 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

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<sup>1</sup> 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). 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 a (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.<sup>2</sup> 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.

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(b) (4)

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.

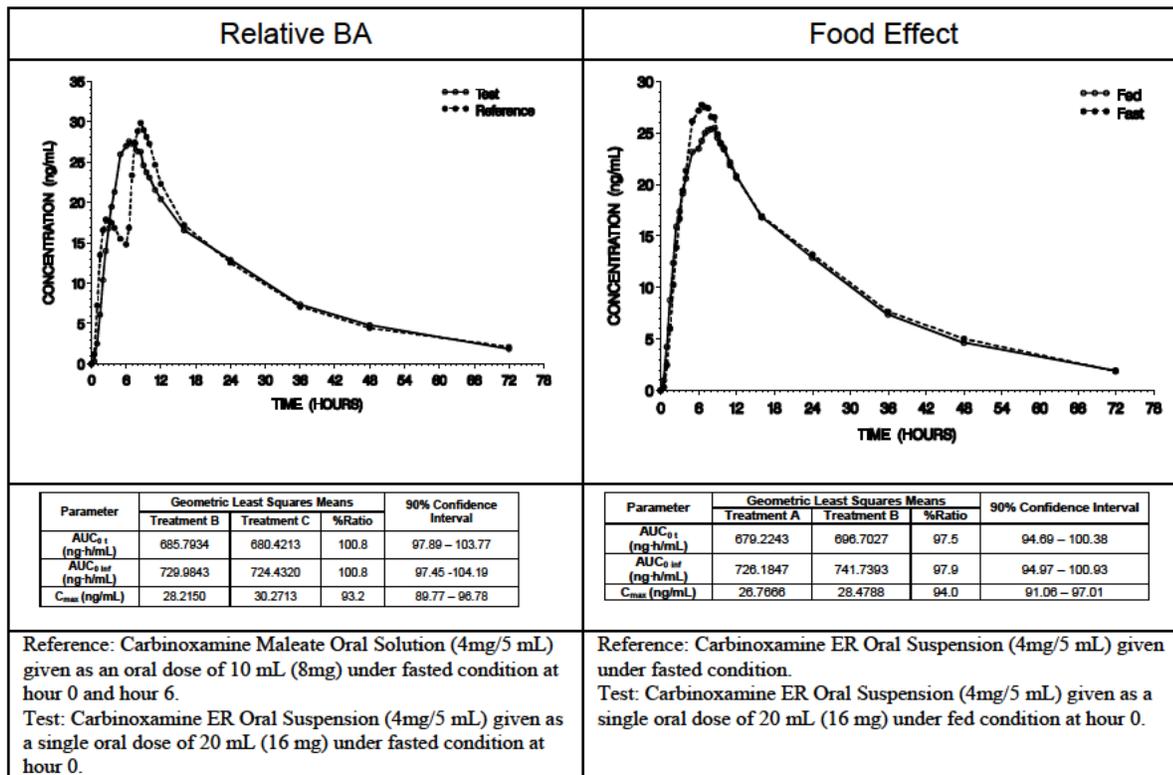
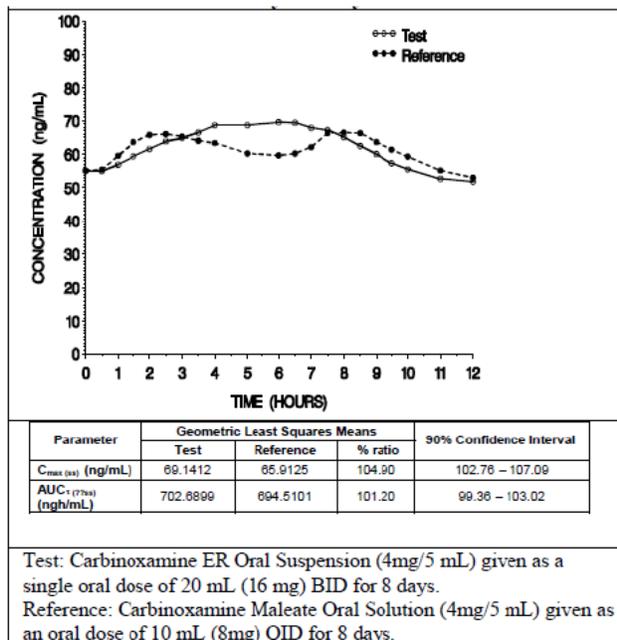


Figure 2. Plasma Concentration-Time Profile and Summary Analysis for M1FT08002.



## 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.<sup>3</sup>

In my first cycle review I recommended limiting the indications to patients with seasonal and perennial allergic rhinitis (SAR and PAR)  $\geq 17$  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, [REDACTED]

(b) (5)

<sup>3</sup> 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 H<sub>1</sub>-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, 1954<sup>4</sup>. 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)

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<sup>4</sup> 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.<sup>5,6</sup> 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

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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

(b) (5)



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.<sup>7</sup> 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

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<sup>7</sup> 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.<sup>8</sup> 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 Agency<sup>9</sup> and discussed at an Advisory Committee meeting<sup>10</sup>, 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.<sup>11,12,13,14</sup> (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

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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.<sup>15</sup>

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.

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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 AllergyINDICATIONS

## 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, tripeleminamine 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.

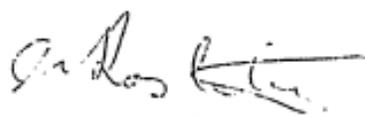
- II. For the symptomatic relief of allergic disorders such as urticaria.

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.**  
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/s/  
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PETER R STARKE  
02/25/2013

THERESA M MICHELE  
02/25/2013

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-556
Priority or Standard	Standard
Submit Date(s)	December 7, 2010
Received Date(s)	December 8, 2010
PDUFA Goal Date	October 8, 2011
Division / Office	Division of Pulmonary, Allergy, and Rheumatology Products / Office of New Drugs
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	August 31, 2011
Established Name	Carbinoxamine Extended Release Oral Suspension
(Proposed) Trade Name	Karbinal ER™
Therapeutic Class	Antihistamine
Applicant	Tris Pharma
Formulation(s)	Extended release oral suspension
Proposed Dosing Regimen	Usual Adult Dosage: [REDACTED] (b) (4) (6 to 16 mg) every 12 hours Usual Child's Dosage (approximately 0.2 to 0.4 mg/kg/day): Two to three years – [REDACTED] (b) (4) (3 to 4 mg) every 12 hours [REDACTED] (b) (4) – [REDACTED] (b) (4) (3 to 8 mg) every 12 hours [REDACTED] (b) (4) – [REDACTED] (b) (4) (6 to 12 mg) every 12 hours
Proposed Indication(s)	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 <i>adjunctive</i> to epinephrine and other standard measures after the acute manifestations have been controlled Amelioration of the severity of allergic reactions to blood or plasma
Intended Population(s)	Ages 2 years and older

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**Submissions Reviewed in this Document**

<b><u>Document Date</u></b>	<b><u>Stamp Date</u></b>	<b><u>Supporting Document</u></b>	<b><u>Comments</u></b>
December 7, 2010	December 8, 2010	N-001	NDA submission
January 20, 2011	January 21, 2011	N-003	Response to clinical IR of January 11, 2011, re laboratory parameters
February 17, 2011	February 18, 2011	N-004	Request for proprietary name review: (b) (4) and (b) (4) (alternative)
April 14, 2011	April 15, 2011	N-005	Response to filing communication, including revised labeling
June 3, 2011	June 6, 2011	N-006	Request for proprietary name review: (b) (4) and (b) (4) alternative)
August 19, 2011	August 22, 2011	N-012	Request to withdraw proprietary name: (b) (4)
August 19, 2011	August 22, 2011	N-013	Request for proprietary name review: Karbinal ER or (b) (4) (alternative)

# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

I recommend a Complete Response to this application. Investigators from the Division of Scientific Investigations (DSI) have identified significant violations to the bioavailability and bioequivalence requirements of 21 CFR 320 in bioanalytical studies conducted by (b) (4) where the bioanalytic analyses for this application were performed. 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. Therefore, DSI has stated that they have “serious questions ... about the validity” of all bioanalytical data generated at (b) (4) between the dates of (b) (4) (b) (4). The bioanalytical analysis for study MIFT08001 was from Feb 12, 2009 to Feb 25, 2009, and for study MIFT08002 was from April 24, 2009 to May 05, 2009. This information was not available until late in the review cycle, when the rest of this review was written. Due to time limitations, the body text in the review was not altered. However, the results of the two bioavailability/bioequivalence (BA/BE) studies submitted with this application and discussed in this review should not be considered valid, and are not acceptable to support this application.

## 1.2 Risk Benefit Assessment

This is a 505(b)(2) application from Tris Pharma for Carbinoxamine Extended Release (ER) Oral Suspension, 4 mg of carbinoxamine maleate (CM) per 5 mL. The formulation is a sustained release formulation of carbinoxamine maleate suspended in a drug-polystyrene resin complex. The reference listed drug (RLD) is the generic immediate release Carbinoxamine Maleate Oral Solution, marketed under the brand name Palgic, and manufactured by Milkart, Inc. As a 505(b)(2) application, which cannot rely on a generic, the application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release Carbinoxamine Maleate Oral Solution for bridging. The proposed Indications are the same as that for the immediate release products, which includes symptomatic treatment of various allergic conditions in patients 2 years of age and older (see next section for details).

The development program included 2 BA/BE studies, but no clinical trials or nonclinical studies. The BA/BE studies show that the Tris Carbinoxamine Extended Release Oral Suspension is bioequivalent to the immediate release reference, Palgic. [See Section

1.1, above for why these data are not acceptable.] Additionally, there are several unresolved CMC issues that could preclude approval, including an unsatisfactory establishment inspection, in addition to some microbiological issues to be resolved. Nevertheless, the Division plans to address labeling and PREA in this review cycle.

I recommend limiting the indications to patients with seasonal and perennial allergic rhinitis (SAR and PAR)  $\geq 17$  years of age. I believe 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. The basis for my recommendation is discussed below.

### 1.2.1 Indications supported

Carbinoxamine maleate is a pre-1962 drug moiety that was the subject of DESI (Drug Efficacy Study Implementation) review(s) by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II, and the Agency then published its findings in the Federal Register (DESI 6303, 38 FR 7265, March 19, 1973). The Agency made the determination that carbinoxamine maleate (then marketed as Clistin Tablets and Elixir) was effective for the symptomatic treatment of the following conditions:

- 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.

As a 505(b)(2) application, this application relies on the Agency's previous findings for efficacy and safety of carbinoxamine maleate [immediate release products]. The proposed indications for this product are the same as that for the immediate-release reference drugs. Since, the innovator product, Clistin, is no longer marketed, the applicant bridged to Clistin in their BA/BE studies through use of the current reference listed drug, immediate-release Palgic Oral Solution, which was approved in 2003 as a generic to Clistin. The indications reflect the indications allowed the originator [Clistin] under the DESI review process, and carried over to the Palgic labeling. Since the Agency previously made a determination of efficacy and safety [under DESI], from a regulatory perspective, this product should carry all the indications as Clistin and Palgic once bioequivalence has been demonstrated.

The DESI process evaluated the effectiveness of a drug, with each indication required to be supported by adequate and well-controlled clinical trials. Nevertheless, when taking into consideration the recommendations of the Panels, it is clear that the Agency also took into consideration what was known about other antihistamines in the same or

similar classes as it made its determination. This view is supported by the fact that the indications allowed by the Agency were more extensive than those reviewed by the actual DESI Panels. The reason why the panels did not review all of the indications is not known. Nevertheless, the Agency allowed the same [or a very similar] set of indications [as carbinoxamine maleate] for many other prescription antihistamines that were reviewed under the DESI process. Other antihistamines with a similar set of DESI indications include: 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 meant to be a complete list]. Diphenhydramine is in the pharmacologic class of ethanolamine antihistamines as carbinoxamine. This indication grouping is understandable, given the prevailing medical view that indications could be based to a large extent on the pharmacologic class of a drug.

However, both the science and the regulatory environment have advanced since the DESI review process. None of the antihistamines approved by the Agency since the DESI process was concluded (e.g. fexofenadine, loratadine, cetirizine) were approved for the multiple indications that were allowed under DESI. Further, in current clinical practice, antihistamines are not used for treatment of many of the indications approved under DESI. In current practice, antihistamines are mainly used to treat the symptoms of allergic rhinitis and chronic idiopathic urticaria, and these are the indications for which newer antihistamines (e.g. fexofenadine, loratadine, cetirizine) were approved.

As a result, the Division considered it reasonable to examine the basis of the Agency's previous effectiveness designation, 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. I reviewed all of the original clinical study publications that were reviewed by the two DESI panels to support DESI determination for carbinoxamine maleate, including the indications for the originator [Clistin]. My review found no support for the current DESI indications for carbinoxamine maleate beyond allergic rhinitis and urticaria. My review of the DESI study publications may be found in Section 6.1 of this document, and the findings are summarized below.

Four published studies served as the basis of the panels' recommendations. Review revealed that only the indications of seasonal and perennial allergic rhinitis (SAR and PAR) are supported by clinical trial data that would be sufficient to meet today's standards for efficacy and safety:

Two of the 4 studies were placebo-controlled, of which 1 used a parallel (Beale) and 1 used a crossover (MacLaren) design. Combined, 3 of the 4 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.

Support for the indication of the treatment of urticaria, is based on the results of three studies, 1 placebo-controlled and 2 open-label. The number of patients treated [28] is 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.

Review 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.

The side effects reported in the clinical pharmacology studies conducted for this application are consistent with the labeling in the current PI. Therefore, the adequacy of current Adverse Reactions section is supported, with the exception that borderline elevations in uric acid, noted in the multiple-dose study should be added to the Adverse Reactions section of the PI.

I recognize that for adults there is no regulatory mechanism to limit DESI indications other than rule making. Therefore, if approved, the Division cannot remove the already-approved DESI indications for this product in adults because we do not have safety concerns about this product in adults that would support limiting the indications. Nevertheless, based on my review of the application, including the scientific supports for each of the indications requested, I recommend limiting the indications for this drug product to the treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). I recommend that the applicant conduct clinical trials to support additional indications for this product.

### 1.2.2 Age groups supported

This application triggers PREA because the extended-release dosage form is a new dosage form. With this submission, the applicant is requesting pediatric 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 safety concerns. With regard to the second request, per guidance, the BA/BE studies were performed in healthy adults; therefore, the results of these studies should be applicable to the adolescents and children 2 to <18 years of age. Although a waiver of BA/BE studies in children 2 to <18 years of age would typically be appropriate, I believe that the need for pediatric studies to support the proposed indications in the 2 to <17 years age group is an overriding issue.

Under the DESI review process, the Agency has made a prior determination of safety and effectiveness for all ages 1 year of age and older (CM is currently approved for 2 years of age and older, although the originator [Clistin] was approved down to 1 year of age). Therefore, the immediate release formulations are approved for use in, and provide dosing recommendations for, children 2 years of age and older.

