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RESEARCH**

APPLICATION NUMBER:

22-556Orig1s000

PROPRIETARY NAME REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: January 2, 2013

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Drug Name(s) and Strength(s): Karbinal ER (Carbinoxamine Maleate) Extended-release
Oral Suspension, 4 mg/5 mL

Application Type/Number: NDA 022556

Applicant/Sponsor: Tris Pharma Inc

OSE RCM #: 2012-2487

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Karbinal ER, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension is the subject of a 505(b)(2) application. The name Karbinal ER was the third proposed proprietary name for this product, first submitted by the Applicant on August 19, 2011. We evaluated the name in OSE Review # 2011-3192 dated November 15, 2011 and found it acceptable. However, the application received a CR on October 7, 2011. The Applicant has now resubmitted the NDA for the request for review of the proprietary name on October 17, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the October 17, 2012 proprietary name submission.

- Active Ingredient: Carbinoxamine Maleate
- Indication of Use: For 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, dermatographism, As therapy for anaphylactic reaction adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled, and Amelioration of the severity of allergic reaction to blood or plasma
- Route of Administration: Oral
- Dosage Form: Extended-release oral suspension
- Strength: 4 mg/5 mL
- Dose and Frequency: (b) (4) (6 to 16 mg) administered orally every 12 hours. (b) (4) (0.2 to 0.4 mg/kg/day) administered orally every 12 hours
- How Supplied: (b) (4) 10 oz, 16 oz bottles with a (b) (4)
- Storage: Room temperature

2. RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. However, OPDP noted that the name Karbinal ER sounds and looks like another product name “Carbatrol”. DMEPA and the Division of

Pulmonary, Allergy, and Rheumatology Products concurred with the findings of OPDP's promotional assessment of the proposed name and DMEPA evaluated the name Carbatrol in the previous review (OSE RCM # 2011-3192 dated November 15, 2011).

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

The October 30, 2012 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The proposed proprietary name contains two components: 1) the proposed root name, Karbinal, and 2) a modifier, ER. The Applicant stated that the derivation of the proposed proprietary name, Karbinal ER, is (b) (4). Additionally, the modifier "ER" is intended to mean "extended release."

We evaluated the modifier "ER" in the OSE Review # 2011-3191 dated November 15, 2011 and found that "ER" adequately represents the extended-release property of this product. In addition, the modifier has been used with products administered once or twice daily. Because the modifier has been in use on the market, the "ER" modifier can provide an indication to healthcare practitioners that this is an extended-release product that is administered less frequently than the currently marketed immediate-release Carbinoxamine products (every 12 hours vs. three to four times daily).

Although there is no product currently marketed with just the root name Karbinal, there is also precedence for products marketed with a root name plus a modifier when there is no product marketed by the root name alone such as Dynahist ER, Entex ER, and TriTuss ER (See Appendix F). Because there are Carbinoxamine immediate-release products marketed and this is the first extended-release product it may be important to differentiate this extended-release from the immediate-release Carbinoxamine products because the frequency of administration differs (every 12 hours vs. three to four times daily).

Thus, we find the use of the modifier "ER" in the proposed name Karbinal ER appropriate for this product. For an in-depth evaluation see OSE RCM # 2011-169 dated August 29, 2011.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched FAERS database for medication errors involving Carbinoxamine Maleate which would be relevant for this review.

The search was limited from the date of our last AERS search in OSE RCM # 2011-169 dated August 29, 2011. The October 30, 2012 FDA Adverse Event Reporting System (FAERS) database search used the following search terms: 'Carbinoxamin%' (active ingredient, 'Carbinoxamin%' (verbatim term), Medication Errors (HLGT), Product Packaging Issues (HLT), Product Label Issues (HLT), Product Quality Issues (NEC) (HLT).

There were no reports retrieved from this search.

2.2.4 FDA Name Simulation Studies

Eighty-six practitioners participated in DMEPA’s prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Twenty-three participants (inpatient: n=16, outpatient: n=7) interpreted the name correctly as ‘Karbinal ER’, Twelve participants (voice: n=12) interpreted the name as ‘Carbinol ER’, Six (voice: n=6) interpreted the name as ‘Carbanol ER’ and Six (voice: n=6) interpreted the name as ‘Carbonal ER’. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, November 7, 2012 e-mail, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Karbinal ER. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Karbinal ER identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1 list names which were not initially identified and evaluated in OSE Review #2011-3192 dated November 15, 2011

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, and External Name Study)					
Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Kedbumin	FDA	Resperal DM	FDA	Restoril	FDA
Hectoral	FDA	Klebcil	FDA		
Look and Sound Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Karbinal	FDA	(b) (4)	FDA	Karbinal ER	FDA

Our analysis of the 8 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined none of the names listed will not pose a risk for confusion as described in Appendix D through E.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Pulmonary, Allergy, and Rheumatology Products via e-mail on November 19, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Pulmonary, Allergy, and Rheumatology Products, they stated no additional concerns with the proposed proprietary name, Karbinal ER.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Nichelle Rashid, OSE project manager, at 301-796-3904

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Karbinal ER, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your October 17, 2012 submission are altered, the name must be resubmitted for review.

Additionally, the proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The conclusions upon re-review are subject to change.

4 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. Access Medicine (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

13. Red Book (www.thomsonhc.com/home/dispatch)

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. Medical Abbreviations (www.medilexicon.com)

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. CVS/Pharmacy (www.CVS.com)

This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a [Metasearch](#) engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

20. Natural Standard (<http://www.naturalstandard.com>)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.²

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.³ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

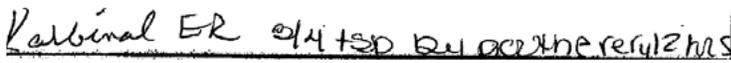
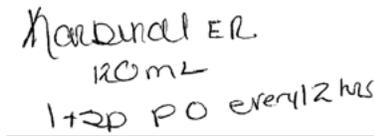
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name,	Scripted May Appear as	Spoken May Be Interpreted as
Upper Case 'K	H, R, X	G
lower case 'k'	h, x, lc	c, g
lower case 'a	el, ci, cl, d, o, u	Any Vowel
lower case 'r	n, u, v	l
lower case 'b	d, h	p
lower case 'i	Any vowel	Any vowel
lower case 'n	m, r, u, v	r
lower case 'l	b, e, s, A, P, i	none
Upper Case 'E'	A, F	Any Vowel
Upper Case 'R'	K, P, n, u, v	l
Letter strings		
Kar	Kor, Hor, Ror, Xor, Kon, Kan, Han, Hon, Ron, Ran, Xan, Kel, Hel, Rel, Xel,	Car
arb	arh, orh, dib,	rb
bin	hib, dib, ben, hen, bir, hir, ber, her,	ben,
nal	rel, ral, rar, rer, ror, rol,	nawl
Al	cil	all, awl

Appendix C: Prescription Simulation Samples and Results

Figure 1. Karbinal ER Study (Conducted on November 6, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u> </p> <p><u>Outpatient Prescription