However, from a scientific perspective the risk/benefit assessment for this product does not support approval for patients under 17 years of age. My review of the study report publications that comprised the DESI review revealed that several indications were not studied at all, and for others there was insufficient efficacy and safety data in the pediatric population to support the indications in pediatric patients. Additionally, none of the DESI study publications included pediatric PK data, and I was unable to find any pediatric PK data for CM in the published literature. Lacking PK data in children, it is my conclusion that the appropriate dose to support the safety of CM in children is an open question.

Without PK data, it is most likely that the pediatric dosing schema for CM 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 and Rx cough, cold, allergy, bronchodilator, and asthmatic [CCABA] drugs at the time that CM was developed in the early 1950s and eventually incorporated into the OTC CCABA Monograph in 1976.<sup>2</sup> 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 CM in children.

It is important to note that the adequacy of the *ad hoc* dose selection schema has since been raised by the Agency<sup>3</sup> and discussed at an Advisory Committee meeting<sup>4</sup>, with the

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

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

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

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.<sup>5,6,7,8</sup> Since the science for choosing the appropriate pediatric dose has changed, and since pediatric PK data are not available for CM, the correct dose to appropriately label this product is unknown. Therefore, from a safety perspective, I believe that it is not reasonable to approve the requested pediatric age range for this extended release product.

My view, i.e., that the science does not support extension of use of the prior DESI determination of efficacy and safety for the immediate release products to use of this extended release formulation in the pediatric population, 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.<sup>9</sup>

It is my understanding that under PREA, the Agency may require pediatric studies to support all the indications considered appropriate for the pediatric age range when data are lacking to support efficacy, safety, or dosing. Since there is no information to adequately support the safety of the proposed dosing of this product in children, I recommend that the Agency not grant the requested waiver of BA/BE studies for patients 2 to <17 years of age, and that the Agency require a submission of pediatric plan for studies to support all pediatric age groups and indications under PREA. The safety concerns for CM in the pediatric population less than 2 years of age, the lack of pediatric PK and safety data for CM, and the lack of efficacy data for many of the requested DESI indications in adults [that would allow for extrapolation of those indications to the pediatric population], provide the justification that these data be

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5 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.

6 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.

7 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.

8 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

9 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.

requested prior to approval of this extended release carbinoxamine product in the pediatric population.

Therefore, I make the following recommendations:

1. I concur with the applicant's request for a waiver of pediatric studies in children 0-2 years of age, and recommend that this request be granted.
2. For children 2 through 16 years of age, I recommend that the Agency request the following:
  - a. PK data for Carbinoxamine Extended Release Oral Suspension broken down by the following age groups: 2-5, 6-11, and 12-16 years of age. My preference is for a study comparing Carbinoxamine Extended Release Oral Suspension with the immediate release oral product, although it may be acceptable to provide PK data for the Carbinoxamine Extended Release Oral Suspension product only, as long as there is sufficient data to show that the proposed pediatric dose(s) provide(s) systemic exposure that is within the systemic exposure provided by the range of approved adult doses.
  - b. Safety data for children 2-16 years of age, broken down by the same age groups as for PK data.
  - c. Data/studies to support each indication, as follows:
    - i. SAR, and PAR: Since there are adequate data in adults to support the indications of SAR and PAR, submission of PK and safety data should be sufficient to allow use of the typical extrapolation paradigm for systemically active drugs to extrapolate efficacy for allergic rhinitis from adults to children 2 years of age and older.
    - ii. Urticaria: Since there are limited data in adults to support the urticaria indication, additional efficacy data in children will be needed. A single efficacy and safety study in pediatric patients, along with PK and safety data in all pediatric age ranges, should provide adequate support for extrapolation of efficacy from adults to children 2 years of age and older for this indication. The study could be performed in patients 6-17 years or in patients 6-11 years of age, as long as additional safety and PK data are available for the age groups not covered in the study.
    - iii. All other indications: For none of these indications is there sufficient data in adults to allow for extrapolation of efficacy from adults to children. Therefore, the Division would require 2 efficacy and safety studies for each indication in all pediatric age groups. Additionally, the Agency has little experience with clinical trials demonstrating the effectiveness of antihistamines for these indications. As a result, the proposed endpoints would require validation prior to use in the pivotal studies. It is of note that, although the Agency cannot require adult studies under PREA, studies to validate endpoints generally need to be performed in adults. As a result, the clinical program needed to support each indication is likely to be very extensive.

The pediatric issues for this application were discussed with the Pediatric Review Committee (PeRC) on August 31, 2011. PeRC agreed with the waiver for children under 2 years of age, but (b) (5) for further discussion with the Division prior to finalization of the regulatory decision. As a result, notwithstanding the recommendations contained in this review, at the time this review is being finalized, a final determination has not been made with regard to the need for pediatric studies for this application.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

None

### **1.4 Recommendations for Postmarket Requirements and Commitments**

See Section 1.2.2 above.

## **2 Introduction and Regulatory Background**

This is a 505(b)(2) application from Tris Pharma for Carbinoxamine Extended Release (ER) Oral Suspension, 4 mg of carbinoxamine maleate (CM) per 5 mL. The formulation is a sustained release formulation of carbinoxamine maleate suspended in a drug-polistirex resin complex. The reference listed drug (RLD) is the generic immediate release Carbinoxamine Maleate Oral Solution, marketed under the brand name Palgic, and manufactured by Milkart, Inc. As a 505(b)(2) application, which cannot rely on a generic, the application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release RLD for bridging. The proposed Indications are the same as that for the immediate release products, which includes symptomatic treatment of various allergic conditions in patients 2 years of age and older. The development program for this product included 2 bioavailability studies, but no clinical trials or nonclinical studies.

The submission is electronic in eCTD format. It includes quality information, the results of the 2 biopharmaceutical studies, information to qualify the sodium polystyrene sulfonate ((b) (4)) resin, and labeling.

### **2.1 Product Information**

#### **2.1.1 Drug Substance and Drug Product**

The Carbinoxamine Maleate, USP, to be used in the proposed product is manufactured by (b) (4)

The oral suspension contains 4 mg of carbinoxamine maleate and the following inactive ingredients: citric acid anhydrous, flavor, glycerin, high fructose corn syrup, methylparaben, modified food starch, polysorbate 80, polyvinyl acetate, povidone, propylparaben, purified water, sodium metabisulfite, sodium polystyrene sulfonate (SPS), sucrose, triacetin, and xanthan gum.

The drug substance is (b) (4) per 5 mL.

### 2.1.2 Proprietary Name

As of the date of this review, the applicant's requested proprietary name is still under review by the Agency. On August 19, 2011, the applicant requested review of the proprietary name Karbinal ER™. The proprietary name review history for this application includes the following:

On February 18, 2011, the applicant requested review of two possible proprietary names, (b) (4) and alternatively (b) (4). After review, on March 28, 2011, the Agency sent a proposed names unacceptable letter denying the request because of a potential promotional concern with the suffix " (b) (4) ", which suggests that the drug can be used in all pediatric patients, whereas the product is contraindicated in patients less than two years of age.

On June 3, 2011, the applicant requested review of two additional proprietary names, (b) (4) [pronounced (b) (4)] or alternatively (b) (4) [pronounced (b) (4)], with the (b) (4) suffix intended to connote (b) (4). In a teleconference dated August 18, 2011, the Division of Medication Error Prevention and Analysis (DMEPA) informed the applicant that the name (b) (4) was unacceptable because the modifier (b) (4) usually denotes (b) (4) (e.g. (b) (4) marketed by Tris).

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Many other antihistamines are available for treatment of allergic conditions. The listing includes both prescription and over the counter (OTC) antihistamines. Please see Section 2.6 for additional information.

## 2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, carbinoxamine maleate is available as an Oral Solution [and as Tablets] from several generic manufacturers in the United States, with the current reference listed drug (RLD) product being immediate release Carbinoxamine Maleate Oral Solution marketed under the brand name Palgic and manufactured by Milkart, Inc.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Over the last 20 years, a number of antihistamines have been associated with prolongation of the QT interval, and two (Seldane and Hismanal) were removed from the market. It is unknown whether carbinoxamine exerts an effect on the QT interval. See Section 2.6.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Study designs for the two studies in this submission were discussed at a pre-IND meeting on May 15, 2008. Tris originally wanted to

(b) (4)

(b) (4)

The Agency also requested Tris to provide information on the potential for alcohol-induced dose dumping.

## 2.6 Other Relevant Background Information

Carbinoxamine maleate (CM) (chemical name: Ethanolamine, 2-[(4-chlorophenyl)-2pyridineylmethoxy]-N, N-dimethyl-(Z)-butenedioate) is a first-generation histamine H<sub>1</sub> receptor blocking agent (antihistamine) of the ethanolamine class. This antihistamine class also includes diphenhydramine, an OTC drug product. This class exhibits antihistaminic, anticholinergic, and sedative properties. Anticholinergic (antimuscarinic) activity results in drying effects on the mucous lining of the respiratory tract, one reason for previous unapproved use in the treatment of upper respiratory infections (along with its sedation effect). Pharmacologic effects include both stimulation and depression the

CNS, resulting in restlessness, nervousness, inability to sleep, and also sedation, diminished alertness, slowed reaction times, and somnolence.

Carbinoxamine maleate is a pre-1962 drug moiety that was the subject of DESI (Drug Efficacy Study Implementation) review(s), and subsequently, several ANDAs. The NDAs for the original carbinoxamine maleate drug products were marketed by McNeil Laboratories under the trade name Clistin as tablets (NDA 08-915, June 22, 1953), elixir (NDA 08-955, June 23, 1953), and repeat action (RA) tablets (NDA 08-915, June 15, 1954), and in a combination as Clistin Expectorant syrup (contained CM, ammonium chloride, sodium citrate, potassium guaiacolsulfonate, and citric acid) (NDA 09-248, February 5, 1962). The original indication statement for Clistin Tablets and Elixir read: “Clistin is especially useful in the symptomatic treatment of allergic disorders such as seasonal and perennial allergic rhinitis, urticaria, minor drug reactions, pruritic skin conditions, and as adjunctive therapy in asthma.”

DESI was a retrospective evaluation of the efficacy of drugs that had been approved on safety grounds alone between 1938 and 1962, and drugs identical, related, or similar to those drugs. This evaluation was necessitated by the 1962 amendment to the FD&C Act, which added the requirement that a drug be evaluated for efficacy, not only for safety, for FDA approval. The DESI review was conducted by the National Academy of Sciences - National Research Council, Drug Efficacy Study Group. Recommendations from the Panels were given to the Agency, and the Agency then published its findings in the Federal Register.

Clistin products specifically, and CM generally, were reviewed by two panels under DESI, the Panel on Drugs Used in Allergy, and the Panel on Drugs Used in Dermatology II. Subsequently, the Agency its finding that Clistin Tablets and Elixir was effective for the following Indications (DESI 6303, 38 FR 7265, March 19, 1973):

- For the symptomatic treatment of:
  - seasonal and perennial allergic rhinitis,
  - vasomotor rhinitis,
  - allergic conjunctivitis due to inhalant allergens and foods;
- Mild, uncomplicated allergic skin manifestations of urticaria and angioedema;
- For the amelioration of the severity of allergic reactions to blood or plasma in patients with a known history of such reactions;
- Dermographism;
- As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled.

With publication of the findings in the Federal Register, Carbinoxamine maleate was reclassified as a “new drug” for which an approved NDA, or a supplement for holders of NDAs approved on the basis of safety prior to October 10, 1962, was required prior to marketing. Supplements were then submitted and approved for Clistin Tablets (12/19/1974) and Elixir (12/27/1974).

Several things are of specific note: 1) the only original Clistin indication not to be found effective under DESI was as adjunctive treatment of asthma; 2) the indications allowed by the Agency under the DESI process are more extensive than those reviewed by the DESI panels<sup>10</sup>, but are similar to those that the Agency found to be effective for a number of other orally administered antihistamines under the DESI process<sup>11</sup>, with no explanation given for the differences; and 3) the DESI indications are more extensive than those allowed for all subsequently approved non-DESI orally administered antihistamines when reviewed as new drugs<sup>12</sup>.

It should also be noted that the DESI indications do not include an indication for treatment of colds. Due to safety concerns with use in children under 2 years of age for unapproved indications, marketed unapproved single-ingredient and combinations containing carbinoxamine were subject to enforcement action when the Agency published the Compliance Policy Guide for Marketed Unapproved Drugs in 2006 and simultaneously announced its intention to take enforcement action against unapproved drug products containing carbinoxamine.<sup>13</sup>

When reviewed under DESI, Clistin RA received a final designation of NOT effective because there was no evidence regarding its bioavailability and bioequivalence, as required for a timed-release dosage form of a safe and effective immediate-release drug (DESI 6303; First classification: 36 FR 9339, May 22, 1971; Reclassification: 38 FR 7265, March 19, 1973). Furthermore, Clistin Expectorant received a final designation of NOT effective because there were no well-controlled studies to document the effectiveness of its expectorant ingredients and because the combination of an

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10 The Agency allowed several Indications that were not reviewed by DESI panels, including the indications of vasomotor rhinitis, angioedema, dermatographism, allergic reactions to blood or plasma, and as adjunctive therapy for anaphylactic reactions. For example, the DESI Panel on Drugs Used in Ophthalmology never reviewed the indication of “allergic conjunctivitis due to inhalant allergens and foods.”

11 Including: Chlorpheniramine maleate, Cyproheptadine hydrochloride, Promethazine hydrochloride, Diphenhydramine hydrochloride, Tripelemamine hydrochloride, and Tripolidine hydrochloride, among others (36 FR 11758, June 18, 1971 and 38 FR 7265, March 19, 1973). Note that diphenhydramine is in the pharmacologic class of ethanolamine antihistamines. This indication grouping is understandable, given the prevailing medical view that indications could be based to a large extent on the pharmacologic class of a drug.

12 None of the antihistamines approved by the Agency since the DESI process was concluded (e.g. fexofenadine, loratadine, cetirizine) were allowed the full set of the indications that were allowed under DESI. All were required to perform clinical trials to support each indication, with approved indications including: SAR, PAR, and urticaria.

13 In June 2006, the Agency published a final Guidance for FDA Staff and Industry: *Marketed Unapproved Drugs- Compliance Policy Guide* in which the Agency outlined its plan to address marketed new drugs without NDAs or ANDAs. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>). The compliance policy guide describes how the Agency intends to exercise enforcement discretion with regard to drugs marketed in the United States that do not have the required FDA approval for marketing. To this end, FDA published a Federal Register notice of its intention to take enforcement action against illegally marketed drug products containing carbinoxamine maleate on June 9, 2006 [71 FR 33462]. The FR notice outlines the safety concerns noted with use of carbinoxamine-containing products in children under 2 years of age.

antihistamine and an expectorant was found not to be a rational combination under the CCABA OTC monograph (DESI 6514, 47 FR 11973, March 19, 1982). Marketing approval was subsequently withdrawn for both of these products (47 FR 21301, May 18, 1982; and 48 FR 34514, July 29, 1983; respectively).

Subsequently, marketing approvals of Clistin Elixir and Clistin Tablets were withdrawn in April 1985 and March 1994, respectively, at the request of the application holder (McNeil) because the products were no longer marketed. In response to citizen petitions, the FDA published notices confirming that marketing withdrawal was not for safety or efficacy reasons (Tablets: 63 FR 27986, May 21, 1998; Elixir: 65 FR 18998, April 10, 2000). In March of 2003, ANDAs submitted by Milkart, Inc. for Palgic tablets (4 mg, NDA 40-442) and oral solution (4 mg CM per 5 mL, NDA 40-458) were approved and are now designated as the RLDs. Approval was based on a bioequivalence program with no clinical efficacy trials.

With one exception, as ANDAs to the original Clistin products, the Palgic products retain all of the originator's dosing and DESI indications. Under DESI, the labeling for the Clistin products carried an age range for use down to 1 year of age. However, Palgic now carries a Contraindication for use in children younger than 2 years of age (as well as in nursing mothers and individuals who are hypersensitive to the drug or are on MAO therapy). The Contraindication for children younger than 2 years of age was added at the Agency's request in 2006, at the time that the Agency issued the Compliance Policy Guide for Marketed Unapproved Drugs and simultaneously announced its intention to take enforcement action against unapproved drug products containing carbinoxamine due to safety concerns with use in children under 2 years of age. [See paragraph above and footnote 13]

Also of note is that the extent and quality of data evaluated as part of the original NDAs would not have been of the type and quality that would currently be required in an NDA application for a new molecular entity. Specific areas with information lacking for carbinoxamine include the following:

1. QT effect. No information is available with regard to evaluations of the effect of carbinoxamine on QT interval. Nevertheless, although data on the effect of carbinoxamine on QT are lacking, the Division has made the call that additional data are not needed. PubMed searches [performed by me] in 2006 and again for this review [2/22/2011] did not reveal any reports of evaluations of the effect of carbinoxamine on QT interval, and no reports of an association between use of carbinoxamine and QT prolongation or Torsades de Pointes. This may be due to the fact that most first generation antihistamines exhibit other dose-limiting side effects prior to causing any potential cardiotoxicity.<sup>14</sup> Additionally, AERS searches performed in 2006 did not reveal reports of QT prolongation with use.
2. PK in children. There is no information available regarding PK in children.
3. ADME. There is very little specific information regarding the ADME of carbinoxamine, although most H<sub>1</sub> antihistamines are extensively metabolized. Most

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14 Eseverri, J. (2000). "[Projection of new antihistamines]." *Allergol Immunopathol (Madr)* 28(3): 143-52.

sources do not list a metabolic pathway for carbinoxamine, although one source listed the cytochrome P-450 microsomal enzyme system, just as for many second generation antihistamines.<sup>15</sup> Excretion occurs renally, with an elimination half-life ranging from 10 to 20 hours. Since the metabolic pathway is not known, it is hard to predict whether younger children may experience slower or faster metabolism than older children and adults, except for the general statement that, in general, antihistamines are more rapidly cleared by children than by adults.<sup>16</sup>

## 2.7 Pediatric Considerations

Please see Section 1.2.2, for a detailed discussion of the pediatric issues and my recommendations.

This application will trigger PREA because of the new extended-release dosage form, a PREA trigger. [Note: The new dosage form also requires a new dosing regimen, also a PREA trigger.] With this submission, the applicant has requested waivers for pediatric studies in the following age groups:

1. Pediatric studies birth to <2 years of age, because carbinoxamine carries a Contraindication for use in children under 2 years of age.
2. Pediatric bioequivalence studies in children 2 to <18 years of age. Per guidance, the BA/BE studies were performed in healthy adults; the results of these studies would be applicable to the adolescents and children 2 to <18 years of age.

The pediatric issues for this application were discussed with the Pediatric Review Committee (PeRC) on August 31, 2011. PeRC agreed with the waiver for children under 2 years of age, but referred (b) (5)

(b) (5) for further discussion with the Division prior to finalization of the regulatory decision. As a result, notwithstanding the recommendations contained in this review, at the time this review is being finalized, a final determination has not been made with regard to the need for pediatric studies for this application.

The originator, Clistin, was approved for use in children 1 year of age and older. However, the labeling for the RLD, Palgic, now states that it is for use in children 2 years of age and older. The reason for this difference is as follows. Due to safety concerns with use of marketed unapproved carbinoxamine-containing drug products in children under 2 years of age for unapproved indications, the Agency simultaneously announced its intention to take enforcement action against these drug products (71 FR 33462, June 9, 2006) when it issued the Compliance Policy Guide for Marketed Unapproved Drugs in 2006. At the time that this action was taken, the makers of Palgic voluntarily raised the lower age bound for the dosing of their product from 1 year of age

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15 Clinical Pharmacology Online (1/30/2006 1:33:00 PM). Monograph on carbinoxamine and pseudoephedrine, Gold Standard. (Accessed 1/30/2006 1:33 PM)

16 Hardman, J. G., Limbird, L.E., Gilman, A.G. (2001). Goodman & Gillman's The Pharmacological Basis of Therapeutics. New York, McGraw-Hill.

to 2 years of age and added a Contraindication for use in patients less than 2 years of age. See Section 8, Postmarket Experience, for further details.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

During the review, no issues were noted with regard to the quality and integrity of the data.

#### 3.2 Compliance with Good Clinical Practices

Investigators from the Division of Scientific Investigations (DSI) have identified significant violations to the bioavailability and bioequivalence requirements of 21 CFR 320 in bioanalytical studies conducted by (b) (4) where the bioanalytic analyses for this application were performed. 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. Therefore, DSI has stated that they have “serious questions ... about the validity” of all bioanalytical data generated at (b) (4) between the dates of (b) (4) (b) (4). The bioanalytical analysis for study MIFT08001 was from Feb 12, 2009 to Feb 25, 2009, and for study MIFT08002 was from April 24, 2009 to May 05, 2009. This information was not available until late in the review cycle, when the rest of this review was written. Due to time limitations, the body text in the review was not altered. However, the results of the two BA/BE studies submitted with this application are highly suspect, should not be considered valid, and are not acceptable. I therefore recommend a Complete Response to this application.

Study reports for the two relative bioavailability studies in this submission include statements that the studies were conducted in accordance with ICH guidelines for good clinical practices, the Code of Federal Regulations for protection of human subjects, and the Declaration of Helsinki, that an IRB approved the protocols and consent forms, and that written consent was obtained for all subjects. The IRB for both studies was: Institutional Review Board Services, Dr Robert Bigge (chair), 580 SW 15th Street, Boca Raton, FL 33432. The clinical research facility for both studies was: Cetero Research, 1405 NW 167th Street, Miami Gardens, FL 33169. The bioanalytical site for both studies was (b) (4).

### 3.3 Financial Disclosures

A single Form 3454 was submitted with the application, certifying that Tris Pharma had not entered into any financial arrangement with the listed clinical investigators, and that none of the clinical investigators has a proprietary interest in the product or a significant equity interest in the sponsor. There are two listed clinical investigators on Form 3454: Gilbert Weiner, DO, PI for Cetero Research, and Murray Ducharme, PharmD, Clinical Pharmacologist at Cetero Research. Although three sub-investigators at Cetero Research are listed in the CSRs, they are not listed on Form 3454.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls (CMC)

Below is a brief summary of CMC issues.

The good manufacturing practices (GMP) inspection of the drug product manufacturing site found “multiple and systemic GMP deficiencies,” and the recommendation at the time of completion of this review is “withhold.” If this remains, it would be a deficiency to be addressed prior to approval.

The drug master file (DMF) for the drug substance has been found to be adequate. Although there are 3 impurities, the specifications have been found adequate.

Excipients in the drug product above those in other drug products or above USP include sodium polystyrene and (b) (4) (polyvinyl acetate). Pharm/Tox studies with polyvinyl acetate show sufficient toxicologic margins to accept the proposed dose. Additionally, one product has levels of sodium polystyrene well beyond those proposed herein. While the sodium polystyrene dose in that product may be associated with hypokalemia, there was no evidence of an effect on potassium [in the clinical data presented with this application] for the dose used in this product.

### 4.2 Clinical Microbiology

There are several clinical microbiology deficiencies in this application. There is concern about effectiveness of microbiological controls for the process step in which the (b) (4) Microbiological data were submitted for only one batch, whereas data for three batches are needed. Additionally, the applicant will need to provide data regarding the absence of *Burkholderia cepacia* in the drug product.

### 4.3 Preclinical Pharmacology/Toxicology

The submission relies on published literature supporting nonclinical pharmacology and toxicology of carbinoxamine maleate, the Agency's previous findings of safety and efficacy for the moiety, qualification information for sodium polystyrene sulfonate, USP (b) (4) (b) (4) resin at a concentration of (b) (4) mg/mL, and information to support inclusion of GRAS/GRAE excipients.

### 4.4 Clinical Pharmacology

#### 4.4.1 Clinical Pharmacology Summary and Review Issues

Tris conducted two relative bioavailability / pharmacokinetic studies to support this NDA submission. The studies were designed to show that the relative bioavailability of the test ER formulation was the same as the reference immediate release carbinoxamine product. 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 studies are outlined in Section 4.4.4 below.

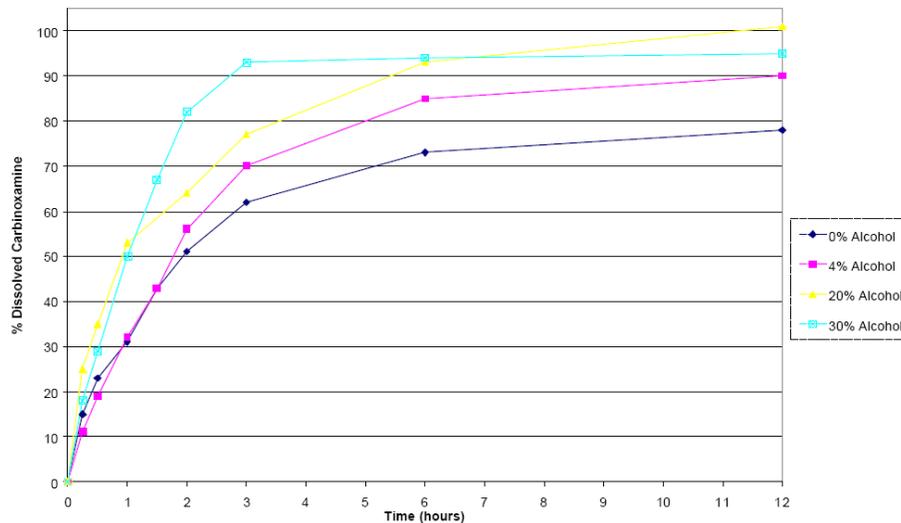
Overall, the results of these studies show that Carbinoxamine ER Oral Suspension meets bioequivalence criteria when compared to Carbinoxamine Maleate Oral Solution after a single dose and at steady state. Additionally, food had no significant impact on the relative bioavailability.

The studies revealed no major safety concerns, although there was an association between carbinoxamine use and constipation, and 16/42 subjects in the multiple dose study had elevated uric acid levels at the end of the second crossover treatment period. Although there is no known scientific basis for these results, it is reasonable to consider labeling the product with the findings.

Several additional Clinical Pharmacology issues came to the Clinical Team's attention and were addressed during the review cycle, as noted below.

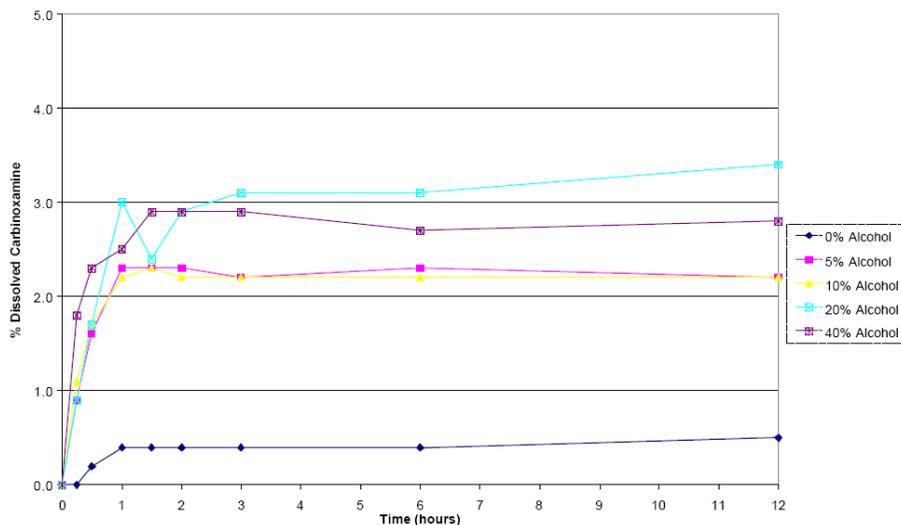
1. The potential for dose dumping was assessed from several different points of view.
  - a. The potential for alcohol to cause dose dumping was assessed in several ways. The results of an *in vitro* alcohol interaction study showed that just over (b) (4) % of the drug is released by 2 hours in the presence of 30% alcohol, whereas only 50% is released by the 2-hour time point without alcohol. This suggested that dose dumping might occur. However, the formulation with sodium polystyrene makes the drug less soluble in acidic media. Additionally, dissolution increases negligibly with all alcohol exposures (range 0.5% to 3%) when in an acid media. Therefore, although there is some potential for increased exposure with alcohol, the review team considered the ~30% increase at 2 hours to not be clinically relevant, given the likely effect of stomach acid on decreasing dissolution. Additionally, any increased exposure would likely result in side effects such as drowsiness that would likely prevent continued dosing. Finally, antihistamines

that cause drowsiness already have class labeling regarding alcohol use, so the review team feels comfortable that any potential interaction with alcohol can be handled by labeling.



**Figure 1. Dissolution Profile Plot Comparison of 0.4M Phosphate Buffer with Alcohol Concentrations of 0%, 5%, 10%, 20%, and 30% Alcohol of Carbinoxamine Polistirex ER Oral Suspension 4mg/5mL**

Source: Submission of April 14, 2011, M5.3.1.3, invitro-invivo-correlation.pdf, p19



**Figure 2. Dissolution Profile Plot Comparison of 0.1 N HCl with Alcohol Concentrations of 0%, 5%, 10%, 20%, and 40% Alcohol of Carbinoxamine Polistirex ER Oral Suspension 4mg/5mL**

Source: Submission of April 14, 2011, M5.3.1.3, alcohol-study-rd.pdf, p11

- b. During the review, the Division became aware that a University of Maryland professor has determined that the drugs in polistirex matrix are more likely to dose dump in the presence of highly ionic solutions, such as Gatorade (Gatorade contains potassium, sodium, magnesium cations to help replenish these minerals in the athletes who sweat lot to avoid dehydration). Since polystyrene-containing

drugs are essentially cationic complexes in the polistirex matrix (cation exchange resins), concentrated cationic solutions will exchange with the active drug moiety and are likely to dump. During drug development, the potential for dose dumping is generally evaluated by *in vitro* dissolution and alcohol testing, as well as by PK testing with and without a (fatty) meal, and not with cationic solutions. The clinical team considered the implications, and decided not to label any of these drugs to NOT be used with salty foods or Gatorade. There are several reasons for this. First, the Division has not experienced any adverse event reports related to this condition of use. Second, although use with Gatorade, salty foods, and other such products might have the potential to cause dose dumping, the only dose dumped under normal conditions would be the single dose administered with the offending agent (Gatorade, etc.), as it is unlikely that a patient would be taking such a product with each dose. The single dose might potentially cause side effects such as make one drowsy, etc., but is unlikely to be associated with any other safety concerns. Publicizing this by either labeling or placing an alert on the FDA website might in fact promote inappropriate use (abuse) of products formulated with a polistirex matrix. Therefore, we would prefer to monitor to see if such use is being reported as a problem, at which time we would consider taking some action.

2. During the review, the primary Pharmacology/Toxicology reviewer (Dr Mukherjee Asoke) brought up a concern with regard to the historical lack of a QTc study for this moiety. Specifically, the issue was raised as to whether a QTc study might be considered for this particular drug product because of a potential drug interaction with the polystyrene resin in the formulation. The clinical review team considered that the lack of a QTc study would not preclude approval, given the Agency's prior findings of safety and efficacy and the lack of adverse event reports of QTc prolongation with this moiety, and specifically the clinical review team did not consider the addition of polystyrene to raise the concern for QTc prolongation with this formulation. The specific concerns raised are discussed below.
  - a. Sodium polystyrene sulfate (SPS) is approved for potassium depletion (Kayexalate - NDA 11-287, and other ANDAs), and the package insert indicates the possibility of QTc prolongation due to potassium deficiency. To evaluate this issue, the clinical team reviewed the labeling for Kayexalate (sodium polystyrene sulfate) and the SPS generics, and came to the conclusion that there are no significant clinical implications with the dose of polystyrene in this product because the lowest recommended single dose of SPS as an ion exchange resin is <sup>(b)</sup><sub>(4)</sub> times higher than a single dose of polystyrene in this product. At high doses, SPS acts as an ion exchange resin in the large intestine, allowing replacement of the sodium ions with potassium ions, thereby ridding the body of excess potassium. Although variable, this ion exchange is not efficient, and it is only when sufficient potassium is absorbed to cause hypokalemia that there is concern for QTc prolongation.
  - b. It was also noted that polystyrene is present in a clonidine extended release tablet (NDA 22-500, approved in 2010), also manufactured by TRIS Pharma. While the package insert for this product does not indicate QTc issues,

conductance disturbance and bradycardia are noted due to the effect of clonidine. Thus, it appears that the active itself is the issue, and not the polystyrene.

- c. It was noted that most of the other approved cough and cold medicines that contain polystyrene would give would expose patients to ~ (b) (4) mg of polystyrene per day. However, the proposed formulation in this product would expose adult patients to a maximum about (b) (4) mg of polystyrene per day. The clinical team did not consider this dose to pose any additional risk beyond that for other cough and cold medicines.
- d. No effects on potassium levels were noted in the clinical studies conducted for this application.

#### 4.4.2 Mechanism of Action

No mechanism of action studies were performed.

#### 4.4.3 Pharmacodynamics

No pharmacodynamic studies were performed.

#### 4.4.4 Pharmacokinetics

This section summarizes the results of the two relative bioavailability / pharmacokinetic studies performed to support this application.

**Reviewer's Note:** Investigators from the Division of Scientific Investigations (DSI) have identified significant violations to the bioavailability and bioequivalence requirements of 21 CFR 320 in bioanalytical studies conducted by (b) (4), where the bioanalytic analyses for this application were performed. Information from DSI regarding the validity of the bioanalytic analyses was not available until late in the review cycle, when the rest of this review was written. Due to time limitations, the review of the two BA/BE studies presented below was not altered. However, the results are highly suspect and should not be considered valid.

##### 4.4.4.1 Study M1FT08001

###### *Summary of the Study*

This study was performed at Cetero Research, Miami, FL. The protocol and consent form were approved by Institutional Review Board Services IRB, Florida.

Study M1FT08001 was a three-way crossover study that assessed the relative bioavailability of a single dose of Carbinoxamine ER Oral Suspension versus Carbinoxamine Maleate Oral Solution under fasting conditions, as well as the impact of

food on the bioavailability of a single dose of Carbinoxamine ER Oral Suspension, in healthy volunteers. Study treatments were as follows:

- Treatment A: Carbinoxamine ER Oral Suspension (4mg/5mL) given as a single oral dose of 20 mL (16 mg) at Hour 0 with 8 fl. oz. of room temperature water 30 minutes after initiation of a standardized high fat – high calorie meal preceded by an overnight fast of at least 10 hours.
- Treatment B: Carbinoxamine ER Oral Suspension (4mg/5mL) given as a single oral dose of 20 mL (16 mg) at Hour 0 with 8 fl. oz. of room temperature water after an overnight fast of at least 10 hours.
- Treatment C: Carbinoxamine Maleate Oral Solution (4mg/5mL) given as an oral dose of 10 mL (8mg) at Hour 0 and at Hour 6 with 8 fl. oz. of room temperature water after an overnight fast of at least 10 hours.

Study parameters are shown in Table 1. Safety assessments included physical examinations, ECG, clinical laboratory studies, monitoring while subjects were confined during each treatment period, vital signs (BP, HR, temp), and adverse events.

**Table 1. M1FT08001, Study Parameters**

Trial Phase Parameter	Screening Day -28 to Day -1	Confinement (each treatment period)			Early Discontinuation or End of Study
		Day -1	Day 1	Days 2 thru 4	
Screening consent	X				
Informed consent		X <sup>a</sup>			
Eligibility criteria	X	X <sup>b</sup>			
Prior medication assessment	X	X <sup>b</sup>			
Medical history	X	X <sup>b</sup>			
Vital signs <sup>c</sup>	X		X	X	X
ECG	X				
Physical exam	X				
Clinical laboratory tests <sup>d</sup>	X				X
Serum pregnancy	X	X			
Urine Drug screen <sup>e</sup>	X	X			
Study drug administration			X		
PK sampling <sup>f</sup>			X	X	
Adverse events			X	X	X

a Period 1 only

b Updated and/or reviewed when subject arrived for study period confinement on Day -1.

c Blood pressure and heart rate were measured within 120 minutes prior to study drug administration to the first study participant (Hour 0 only), at post-dose Hours 2.5, 7.5, and 24 (±30 min), and at the discretion of the clinical staff. Blood pressure, heart rate, respiratory rate, and temperature were measured at screening and study exit.

d Labs included: CBC with diff, BUN, creatinine, total bilirubin, alk phos, AST, ALT, glucose, albumin, LD total, potassium, sodium, chloride, uric acid, urinalysis with micro, serologic screening for HIV HBsAG and HCV

e Urine drug screen for: amphetamines, cannabinoids, cocaine metabolites, opiates, phencyclidine, ethyl alcohol.

f PK samples were collected within 120 minutes prior to study drug administration to the first study participant (Hour 0 only) and post-dose 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6\*, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12, 16, 24, 36, 48,

Trial Phase Parameter	Screening Day -28 to Day -1	Confinement (each treatment period)			Early Discontinuation or End of Study
		Day -1	Day 1	Days 2 thru 4	
72 hours. The Hour 6 sample was taken pre-dose for Treatment C.					

Source: M1FT08001 CSR, T9.5.1-1 and T9.5.1.1-1, p24-5

### Results

Forty-two (42) subjects were enrolled, and a total of 38 subjects completed the study and were included in the pharmacokinetic and statistical analyses. Of the four subjects who did not complete the study, three withdrew voluntarily (# 20, 33, and 41) prior to period 2 dosing, and one (# 02, a 31 year old Caucasian female) was withdrawn by the investigator prior to period 3 because of a positive alcohol screen. Subjects who completed only two periods, during one of which Treatment B was administered, were also included in the analyses. Thus, a total of 38 subjects were included in the bioequivalence analysis (Treatments B vs. C) and 39 subjects were included in the food effect analysis (Treatments A vs. B). Demographic characteristics of subjects are shown in Table 2.

**Table 2. M1FT08001, Summary of Demographics**

Characteristic	All N=42	Males n=29	Females n=13
Age	37 (23-58)	35 (23-56)	40 (25-58)
Weight	75.3 (49.6-93.4)	81.1 (60.4-93.4)	62.4 (49.6-73.6)
Height	166.1 (148.6-182.9)	170.9 (155.9-182.9)	155.3 (148.6-165.4)
BMI	27.1 (21.0-31.8)	27.7 (22.7-31.8)	25.9 (21.0-30.2)
Race			
African American	3 (7.1%)	2 (6.9%)	1 (7.7%)
Asian	0	0	0
Caucasian	38 (90.5%)	26 (89.7%)	12 (92.3%)
Native American	1 (2.4%)	1 (3.4%)	0

Source: M1FT08001 CSR, T11.2-1, p34-5

There were no deaths and no serious AEs, and no subject was withdrawn due to an AE. A total of 3 adverse events (flu, depression/weakness) occurred in 2 subjects; all were mild in severity and resolved without treatment, and none were judged to be related to the study drug.

Regarding laboratory results, baseline results and shift tables were not provided in the study report, only laboratory values outside the reference range at study exit. Assuming that healthy subjects with laboratory results had been pre-screened from participation in the study, it is likely that most study exit values outside the reference range represent a shift from the normal range. That said, 5 subjects (all females) had borderline low hematocrits at study exit, likely due to repeated blood draws for pharmacokinetic testing during the study. Three subjects experienced a mild elevation above the reference range (3.5-7.2 mg/dL for males, 2.5-6.2 mg/dL for females) for uric acid at study exit, and one subject had a result below the reference range.

The study report notes that visual inspection of the plasma concentration versus time profile of carbinoxamine for each subject suggested that six samples may have been switched during the study (5 between 0.5 and 1 hour, and 1 between 1 and 1.5 hours) [CSR, T9.8-1, p31], and further investigation is/was underway to evaluate for this possibility. However, even if the samples had been switched, the differences are not judged to significantly impact the data, so this was not pursued.

The single-dose fasting bioequivalence comparisons between test (Treatment B) and reference (Treatment C) are shown in Table 3. The results showed that single-dose bioequivalence criteria were met, with ratios and 90% confidence intervals for the Ln transformed and non-transformed geometric least squares means for AUC<sub>0-t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub> were within the limits of 80.00 to 125.00%.

The effect of food on the bioavailability of Carbinoxamine ER Oral Suspension is shown in Table 4. Administration with food had no significant effect on bioavailability.

Note that Treatment B results differ between the two tables below because one table used an N of 39 and the other an N of 38.

**Table 3. M1FT08001, Bioequivalence between test and reference (N=38)**

PK Parameter	Geometric LS Means			90% CI
	Test (Treatment B)	Reference (Treatment C)	% Ratio	
<b>LN-Transformed Data</b>				
AUC <sub>0-t</sub> (ng·h/mL)	685.7934	680.4213	100.8	97.89 – 103.77
AUC <sub>0-inf</sub> (ng·h/mL)	729.9843	724.4320	100.8	97.45 -104.19
C <sub>max</sub> (ng/mL)	28.2150	30.2713	93.2	89.77 – 96.78
<b>Non-Transformed Data</b>				
AUC <sub>0-t</sub> (ng·h/mL)	704.2972	698.7477	100.8	97.80 – 103.79
AUC <sub>0-inf</sub> (ng·h/mL)	753.3516	748.0097	100.7	97.20 – 104.22
C <sub>max</sub> (ng/mL)	28.6687	30.7841	93.1	89.73 – 96.52
T <sub>max</sub> (h)	6.67	8.55	78.0	74.35 – 81.70
Kel (h <sup>-1</sup> )	0.0419	0.0424	98.9	95.24 – 102.60
t <sub>1/2</sub> (h)	17.04	16.83	101.3	97.50 – 105.40

Source: M1FT08001 CSR, T14.2-1, p46

**Table 4. M1FT08001, Fed vs fasted results(N=39)**

PK Parameter	Geometric LS Means			90% CI
	Fed (Treatment A)	Fasted (Treatment B)	% Ratio	
<b>LN-Transformed Data</b>				
AUC <sub>0-t</sub> (ng·h/mL)	679.2243	696.7027	97.5	94.69 – 100.38
AUC <sub>0-inf</sub> (ng·h/mL)	726.1847	741.7393	97.9	94.97 – 100.93
C <sub>max</sub> (ng/mL)	26.7666	28.4788	94.0	91.06 – 97.01
<b>Non-Transformed Data</b>				
AUC <sub>0-t</sub> (ng·h/mL)	699.3871	719.3494	97.2	94.16 – 100.29
AUC <sub>0-inf</sub> (ng·h/mL)	752.0027	769.0579	97.8	94.74 – 100.82

PK Parameter	Geometric LS Means			90% CI
	Fed (Treatment A)	Fasted (Treatment B)	% Ratio	
C <sub>max</sub> (ng/mL)	27.2067	28.9597	93.9	90.83 – 97.07
T <sub>max</sub> (h)	7.18	6.69	107.3	99.42 – 115.22
Kel (h <sup>-1</sup> )	0.0408	0.0425	95.9	90.05 – 101.81
t <sub>1/2</sub> (h)	17.50	16.92	103.4	96.96 – 109.94

Source: M1FT08001 CSR, T14.2-2, p46 and Appendix 16.1.9.2.7, p181

#### 4.4.4.2 Study M1FT08002

##### *Summary of the Study*

This study was performed at Cetero Research, Miami, FL. The protocol and consent form were approved by Institutional Review Board Services IRB, Florida.

Study M1FT08002 was a two-way crossover study that assessed the relative bioavailability of Carbinoxamine ER Oral Suspension versus Carbinoxamine Maleate Oral Solution at steady state in healthy volunteers. Both products were administered as multiple doses for 9 days under fasting conditions. Study treatments were as follows:

- Treatment A: Carbinoxamine ER Oral Suspension (4mg/5mL) given as a single oral dose of 20 mL (16 mg) with 8 fl. oz. of room temperature water at Hours 0 and 12 on Days 1, 2, 3, 4, 5, 6, 7, and 8, and Hour 0 only on Day 9.
- Treatment B: Carbinoxamine Maleate Oral Solution (4mg/5mL), given as a single oral dose of 10 mL (8 mg) with 8 fl. oz. of room temperature water at Hours 0, 6, 12, and 18 on Days 1, 2, 3, 4, 5, 6, 7, and 8, and Hour 0 and 6 on Day 9.

Study parameters are shown in Table 5. Safety assessments included physical examinations, ECG, clinical laboratory studies, monitoring while subjects were confined during each treatment period, vital signs (BP, HR, temp), and adverse events.

**Table 5. M1FT08002, Study Parameters**

Trial Phase Parameter	Screening Day -28 to Day -1	Confinement (each treatment period)		Early Discontinuation or End of Study
		Day -1	Study Days 1-9	
Screening consent	X			
Informed consent		X <sup>a</sup>		
Eligibility criteria	X	X <sup>b</sup>		
Prior medication assessment	X	X <sup>b</sup>		
Medical history	X	X <sup>b</sup>		
Vital signs	X		X <sup>c</sup>	X
ECG	X			
Physical exam	X			
Clinical laboratory tests <sup>d</sup>	X			X
Serum pregnancy	X	X		X

Trial Phase Parameter	Screening Day -28 to Day -1	Confinement (each treatment period)		Early Discontinuation or End of Study
		Day -1	Study Days 1-9	
Urine Drug screen <sup>e</sup>	X	X		
Study drug administration			X	
PK sampling <sup>f</sup>			X	
Adverse events			X	X

a Period 1 only  
b Updated and/or reviewed when subject arrived for study period confinement on Day -1.  
c On Day 1, blood pressure and heart rate were measured within 120 minutes prior to study drug administration to the first study participant (Hour 0 only) and at post-dose Hours 2.5, 7.5, and 24 (±30 min). On Days 2 to 8, measurements were to be taken at post-dose Hours 2.5, 7.5, and 24 (±30 min). On Day 9, measurements were to be taken at post-dose Hours 2.5, 7.5, 12 (±30 min). Additional measurements may have been taken at the discretion of the clinical staff. Blood pressure and heart rate were to be measured at study exit or early termination.  
d labs included: CBC with diff, BUN, creatinine, total bilirubin, alk phos, AST, ALT, glucose, albumin, LD total, potassium, sodium, chloride, uric acid, urinalysis with micro, serologic screening for HIV HBsAG and HCV  
e Urine drug screen for: amphetamines, cannabinoids, cocaine metabolites, opiates, phencyclidine, ethyl alcohol.  
f PK sampling: On Day 1, an Hour 0 pre-dose sample were collected within 120 minutes prior to study drug administration. On Days 6, 7 and 8, an Hour 0 pre-dose sample were to be collected within 5 minutes prior to drug administration. On Day 9, pharmacokinetic samples were to be collected within 5 minutes prior to administration of study product at Hour 0, and post-dose Hours 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6\*, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 11, 12 (\*The Hour 6 sample was to be taken pre-dose for Reference Product B)

Source: M1FT08002 CSR, T9.5.1-1 and T9.5.1-2, p18-9

## Results

Forty-two (42) subjects were enrolled in the study, and a total of 41 subjects completed the study and were included in the pharmacokinetic and statistical analyses. No subjects withdrew consent. One subject was discontinued due to an adverse event of vomiting during Period 1 while on test drug. Demographic characteristics of the subjects are summarized in Table 6.

**Table 6. M1FT08002, Summary of Demographics**

Characteristic		Test N=42	Reference N=41
Age (years)	Mean (SD)	43 (10)	43 (10)
	Range	20-43	20-43
Age groups	< 18	0 (0%)	0 (%)
	18 – 39	12 (28.57%)	12 (28.57%)
	40 – 64	30 (71.42%)	29 (69.04%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	19 (45.23%)	19 (45.23%)
	Female	23 (54.76%)	22 (52.38%)
BMI	Mean (SD)	27.3 (2.6)	27.3 (2.6)
	Range	21.0 - 32.0	21.0 - 32.0
Race			
African American		0	0

Characteristic	Test N=42	Reference N=41
Asian	0	0
Caucasian (non-Hispanic)	42 (100%)	41 (100%)
Native American	0	0

Source: M1FT08002 CSR, T11.2-1, p28-9

There were no deaths and no serious AEs. One (1) subject (46 yo CF) was withdrawn from the study due to an AE of vomiting during Period 1 while on test drug. A total of 25 AEs occurred in 17 subjects (40.4% of total subjects enrolled), all mild in severity, 9 of which were judged to be related to the study drug. The most frequently reported AEs were constipation in 10 subjects (6 on test, 4 on reference) and headache in 2 subjects (both on test) (see Table 7 below). While taking test drug, subjects reported one each of the following: sore throat, nausea, and diarrhea; vomiting; dizziness; rash on face; and itching in eyebrows. While taking reference drug, subjects reported one each of the following: upper abdominal pain; heartburn; and rhinorrhea.

Additionally, one patient experienced an elevated BP while on test drug.

**Table 7. M1FT08002, Frequently reported adverse events by treatment arm**

Adverse Event MeDDRA SOC PT	Test N=42	Reference N=41
Constipation	6 (14.28%)	4 (9.75%)
Headache	2 (4.76%)	0

Source: M1FT08002 CSR, T12.2.2-1, p34

Regarding laboratory results, shift tables were not provided in the study report. Several trends were noted on review of the laboratory tests performed at study exit. Thirteen (13/42) subjects (all females) had low RBC, hemoglobin, or hematocrit values at study exit. Most results were borderline below the reference range, although several subjects had hematocrit values in the 31-33% range [CSR, T14.3.4-1, p42-3]. This is likely the result of repeated blood draws for pharmacokinetic testing during the study. Also, multiple subjects had elevated glucose levels at study exit testing, likely the result of having obtained the study exit labs shortly after a meal.

Additionally, 16/42 subjects experienced a mild elevation of uric acid above the reference range (3.5-7.2 mg/dL for males, 2.5-6.2 mg/dL for females) at study exit. Most of the uric acid results were borderline elevated, with only one outlier value in a male subject of 11.3 mg/dL (repeat 10.3 mg/dL) [CSR, T14.3.4-2, p43-5]. These elevations in uric acid were unexplained. Table 8 shows the screening and exit results for each subject (gender not given), along with the mean results. A numerical trend is seen with a shift to borderline higher uric acid levels from screening to study exit. In response to the Division's IR requesting further data related to the clinical significance of the findings, the applicant made the point that this was a crossover study, and subjects were exposed to both drugs (both of which contain carbinoxamine). Further, of the 16 subjects with elevated uric acid levels at study exit, 50% had been exposed to test and 50% to reference in period 2. Therefore, they conclude that one cannot differentiate any differences between the test or reference products with respect to the

findings. Although accurate, the applicant's response does not address the findings observed in this study, with the possibility that exposure to the CM moiety itself (in either test or reference) may be associated with rises in uric acid levels. Although the review team is unaware of a scientific reason for these findings, consideration should nevertheless be given to labeling both test and reference with this observed AE in the Adverse Events section.

**Table 8. M1FT08002, Individual uric acid levels (mg/dL) at screening and study exit**

Subject Number	Screening	Exit	Repeat
01	(b) (4)		
02			
03			
04			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			

Subject Number	Screening	Exit	Repeat
36		(b) (4)	
37			
38			
39			
40			
41			
42			
Mean			

Source: M5.3.1.2, Appendix 16.2.8

The steady state bioequivalence comparisons between test and reference are shown in Table 9. The results showed that steady state bioequivalence criteria were met, with ratios and 90% confidence intervals for the geometric LMSs of the steady-state(ss) pharmacokinetic parameters of AUCt (ss), Cmax (ss), and Cmin (ss) within the limits of 80.00 to 125.00%.

**Table 9. M1FT08002, Bioequivalence between test and reference (N=41)**

PK Parameter	Geometric LS Means			90% CI
	Test	Reference	% Ratio	
<b>LN-Transformed Data</b>				
Cmax (ss) (ng/mL)	69.1412	65.9125	104.90	102.76 – 107.09
AUCt (ss) (ng·h/mL)	702.6899	694.5101	101.20	99.36 – 103.02
Cmin (ss) (ng/mL)	48.3344	49.8040	97.00	94.19 – 99.99
<b>Non-Transformed Data</b>				
Cmax (ss) (ng/mL)	73.0473	69.6773	104.80	102.50 – 107.18
AUCt (ss) (ng·h/mL)	746.2903	737.7528	101.20	99.31 – 103.01
Cmin (ss) (ng/mL)	51.9384	53.1582	97.70	94.82 – 100.59
Cavg (ss) (ng/mL)	62.1909	61.4794	101.20	99.31 – 103.01
Tmax (ss) (h)	5.58	5.92	94.30	82.94 – 105.58
Flux (%)	35.43	27.74	127.20	119.53 – 135.93
Swing (%)	43.60	32.79	132.90	123.11 – 142.79
C min(ss) = trough plasma concentration at steady state				
C avg(ss) = average plasma concentration across the interval at steady state				

Source: M1FT08002 CSR, T 14.2-1, p39; and statistical-methods.pdf Appendix 16.1.9.6, p55

## 5 Sources of Clinical Data

This submission relies entirely on two relative bioavailability studies to show bioequivalence of the test and reference products, and the Agency's previous DESI findings of efficacy and safety of carbinoxamine maleate in patients 2 years of age and older. No clinical trials were performed. The studies are listed in Table 10 below and discussed in Section 4.4.4 above.

To review the basis for the currently approved indications for carbinoxamine maleate, the DESI review for carbinoxamine was requested and reviewed. Please see Section 6.1 of this review for further details.

## Tables of Studies/Clinical Trials

**Table 10. Table of Studies**

Study	Study Design	Products Tested	Dose(s)	Number of Subjects
M1FT08001	Open-label, single-dose, 3-way crossover, food and non-food effect, relative bioavailability study in healthy subjects	A) Carbinoxamine Polistirex ER Oral Suspension, 4mg/5mL* B) Carbinoxamine Polistirex ER Oral Suspension, 4mg/5mL* C) Carbinoxamine Maleate Oral Solution, 4mg/5mL	16 mg (20 mL) after high fat meal 16 mg (20 mL) fasted 2 doses of 8 mg (10 mL) q 6 hours fasted	42 (38 completed)
M1FT08002	Open-label, multiple-dose, 2-way crossover, steady-state, relative bioavailability study in healthy subjects	A) Carbinoxamine Polistirex ER Oral Suspension, 4mg/5mL* B) Carbinoxamine Maleate Oral Solution, 4mg/5mL	16 mg (20 mL) q 12 hours for 9 days 8 mg (10 mL) q 6 hours for 9 days	42 (41 completed)

\* The test drug is listed as Carbinoxamine Polistirex ER Oral Suspension, 4mg/5mL in the tables of

## 5.2 Review Strategy and Review Issues

The two relative bioavailability / pharmacokinetic studies were reviewed. The two studies were reviewed, primarily for safety. See Section 4.4.4 above and Section 7.

As a 505(b)(2) application, which cannot rely on a generic, the application relies on the no-longer-marketed innovator NDA product (brand name Clistin, manufactured by McNeil) while using the marketed generic immediate release Carbinoxamine Maleate Oral Solution (brand name Palgic, manufactured by Milkart, Inc.) for bridging. The proposed Indications are the same as that for the immediate release products, which includes symptomatic treatment of various allergic conditions in patients 2 years of age and older. Palgic was approved in 2003 as a generic to the innovator product, Clistin, which is no longer marketed. Carbinoxamine maleate underwent DESI review, and the current indications for Palgic reflect the indications allowed the originator, Clistin, under the DESI review process. Therefore, once bioequivalence between this product and Palgic has been demonstrated, this product should technically be able to carry all the indications as Palgic and Clistin.

However, there are a number of issues with simply carrying over all of the DESI indications. The indications for prescription antihistamines approved under DESI, including carbinoxamine, include a long list for which antihistamines are not used in current clinical practice. In current practice antihistamines are mainly used to treat the symptoms of allergic rhinitis and chronic idiopathic urticaria. None of the antihistamines that have been approved by the Agency since the DESI process (e.g. fexofenadine, loratadine, cetirizine, etc.) include the same indications that were allowed under DESI

[beyond SAR, PAR and urticaria]. Under today's standards, each indication should be supported by adequate and well-controlled clinical trials. Further, it was unclear at the outset whether the data evaluated by the DESI panels and used to support each of the current indications for the originator product would meet today's standards for efficacy and safety.

Therefore, the Division considered it reasonable to revisit the current list of indications for carbinoxamine and re-evaluate the merit of each based on today's standards. As a result, the adequacy of those studies evaluated under the DESI process and the relevance of indications [other than allergic rhinitis and urticaria] to today's current practice standards was a review issue. To accomplish this, the DESI review for carbinoxamine was requested and all relevant studies (i.e., literature reports) were reviewed (see Sections 6.1.1 and 6.1.2). Additionally, all relevant literature for carbinoxamine maleate was reviewed via PubMed searches, and all relevant current practice parameters for use of antihistamines in the treatment of allergic conditions were reviewed (see Section 6.1.3).

### **5.3 Discussion of Individual Studies/Clinical Trials**

No clinical trials were performed for this NDA. The two relative bioavailability / pharmacokinetic studies were reviewed. See Section 4.4.4 above.

## **6 Review of Efficacy**

No clinical trials were performed for this NDA. This submission relies entirely on two relative bioavailability studies to show bioequivalence of the test and reference products, and the Agency's previous DESI findings of efficacy of carbinoxamine maleate in patients 2 years of age and older. The two relative bioavailability / pharmacokinetic studies were reviewed. See Section 4.4.4 above.

### **6.1 Review of the DESI Indications**

To review the basis for the currently approved indications for carbinoxamine maleate, the DESI reviews (Allergy Panel and Dermatology Panel) for each of the carbinoxamine products were requested and reviewed. The DESI reviews were based on studies published in the literature, each of which was requested and reviewed. A total of 8 articles or books were submitted to the docket, of which 4 served as support for all of the indications. (Beale 1954; Garat 1956; Johnson 1954; MacLaren 1955) The evidence provided by each study is summarized below. Following that evidence, the indications currently supported by accepted clinical practice and clinical practice parameters are discussed.

### 6.1.1 Summary of the Carbinoxamine Maleate DESI Review

This section summarizes the findings of the National Academy of Sciences - National Research Council, Drug Efficacy Study Group, DESI reviews of Clistin Tablets and Clistin RA (NDA 08-915; DESI 6303, Log No. 1882) and Clistin Elixir (NDA 08-955; Log No. 1847). The DESI reviews for the two sets of products were identical in their documentation and recommendations, and are therefore presented below as if one review. Reviews were performed by two panels, the Panel on Drugs Used in Allergy and the Panel on Drugs Used in Dermatology II. The Panel on Drugs Used in Allergy assessed the efficacy of carbinoxamine maleate for SAR and PAR, urticaria, and as an adjunctive therapy in asthma. The Panel on Drugs Used in Dermatology II assessed the efficacy of carbinoxamine maleate for allergic disorders such as pruritic skin conditions and allergic disorders such as urticaria.

The indications that were reviewed by the DESI panels and the results of their assessments are shown in Table 11. Based on the DESI review(s), Clistin Tabs and Elixir received the Indications shown below (38 FR 7265, March 19, 1973):

1. Seasonal and perennial allergic rhinitis;
2. Vasomotor rhinitis;
3. Allergic conjunctivitis due to inhalant allergens and foods;
4. Mild, uncomplicated allergic skin manifestations of urticaria and angioedema;
5. Dermatographism;
6. As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled;
7. Amelioration of the severity of allergic reactions to blood or plasma in patients with a known history of such reactions.

The reader will note that there is a mismatch between the indications that the Agency allowed under DESI and those reviewed by DESI panels. Indications not reviewed by the panels included: vasomotor rhinitis, angioedema, dermatographism, allergic reactions to blood or plasma, and as adjunctive therapy for anaphylactic reactions. For example, the DESI Panel on Drugs Used in Ophthalmology never reviewed the indication of “allergic conjunctivitis due to inhalant allergens and foods.” I was unable to find an explanation for why this was the case.

**Table 11. Summary of DESI review of studies to support each indication for immediate release carbinoxamine maleate [Clistin Tabs and Elixir]**

Panel and Indication	Evaluation	Comments from DESI Panel*
<b>Allergy Drug Panel</b>		
SAR and PAR	Probably Effective <sup>1,2,3,4</sup>	None
Urticaria	Probably Effective <sup>1,2,3</sup>	None
Adjunctive therapy in asthma	Possibly Effective <sup>1,2,3</sup>	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.
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.
<b>Dermatology Drug Panel</b>		
Allergic disorders such as pruritic skin conditions	Possibly Effective <sup>1,2,3,4</sup>	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.
Allergic disorders such as urticaria	Effective <sup>1,2,3,4</sup>	This product is an effective form of treatment in mild and uncomplicated cases of these types of allergic cutaneous reactions.
* The DESI Panels exact comments are reproduced herein. DESI Review Study Documentation: 1 Beale; 2 Garat; 3 Johnson; 4 MacLaren.		

### 6.1.2 Review of the DESI studies

Four studies were documented in the DESI review as having served as the basis of the panels' recommendations. All were published studies, and all were reviewed. The studies and recommendations are summarized below, with the summaries of the individual studies following.

Table 12 presents a summary of the designs of the four studies including the number of patients included in the study and the number of patients studied for each indication. Table 13 presents the DESI Indications [not the indications listed by the Panels] for antihistamines such as carbinoxamine maleate, along with the results of my evaluation and recommendations.

Two of the four studies were placebo-controlled, of which 1 used a parallel (Beale) and 1 used a crossover (MacLaren) design. Combined, 3 of the 4 studies give some support for the most common indication studied, namely allergic rhinitis, including both SAR and PAR. The results are considered sufficient to support this indication.

Three studies, 1 placebo-controlled and 2 open-label, provide a small degree of support for treatment of urticaria. However, the numbers of patients treated [28] are small and the results are somewhat conflicting. Therefore, the studies are not considered to provide definitive evidence of efficacy for this indication.

The review revealed that there was insufficient data to support other DESI indications for carbinoxamine.

However, the side effects reported in the studies are consistent with the labeling in the current PI. Therefore, the review supports the adequacy of current Adverse Events section.

**Table 12. Summary of the study design of CM studies reviewed under DESI**

Study	Design	Indications studied	N	Assessments*	Comments
Beale	Placebo-controlled, parallel group	AR, urticaria, asthma, AR and asthma, allergic conjunctivitis	126 113 11 1 26 1	S	Randomization and blinding methodology unstated.
Garat	Open label	PAR, PAR with asthma, asthma, pruritus or urticaria, allergic conjunctivitis, SAR	94 68 12 3 9 1 1	C	Open label study. Provides open-label safety information in patients with PAR.
Johnson	Open label	Acute rhinitis, (common cold) SAR or PAR, asthma, urticaria, poison ivy, pruritus, bronchitis, or periorbital edema.	116 77 23 2 8 3 3	C	Open label study. Most patients had acute rhinitis (common cold). Provides open-label safety information in a limited number of patients with SAR, PAR, and urticaria.
MacLaren	Placebo- and active-controlled, 4-way crossover	AR, AR and asthma, AR and eczema	70 41 26 3	S	Randomization and blinding methodology unstated. Crossover design with no washout.

\*Assessments: S=Assessments made by Subject, C= Assessments made by Caregiver

**Table 13. Summary of My Evaluation and Recommendation for each DESI Indication**

Indication	Evaluation	Recommendation	Comments
SAR and PAR	Effective	Acceptable	2 controlled studies support this indication with OL safety support from 1 study
Vasomotor rhinitis	No evidence presented	Not acceptable without further data	Not studied
Allergic conjunctivitis due to inhalant allergens and foods	Insufficient evidence presented	Not acceptable	Insufficient numbers of patients
Mild, uncomplicated allergic skin manifestations of urticaria and angioedema	Probably effective, but insufficient evidence presented	Not acceptable without further data	Insufficient numbers of patients
Dermatographism	No evidence presented	Not acceptable without further data	Not studied
As therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled	No evidence presented	Not acceptable without further data	Not studied
Amelioration of the severity of allergic reactions to blood or plasma	No evidence presented	Not acceptable without further data	Not studied
Documentation: 1 Beale; 2 Garat; 3 Johnson; 4 MacLaren.			

#### 6.1.2.1 Beale 1954

This was a placebo-controlled study conducted in 126 patients in a private practice setting in Ohio. The study was supported by McNeil Laboratories. All patients had what was characterized as severe allergic symptoms not relieved by other measures, including antihistamines. The population ranged from 3 to 67 years of age, with 10 ≤6 years, and 31 ≤12 years of age, but little else about the population is described other than their allergic disease, which is shown in Table 15. Randomization and blinding methodology is not stated. It appears that the study was blinded for patients, but it is not stated whether the investigators were blinded. Patients were treated with 4 or 6 mg tablets of Clistin or matched placebo, and instructed to take one tablet every 4 hours as needed. At each visit, patients were asked about the effect of the tablets. If symptoms were persistent, or where it was necessary to continue medication over time, the patient was switched to “each dosage of Clistin and to the placebo without being informed of the change.”

The effect of various doses of Clistin or Placebo on relief of allergic symptoms is shown in Table 14. Whereas 16/28 (57%) patients noted some degree of relief on placebo, 79/91 (87%) noted some degree of relief at the 4 mg dosage, and 45/56 (80%) showed some degree of relief on the 6 mg dosage. Complete relief was achieved in 1/28 (4%) on placebo, 15 (16%) on 4 mg, and 8 (14%) on 6 mg.

The number of patients with, and the degree of relief achieved for various allergic conditions, are shown in Table 15. On the basis of these results, the study concluded that Clistin was effective for treatment of various allergic conditions.

**Table 14. Beale. Effect of various doses of Clistin or Placebo on relief of allergic symptoms**

Degree of Relief	Clistin dosage (mg every 4 hours)					Placebo
	3	4	6	8	10	
None		12 (13%)	11 (20%)			12 (43%)
Slight		13 (14%)	13 (23%)	3		2 (7%)
Moderate		23 (25%)	11 (20%)			5 (18%)
Marked		28 (31%)	13 (23%)	1	1	8 (28%)
Complete	1	15 (16%)	8 (14%)			1 (4%)
Total at each dose	1	91	56	4	1	28

**Table 15. Beale. Degree of relief for various allergic conditions**

Condition	Degree of Relief			Total
	None	Slight to Moderate	Marked to Complete	
Allergic rhinitis*	15 (13%)	44 (39%)	54 (48%)	113
Urticaria	0	3 (27%)	8 (73%)	11
Asthma	1	0	0	1
Allergic rhinitis and asthma	3 (16%)	18 (65%)	5 (19%)	26
Allergic conjunctivitis	0	0	1	1
*The publication does not specify the type of allergic rhinitis, seasonal or perennial.				

Adverse events were not specifically solicited during the study because “all patients were well known to us and could be expected to volunteer such information.”

Therefore, the side effects reported may not include all the adverse events noted by patients.

Side effects reported by patients while on study medication are shown in Table 16. The most common side effect was drowsiness. One patient, who had experienced drowsiness on other antihistamines, was given 3 mg of Clistin and did not experience drowsiness (but, the publication also does not say whether this patient experienced relief at this dose).

Of the patients enrolled in the study, 20 received Clistin at doses of 18-24 mg per day for a period of 4-6 weeks, of whom 3 experienced mild sedation. In these patients, complete CBCs with differentials are reported to have “shown no changes.”

**Table 16. Beale. Side effects noted while on study drug**

Side Effect	Clistin N=126	Placebo N=28
Drowsiness		
Mild	14	1
Moderate	4	0
Severe	1	0
Dizziness	1	0
Nausea	1	0
Insomnia	0	1
Headache	1	0

*Reviewer's Note: This study lends support for the efficacy of CM for allergic rhinitis, and also to some extent (because the number of patients is small) for urticaria. Only 1 patient was included with allergic conjunctivitis, although such symptoms are part of allergic rhinitis and typically respond to oral antihistamines. The study also provides some support for safety with up to 4-6 weeks of chronic use.*

#### 6.1.2.2 Garat 1956

This publication includes open-label 'studies' conducted during the fall, winter, and spring of 1953 at the National Institute of Allergic Diseases in Buenos Aires, Argentina. Study drug was supplied by McNeil Laboratories.

The publication first compares the chemical structure of CM with those of other antihistamines, relating potential activity of the drug with the structural changes to the molecule. Pharmacologic activity is also reviewed, suggesting that in animal models CM has a wider ratio between the median effective dose (median oral dose to protect 75% of animals given a certain lethal dose [1.0 mg/kg] of histamine IV 1 hour later) and medial lethal dose than several other antihistamines, including diphenhydramine hydrochloride and triplenamine hydrochloride (among others).

This was an open-label (unblinded and uncontrolled) evaluation of CM. Although the publication states that CM was given to 200 patients, it also states that only 94 patients were followed for a sufficient period of time to allow what the investigators considered to be a satisfactory evaluation of effectiveness and safety. Most of the 94 patients had perennial allergic rhinitis (PAR) alone (68), 12 had PAR with asthma, 3 had asthma alone, 9 had pruritus or urticaria, 1 had allergic conjunctivitis, and 1 had seasonal allergic rhinitis (SAR). The age range was 6 to 75 years, 68 were females, and the weight range was 18 to 91 kg. The dosage of Clistin was adjusted according to weight, age, and sex, but the publication does not state how. The daily dosage of CM was up to 24 mg, administered at 2 to 8 hour intervals, starting with daily dosages between 4 and 16 mg. Sixty-three of the patients also received specific hyposensitization. Clinical results were characterized as excellent (symptoms disappeared without side effects), very good (considerable improvement with only mild side effects), good (significant improvement but definite signs of intolerance), fair (scant relief or significant side effects), or poor (no improvement or pronounced side effects). Note that this grading system combined an evaluation of both effectiveness and side effects. Although the report does not define who made the judgment regarding efficacy or how side effects were collected, the nature of the endpoint makes it likely that investigator judgment was included.

The number of patients with, and the results for various allergic conditions, are shown in Table 17. On the basis of these results, the study concluded that Clistin was effective for treatment of various allergic conditions, at doses between 8 and 16 mg per day.

The side effects reported included somnolence, lassitude, dizziness, gastric pain, and dry mouth. These were stated to be mild and tolerable except for 4 patients with moderate drowsiness, 1 patient with severe drowsiness, and two patients whose results were judged to be poor (acute intestinal pain on the second day requiring cessation of

treatment, and intense stupor accompanied by dizziness and vertigo following the first dose). Other side effects included restlessness and fever (stated to be rarely observed).

**Table 17. Garat. Results of treatment**

Disorder	Response to Treatment					Total
	Poor	Fair	Good	Very Good	Excellent	
PAR	2	7	14	35	10	68
PAR with asthma	5	4	0	2	1	12
Asthma		2		1		3
Pruritus or urticaria	2		1	5	1	9
Allergic conjunctivitis			1			1
SAR					1	1

*Reviewer's Note: Because this was an unblinded, uncontrolled study, and because the report does not define who made the judgment regarding efficacy or how side effects were collected, it is difficult to assess the results of this study or to conclude that this study supports the efficacy of CM. The report, however, does provide some evidence regarding open-label side effects.*

#### 6.1.2.3 Johnson 1954

This was an open-label (unblinded and uncontrolled) evaluation of CM in 116 patients in an industrial practice in Philadelphia, PA. Study drug was supplied by McNeil Laboratories. The dosage studied was 2 to 4 mg administered at 3 to 12 hour intervals depending upon the circumstances. The study population included 79 males and 37 females, ages unstated. Twenty-three patients had SAR or PAR, 2 asthma, 8 urticaria, 3 poison ivy, and 3 pruritus, bronchitis, or periorbital edema. The other 77 patients had acute rhinitis, etiology undetermined, but with signs and symptoms of the common cold. Results were graded by the patients symptom response as none, slight, moderate, marked, or complete. Undesirable side effects were elicited by questioning, and graded as slight, moderate, or severe. Results of treatment are shown in Table 18.

The study report appears to make light of the degree of sedation in patients. However, sedation of a mild and transient nature reported in 9% of patients, moderate sedation in 4%, and more severe sedation in 7% of patients. Other side effects reported included: 2 dry mouth, 1 dizziness, 1 headache, and 1 scalp tingling.

**Table 18. Johnson. Results of treatment**

Diagnosis	N	Percent with Relief of Symptoms			
		None	Slight	Moderate	Marked to Complete
Acute rhinitis	77	9.3	9.3	9.3	72
SAR or PAR	23	9	13.6	9	68.1
Asthma	2				100
Acute urticaria	8	62.5			37.5

Diagnosis	N	Percent with Relief of Symptoms			
		None	Slight	Moderate	Marked to Complete
Poison Ivy	3	33.3		33.3	33.3
Pruritus	1				100
Bronchitis	1				100
Periorbital edema	1				100

*Reviewer's Note: Because this was an unblinded, uncontrolled study, it is difficult to assess the result of this study or to conclude that this study supports the efficacy of CM. In particular, the majority of patients had a diagnosis of acute rhinitis, stated likely due to the common cold, which improves over time without treatment. The number of patients with other allergic diagnoses was too small to provide much value regarding efficacy. Of particular note, the lack of response of patients with acute urticaria suggests that this diagnosis may not be supported.*

#### 6.1.2.4 MacLaren 1955

This publication presents 3 sub-studies, corresponding to each of the 3 participating study sites in southern California, in one report. The design was a placebo-controlled, 4-period crossover study in 70 patients at three study centers, comparing the efficacy and safety of Clistin with Pyribenzamine® (tripelennamine, Ciba), Ambodryl® (bromodiphenhydramine hydrochloride, Parke Davis), and placebo to Clistin. The study was supported by McNeil Laboratories. The study population included 30 males and 40 females, including 16 patients between 1-10 years, 10 between 11-20 years, and 1 patient over 61 years of age. Forty-one patients had allergic rhinitis (unspecified), 26 AR and asthma, and 3 AR and eczema.

The three study centers treated each group of patients slightly differently. Randomization and blinding methodology is not stated. Group 1 consisted of 36 patients from an allergy clinic at Los Angeles County Hospital. Over 8 weeks, patients were cycled in 2 week intervals among the 4 treatments without a washout. During this time, other medications were held, including desensitization. Group 2 consisted of 10 patients from private practice, who were rotated among the 4 treatments at weekly intervals without a washout. Group 3 consisted of 24 patients from private practice who were cycled in 2 week intervals among the 4 treatments, just as for Group 1. For both Groups 1 and 2, a daily scoring sheet was completed by patients and used to count the number of events such as sneezing, wheezing, runny nose, or itchy eyes, long with the daily count of study and other medication taken. Patient-reported symptoms were scored as totals per week for all combined allergy symptoms. However, scoring for patients in Group 3 was based on the degree of subjective relief (none = 0, slight = 1, moderate = 2, marked = 3, and complete = 4) captured on a weekly (rather than daily) basis.

Because of the similarity of scoring for Groups 1 and 2, these two groups were presented separately (Table 19) from results for a combination of all 3 groups (Table 20). Table 19 shows the results for Groups 1 and 2 in 46 patients with allergic rhinitis

as the number of symptom units reported per week. Table 20 shows the results for all three groups when scores were converted to values assigned to the degree of subjective relief (none = 0, slight = 1, moderate = 2, marked = 3, and complete = 4), with the maximum relief score being 280 units (70 patients x 4 units).

**Table 19. MacLaren. Average symptom units per week in 46 patients with AR (Groups 1 and 2)**

Drug	Symptom Units per Week
Clistin	22.7
Pyribenzamine	21.2
Ambodryl	24.0
Placebo	28.0

**Table 20. MacLaren. Subjective relief scores in 70 patients with AR (Groups 1, 2, and 3)**

Drug	Symptom Units per Week
Clistin	137
Pyribenzamine	160
Ambodryl	146
Placebo	85

Side effects were collected (Table 21). Sedation was scored as 1+ if spontaneously noted by the patient but causing no difficulty, 2+ if conscious effort was required to stay fully alert, and 3+ if effort was necessary to stay awake. While still sedating, Clistin was less sedating than the other two antihistamines studied.

**Table 21. MacLaren. Side effects**

Side Effect	Clistin	Pyribenzamine	Ambodryl	Placebo
Sedation	11 (15.7%)	23 (32.8%)	22 (31.5%)	1 (1.4%)
1+	8 (11.4%)	14 (20%)	12 (17.2%)	0
2+	1 (1.4%)	5 (7.1%)	8 (11.4%)	1 (1.4%)
3+	2 (2.9%)	4 (5.7%)	2 (2.9%)	0
Dizziness	4 (5.7%)	1 (1.4%)	2 (2.9%)	2 (2.9%)
GI distress	4 (5.7%)	3 (4.3%)	4 (5.7%)	3 (4.3%)
Headache	1 (1.4%)	3 (4.3%)	3 (4.3%)	0
Dry mouth or nose	1 (1.4%)	0	0	0
Total	18 (25.7%)	33 (47%)	31 (44.4%)	6 (8.6%)

*Reviewer's Note: Although there are a number of weaknesses with the study design, this placebo-controlled, 4-period crossover study provides reasonable comparative evidence of the efficacy and safety of CM compared with several other antihistamines [although neither is currently marketed] and placebo. However, the only indication supported by this study is allergic rhinitis (unspecified).*

### 6.1.3 Indications Supported by Accepted Clinical Practice

A review of practice parameters for various allergic conditions revealed that first generation antihistamines may be considered for a wide range of indications, although (with the exception of allergic rhinitis) 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. Specifically, there was little support in practice parameters for the current indications for carbinoxamine maleate beyond allergic rhinitis and urticaria.

Searches were performed to locate sources of practice parameters for allergy-related diagnoses and treatments, including searches of websites of the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), the Joint Council on Allergy, Asthma and Immunology, and others. 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 ([http://www.jcaai.org/page/Practice\\_Parameters/](http://www.jcaai.org/page/Practice_Parameters/)). These include practice parameters for the diagnosis and treatment of anaphylaxis, asthma, atopic dermatitis, drug hypersensitivity, immunology, rhinitis, sinusitis, stinging insect hypersensitivity, and urticaria, as well as for allergen immunotherapy and allergy diagnostic testing. The World Allergy Organization has also published a White Book on Allergy.

With regard to use of 'antihistamines' [used as a general term], the practice parameters may be briefly summarized as follows: Second generation antihistamines are first line therapy for allergic rhinitis. However, the first generation antihistamines should be considered as second line therapy because of the risks of sedation, anti-cholinergic effects, and performance impairment. Data suggest that first generation antihistamines may cause CNS impairment even when sedation is not reported, and this may persist into the daytime hours even when the medication is dosed only before bed. For other forms of rhinitis (eg, vasomotor, infectious), antihistamines are less efficacious (if at all); therefore, establishing a correct diagnosis is critical before initiation of therapy. Antihistamines are not indicated for use in acute bacterial sinusitis, although they may have a secondary role in ameliorating chronic sinusitis in patients with concomitant allergic rhinitis. Antihistamines are recommended as first line treatment for controlling the skin flare and itching associated with urticaria. In some patients, antihistamines may also relieve pruritus associated with atopic dermatitis (topical antihistamines are not recommended in atopic disease because of the potential to cause cutaneous sensitization). For anaphylaxis, antihistamines (specifically, parenteral diphenhydramine) and corticosteroids are adjunctive therapy to epinephrine, particularly for symptoms of urticaria, angioedema, or both. Antihistamines and analgesics may also reduce the pain and itch associated with cutaneous drug reactions, and antihistamines and non-steroidal anti-inflammatory drugs may be beneficial for treatment of immune complex reactions.

Although the practice parameters recommend use of 'antihistamines' in treatment of a number of the above conditions, it is important to note that there is a difference between the listing of a drug or class of drugs as recommended for treatment in a practice

parameter and a specific drug having an indication for treatment. One is based on experience in clinical use, and the other is based on fulfillment of regulatory requirements.

Nevertheless, based on my review, I found little specific support from practice parameters for the use of carbinoxamine maleate in the treatment of various allergic conditions. Carbinoxamine is not listed by name in any of the practice parameters as a specifically recommended antihistamine, whereas many of the second generation antihistamines are listed by name for treatment of allergic rhinitis and several of other allergic conditions, and diphenhydramine is listed in the treatment of anaphylaxis. However, as a first generation antihistamine, carbinoxamine use is supported as second line therapy for allergic rhinitis and urticaria.

Finally, while none of the practice parameters addressed the issue, it would be misleading not to note the following. One could reasonably make a case that carbinoxamine, being in the same class of H<sub>1</sub>-antihistamines as diphenhydramine, might be expected to be effective for treatment of other allergic condition such as urticaria and/or angioedema associated with anaphylaxis, drug reactions, and immune complex reactions. That said, it is likely that the lack of availability of carbinoxamine in a parenteral dosage form has hindered use (and recommendations for use) for these conditions, since the preferred route of administration of an antihistamine for anaphylaxis is parenteral and not oral, although the oral route is an acceptable alternative when parenteral drugs are not available. Therefore, use for these conditions does not appear appropriate unless alternative treatments are not available. Furthermore, without a specific recommendation from expert panels, clinical practice recommendations provide no specific support for the current indications for carbinoxamine.

#### 6.1.4 Summary of the Supported Indications

I reviewed the original data that had been reviewed by the two DESI panels to support the indications for the originator [Clistin]. Four published studies served as the basis of the panels' recommendations. My review of the published studies revealed that only the indications of seasonal and perennial allergic rhinitis (SAR and PAR) were supported by clinical trial data sufficient to meet today's standards for efficacy and safety.

Two of the 4 studies were placebo-controlled, of which 1 used a parallel (Beale) and 1 used a crossover (MacLaren) design. Combined, 3 of the 4 studies give support for the most common indication studied, namely allergic rhinitis, including both SAR and PAR. The results are considered sufficient to support this indication.

Three studies, 1 placebo-controlled and 2 open-label, provide a small degree of support for treatment of urticaria. However, the numbers of patients treated [28] are small and the results are somewhat conflicting. Therefore, the studies are not considered to provide definitive evidence of efficacy for this indication.

My review revealed that there was insufficient scientific data to support other DESI indications for carbinoxamine. For each of the other indications, either no patients were

studied, or the numbers of patients included in studies were too few, or the trial design was not sufficient, to make a reasonable conclusion about either the efficacy or safety of carbinoxamine maleate for treatment of that condition.

A review of practice parameters for various allergic conditions revealed that first generation antihistamines may be considered for a wide range of indications, although (with the exception of allergic rhinitis) their use is infrequent and often as second line or adjunctive therapy, with second generation antihistamines preferred because of unwanted side effects of sedation anti-cholinergic effects, and performance impairment. Specifically, there was little support in practice parameters for the current indications for carbinoxamine maleate beyond allergic rhinitis and urticaria.

## **7 Review of Safety**

### **Safety Summary**

#### **7.1 Methods**

All safety assessments from the two studies were reviewed.

Additionally, side effects noted in the studies submitted to support the DESI review of CM were reviewed at the same time that supports for each of the DESI indications were reviewed. See the Review of Efficacy section above.

#### **7.2 Adequacy of Safety Assessments**

The safety assessments were judged adequate.

#### **7.3 Major Safety Results**

There were no deaths or serious adverse events reported in the two studies. There were no significant AE findings during the single-dose study. During Period 1 of the multiple-dose study, one subject dropped out due to vomiting while on test product. During the multiple-dose study, the most frequently reported AEs were constipation and headache, with no significant imbalances between test and reference drug dosing. These AE are already listed for carbinoxamine, so no additional labeling is necessary.

Evaluation of laboratory studies during the multiple-dose study revealed a trend to elevation above the reference range for uric acid (3.5-7.2 mg/dL for males, 2.5-6.2 mg/dL for females) at study exit. Most of the uric acid results were borderline elevated, although one value in a male subject was 11.3 mg/dL, with a repeat of 10.3 mg/dL. An elevated uric acid level is not a listed AE for this drug. Based on these findings, I recommend adding elevation in uric acid to the ADVERSE REACTIONS section of the labeling.

Side effects noted in the studies submitted to support the DESI review of CM were reviewed at the same time that supports for each of the DESI indications were reviewed. See the Review of Efficacy section above. Except for one study that performed CBCs with differentials on a group of patients being treated chronically for up to 8 weeks, no laboratory testing was reported as having been performed. The side effects reported in the studies are consistent with the labeling for CM in the current PI.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The most commonly reported AEs with multiple doses were constipation and headache. Both AEs are listed. While taking test drug, subjects reported one each of the following: sore throat, nausea, and diarrhea; vomiting; dizziness; rash on face; and itching in eyebrows. While taking reference drug, subjects reported one each of the following: upper abdominal pain; heartburn; and rhinorrhea. Currently, constipation, headache, nausea, vomiting, diarrhea, dizziness, drug rash, and upper abdominal pain are all listed AEs with carbinoxamine. I recommend no changes to the labeling based on these findings.

### 7.4.2 Laboratory Findings

Evaluation of laboratory studies during the multiple-dose study revealed one trend of note. Fifteen (15/42) subjects experienced some elevation above the reference range (3.5-7.2 mg/dL for males, 2.5-6.2 mg/dL for females) for uric acid at study exit. Most of the uric acid results were borderline elevated, although one value in a male subject was 11.3 mg/dL, with a repeat of 10.3 mg/dL. PubMed searches [performed 1/5/2011] using the terms 'carbinoxamine' and 'uric acid', and 'carbinoxamine' and 'gout', did not reveal any articles or other information about an association between the use of carbinoxamine and elevations in uric acid. An elevated uric acid level is not a listed AE for this drug. Based on these findings, I recommend adding elevation in uric acid to the ADVERSE REACTIONS section of the labeling.

### 7.4.3 Vital Signs

Evaluation of vital signs during the multiple-dose study revealed no trends.

### 7.4.4 Electrocardiograms (ECGs)

ECGs were only performed during screening. No evaluations were done to evaluate for the potential of carbinoxamine to affect the QT interval.

#### 7.4.5 Special Safety Studies/Clinical Trials

None were performed.

#### 7.4.6 Immunogenicity

NA

### 7.5 Other Safety Explorations

None were performed.

### 7.6 Additional Safety Evaluations

None were performed.

#### 7.6.1 Human Carcinogenicity

Not evaluated.

#### 7.6.2 Human Reproduction and Pregnancy Data

Not evaluated.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

No evaluations were performed in the pediatric population. The effects of carbinoxamine on growth were not evaluated.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not evaluated.

### 7.7 Additional Submissions / Safety Issues

There were no additional submissions to, and no other safety issues identified for, this NDA.

## 8 Postmarket Experience

In June 2006, as part of its ongoing drug safety initiative, the FDA announced its intent to take enforcement action to stop the manufacturing and sale of unapproved products

containing the antihistamine carbinoxamine because of safety concerns regarding their use in children under 2 years of age (71 FR 33462, June 9, 2006). In a related action, the Agency issued a final Guidance document outlining its approach to addressing medicines that are marketed without FDA approval (Compliance Policy Guide for Marketed Unapproved Drugs, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>). At that time, many unapproved products containing carbinoxamine, either as single ingredient products or in combination with other cough/cold ingredients, were marketed and available by prescription. Additionally, many companies were selling carbinoxamine drops and syrups that were specifically labeled for use in children as young as one month of age.

The action against unapproved carbinoxamine-containing products was based on reports of 21 deaths in children under two years of age associated with use of carbinoxamine-containing drugs. However, in most of those cases, other active ingredients or other factors could have been responsible for the death. Although a causative relationship was not established, FDA was sufficiently concerned about the risks of these unapproved products, which were being promoted for infants and young children, to take the action to remove these products from the market. At the time that this action was taken, the makers of Palgic voluntarily raised the lower age bound for the dosing of their product from 1 year of age to 2 years of age and added a Contraindication for use in patients less than 2 years of age.

## 9 Appendices

### 9.1 Literature Review/References

Beale H.D., Rawling, F.F.A., Figley, K.D. Clistin maleate: a clinical appraisal of a new antihistaminic. *J Allergy* 1954; 25:521-524.

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Garat, B.R., C.R. Landa,, O.F. Possi Richeri, and R.O. Tracchia. Clinical, chemical and pharmacologic relationships of antihistamines. *J Allergy* 1956; 27:57-62.

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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. Allergy* 1955; 13:307-312.

Plaut M, Valentine MD, Allergic Rhinitis. *N Engl J Med* 2005;353;1934-44.

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Diagnosis and Management of Urticaria: A Practice Parameter. [part 1: Acute Urticaria] [part 2: Chronic Urticaria] *Ann Allergy* 2000; 85:S521-S544.

Disease Management of Drug Hypersensitivity: A Practice Parameter. *Ann Allergy* 1999; 83:S665 - S700.

Disease Management of Atopic Dermatitis: A Practice Parameter. *Ann Allergy* 1997; 79:197-211.

Disease Management of Atopic Dermatitis: An Updated Practice Parameter. *Ann Allergy* 2004; 93:S1-S21.

The Diagnosis and Management of Anaphylaxis. *J Allergy Clin Immunol* 1998;101:S465-528.

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The Diagnosis and Management of Rhinitis: An Updated Practice Parameter. *J Allergy Clin Immunol* 2008; 122:S1-S84

Parameters for the Diagnosis and Management of Sinusitis. *J Allergy Clin Immunol* 1998; 102:S107-S144.

Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol* 1999; 103:963-80.

Stinging Insect Hypersensitivity: A Practice Parameter Update. *J Allergy Clin Immunol* 2004; 114; 4:869-886.

Stinging insect hypersensitivity: A practice parameter update 2011. *J Allergy Clin Immunol* 2011 Apr; 127(4):852-4 e23.

Valentine MD, Sanico A. Allergy and related conditions. In: Barker LR, Burton JR, Zieve PS, eds. *Principles of ambulatory medicine*. 6th ed. Baltimore: Lippincott Williams & Wilkins, 2003:387-405.

## 9.2 Labeling Recommendations

Labeling will be addressed after this review is completed. However, a number of issues are noted that will be addressed during the labeling phase, including the following:

1. This application represents the first PLR labeling for a carbinoxamine product. Therefore, the labeling will necessarily differ from other carbinoxamine maleate products in this respect.
2. The recommendations herein with regard to the appropriate indications and age ranges for approval will be only partially reflected in the labeling, since there is no regulatory support for deleting DESI indications without rule making. The final labeling with regard to indications and age ranges will represent the views of the Division, which are not necessarily the same as the recommendations expressed in this review.
3. The Dosing and Administration section uses age- but not weight-based dosing for children. This is problematic in that it reflects on the lack of a PK and safety data to support the proposed dose in children. Therefore, I recommend not approving this product for pediatric patients. Under this labeling scenario, it will be inappropriate to include the current Contraindication for carbinoxamine maleate for use in patients less than 2 years of age, as inclusion would potentially imply an indication for the rest of the pediatric age range. Should an indication or indications be approved in the pediatric age range now or in the future, the Contraindication should remain or return.
4. 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.
5. The potential for increased exposure with concomitant alcohol use (see Section 4.4.1) can be handled by appropriate labeling, which is already present in the labeling.

6. The proposed dosing is in (b) (4), whereas the proposed (b) (4) (included in the (b) (4), submission) (b) (4). However, the Agency is moving to a more standardized approach to expressing volumes of liquids, as noted in the Guidance for Industry, Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188992.pdf>), the preference being to only having one set of markings, as well as to express all volumes in mL.

### 9.3 Advisory Committee Meeting

An Advisory Committee was not convened to discuss this application.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PETER R STARKE  
08/31/2011

LYDIA I GILBERT MCCLAIN  
08/31/2011

**MEDICAL OFFICER REVIEW: CLINICAL FILING REVIEW / CHECKLIST**  
**Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)**

<b>APPLICATION:</b> NDA 22-556	<b>TRADE NAME:</b> --
<b>APPLICANT/SPONSOR:</b> Tris Pharma	<b>USAN NAME:</b> Carbinoxamine ER (Extended Release) Suspension
<b>MEDICAL OFFICER:</b> Peter Starke, MD	
<b>DEPUTY DIRECTOR:</b> Lydia Gilbert-McClain, MD	<b>CATEGORY:</b> Antihistamine
<b>FILING DATE:</b> February 2, 2011	<b>ROUTE:</b> Oral
<b>REVIEW DATE:</b> January 24, 2011	<b>NDA Type:</b> 505(b)(2)

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
December 7, 2010	December 8, 2010	N-000	Original NDA Submission

**RELATED APPLICATIONS**

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>

**REVIEW SUMMARY:**

This is filing review for a 505(b)(2) application from Tris Pharma for Carbinoxamine ER (Extended Release) Oral Suspension, eq. 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 reference product being the immediate release Carbinoxamine Maleate Oral Solution marketed under the brand name Palgic and manufactured by Milkart, Inc. The proposed indications are the same as that for the reference drug, which includes symptomatic treatment of various allergic conditions in patients 2 years of age and older. The development program for this product included 2 bioavailability studies, but no clinical trials or nonclinical studies.

The submission is electronic in eCTD format. It includes administrative information, quality information, dissolution studies (at 3 pHs [1.2, 4.5, 6.8] and 4 alcohol concentrations [0, 4%, 20%, 30%]), information to qualify the sodium polystyrene sulfonate ((b)(4)) resin, the results of the 2 relative bioavailability studies, a literature review, summaries, and labeling.

**OUTSTANDING ISSUES:**

No significant filing issues. See review for review issues and 74-day comments.

**RECOMMENDED REGULATORY ACTION**

<b>NDA/SUPPLEMENTS:</b>	<u>  X  </u>	<b>FILEABLE</b>	<u>      </u>	<b>NOT FILEABLE</b>
<b>OTHER ACTION:</b>	<u>  X  </u>	<b>74-DAY COMMENTS</b>		

## Introduction

This is filing review for a 505(b)(2) application from Tris Pharma for Carbinoxamine ER (extended release) Oral Suspension, eq. to 4 mg of carbinoxamine maleate (CM) per 5 mL. The formulation is a sustained release formulation of carbinoxamine suspended in a drug-polystyrene resin complex, the reference product being the immediate release Carbinoxamine Maleate Oral Solution marketed under the brand name Palgic and manufactured by Milkart, Inc. The proposed indications are the same as that for the reference drug, which includes symptomatic treatment of various allergic conditions in patients 2 years of age and older. The development program for this product included 2 bioavailability studies, but no clinical trials or nonclinical studies.

The submission is electronic in eCTD format. It includes administrative information, quality information, dissolution studies (at 3 pHs [1.2, 4.5, 6.8] and 4 alcohol concentrations [0, 4%, 20%, 30%]), information to qualify the sodium polystyrene sulfonate (b) (4) resin, the results of the 2 relative bioavailability studies, a literature review, summaries, a pediatric waiver request, and labeling.

## Regulatory Background of Carbinoxamine

Carbinoxamine maleate (Ethanolamine, 2-[(4-chlorophenyl)-2pyridineylmethoxy]-N, N-dimethyl-(Z)-butenedioate) is a first-generation histamine H<sub>1</sub> receptor blocking agent (antihistamine) of the ethanolamine class. This antihistamine class also includes diphenhydramine, also reviewed under DESI, and now an OTC drug product. This class exhibits antihistaminic, anticholinergic, and sedative properties. Anticholinergic (antimuscarinic) activity results in drying effects on the mucous lining of the respiratory tract, one reason for previous unapproved use in the treatment of upper respiratory infections (along with its sedation effect). Pharmacologic effects include both stimulation and depression the CNS, resulting in restlessness, nervousness, inability to sleep, and also sedation, diminished alertness, slowed reaction times, and somnolence.

Carbinoxamine is a pre-1962 drug that was the subject of a DESI review, and subsequently, several ANDAs. The NDAs for the original carbinoxamine maleate drug products were marketed by McNeil Laboratories under the trade name Clistin as tablets (NDA 8-915, June 22, 1953), elixir (NDA 8-955, June 23, 1953), and repeat action (RA) tablets (NDA 8-915, June 15, 1954), and in a combination as Clistin Expectorant syrup (contained CM, ammonium chloride, sodium citrate, potassium guaiacolsulfonate, and citric acid) (NDA 9-248, February 5, 1962).

Subsequently, Clistin products specifically, and CM generally, were reviewed under DESI (DESI 6303, 38 FR 7265, March 19, 1973). Under DESI, Clistin tablets and elixir were found effective for the following INDICATIONS:

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

It should be noted that these DESI indications are more extensive than those currently allowed for non-DESI antihistamines.

When reviewed under DESI, Clistin RA received a designation of probably NOT effective because there was no evidence regarding its bioavailability and bioequivalence, as required for a timed-release dosage form of a safe and effective immediate-release drug (FR38, N53, 3/19/1973). Furthermore, Clistin Expectorant received a designation of probably NOT effective because there were no well-controlled studies to document the effectiveness of its expectorant ingredients and because the combination of an antihistamine and an expectorant was found not to be a rational combination (DESI 6514, 47 FR 11973, March 19, 1982). Marketing approval was subsequently withdrawn for both of these products (47 FR 21301, May 18, 1982; and 48 FR 34514, July 29, 1983; respectively).

Subsequently, McNeil withdrew the remaining Clistin products from the market at various times during the 1990s, but not for safety or efficacy reasons. In March of 2003, ANDAs for Palgic tablets (4 mg, NDA 40-442) and oral solution (4 mg CM per teaspoon, NDA 40-458) were approved, based on a bioequivalence program and not clinical studies. As ANDAs to the original Clistin products, the Clistin products inherited all of the DESI indications.

Additionally, the labeling for these products originally carried an age range for use down to 1 year of age. However, these products now carry CONTRAINDICATIONS for use in children younger than 2 years of age (as well as in nursing mothers and individuals who are hypersensitive to the drug or are on MAO therapy). The contraindication for children younger than 2 years of age was added at the Agency's request in 2006, at the time that the Agency issued a Compliance Policy Guide for Marketed Unapproved Drugs and simultaneously announced its intention to take enforcement action against unapproved drug products containing carbinoxamine.

### Clinical Filing Checklist

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			There is a minor issue with eCTD electronic formatting for the two study reports, which will not interfere with the ability to review the data.*
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			



	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	the applicability of foreign data to U.S. population/practice of medicine in the submission?				
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Provided in clinical overview document.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		No QT evaluation was ever performed for this moiety. Efficacy and safety is based on two bioequivalence studies and the Agency's previous DESI finding of efficacy and safety.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?		X		Submission of the coding dictionary is not necessary. The AE listings for the studies are adequate to assess the adverse events in the two studies.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			In general, adequacy of the safety assessment is a review issue. However, the applicant has provided studies to support bioequivalence of their product to the reference product, thereby allowing use of the Agency's previous DESI findings of efficacy and safety for the moiety.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No deaths, SAEs, or withdrawals.

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant requests waivers for 1) pediatric studies birth to <2 years of age because carbinoxamine is contraindicated in children under 2 years of age 2) pediatric bioequivalence studies in children 2 to <18 years of age. Per guidance, the BA/BE studies were performed in healthy adults; the results of these studies would be applicable to the adolescents and children 2 to <18 years of age.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			None needed
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and			X	None needed

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	adverse drop-outs) as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
<p>* There is a deviation in the eCTD formatting for this NDA that is noted only when accessing the files using GlobalSubmit, but not when accessing the files directly in the electronic data repository (EDR). It may be found in section 5.3.1.2, where the study reports and some of the datasets for the two Comparative BA and Bioequivalence studies are located. Within this main folder may be found some datafiles and a single subfolder that includes additional folders, each of which contain files for both studies side-by-side. The dataset files within this folder are not clearly marked as to which study each file belongs. So, for example, there are two define.pdf files, one for each study, and one must open each to determine the study to which it relates. There is also a separate folder called "datasets" that has separate sub-folders for the two studies, so it is not clear why data files are present in this folder. The main problem is that the single subfolder contains multiple folders, each of which contains files for both studies without delineating which one belongs to which study. So, for example, the study reports for both studies are both found side-by-side within section 5.3.1.2.3, each marked as report-body.pdf. One has to open each file to determine to which study the report pertains. The applicant should have provided within section 5.3.1.2 one sub-folder for each of the 2 studies, with each folder containing all the files and subfolders relating to that study. However, given that each file is clearly marked (not the file name but inside when the file is opened), the NDA is reviewable.</p>					

**Is the Clinical Section of the Application Fileable?**

Yes

**Reasons, if any, why the Application is not fileable from the clinical perspective**

None

**Potential Review Issues**

As noted in the Regulatory History section above, the Indications requested for this product are the same as those for the generic reference drug product (Palgic). Carbinoxamine underwent DESI review, and the current indications for the reference generic drug product reflect those indications. However, it is unclear that the support for each of the current indications for the original NDA [and the generic reference drug product] would meet today’s standards for efficacy and safety to support approval. The prescription antihistamines approved under DESI, such as promethazine and carbinoxamine, have a long list of indications for which antihistamines are not used in current practice. In current practice antihistamines are mainly used to treat the symptoms of allergic rhinitis and chronic idiopathic urticaria. The newer antihistamines that have been approved by the Agency (e.g. fexofenadine, loratadine, cetirizine etc) do not have the long list of indications that the DESI antihistamines have. Under today’s standards, each indication should be supported by adequate and well-controlled clinical trials. That said, this application is based on a bioequivalence program to the generic reference product, which was approved based on the carbinoxamine innovator product. Therefore, technically, once bioequivalence has been demonstrated, this new product should be able to carry all the indications as the innovator.

However, it is not unreasonable to revisit the current list of indications for carbinoxamine and re-evaluate the merit of those indications based on today's standards. This review exercise is important considering that many of the listed indications could arguably be removed given that antihistamines are not used for those indications in current practice and antihistamines approved under the more current approval process do not carry these indications. Although the original studies to support the DESI indications were not reviewed for this filing review, the adequacy of those studies to support indications other than seasonal and perennial allergic rhinitis and the relevance of these indications to today's current practice standards will be a review issue. The DESI review for carbinoxamine will be requested and reviewed during the review cycle.

There is no information available regarding PK in children and there is very little specific information regarding the ADME of carbinoxamine, although most H<sub>1</sub> antihistamines are extensively metabolized. Most sources do not list a metabolic pathway for carbinoxamine, although one source listed the cytochrome P-450 microsomal enzyme system, just as for many second generation antihistamines.<sup>3</sup> Excretion occurs renally, with an elimination half-life ranging from 10 to 20 hours. Since the metabolic pathway is not known, it is hard to predict whether younger children may experience slower or faster metabolism than older children and adults, except for the general statement that, in general, antihistamines are more rapidly cleared by children than by adults.<sup>4</sup>

### **Pediatric Waiver Request**

This application will trigger PREA because of the new extended release formulation. With this submission, the applicant is requesting pediatric 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. Per guidance, the BA/BE studies were performed in healthy adults; the results of these studies would be applicable to the adolescents and 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.

While a waiver of BA/BE studies in children 2 to <18 years of age is appropriate, the need for pediatric studies to support the proposed indications in the 2 to <17 years age group is a separate issue. Under PREA the Agency could require pediatric studies to support all the Indications considered appropriate for the pediatric age range. Therefore, a waiver of pediatric studies may not be appropriate for 2 to <17 years age range, and review of what Indications may be supported in the pediatric age range will be a review issue.

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<sup>3</sup> Clinical Pharmacology Online (1/30/2006 1:33:00 PM). Monograph on carbinoxamine and pseudoephedrine, Gold Standard. (Accessed 1/30/2006 1:33 PM)

<sup>4</sup> Hardman, J. G., Limbird, L.E., Gilman, A.G. (2001). Goodman & Gillman's The Pharmacological Basis of Therapeutics. New York, McGraw-Hill.

**Potential Review Issues for the 74-day Letter**

I recommend that the Division send the following 74-day comments:

1. The proposed indications for your carbinoxamine extended release product reflect the current list of indications for the carbinoxamine reference product. We acknowledge that carbinoxamine underwent DESI review and this list of indications is reflective of that review. The DESI review notwithstanding, given current approval standards where each indication must be supported by adequate and well controlled clinical trials, whether your extended release carbinoxamine product would retain all the currently listed DESI indications will be a review issue.
2. This application will trigger PREA. Under PREA, pediatric studies may be required to support all the indications considered appropriate for the pediatric age range. As a result, we inform you that, although a waiver of bioequivalence studies is appropriate, a waiver of other pediatric studies may not be appropriate for children 2 to 17 years of age and an evaluation of what indications may be supported in the pediatric age range will be a review issue.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PETER R STARKE  
01/24/2011

LYDIA I GILBERT MCCLAIN  
01/24/2011  
I concur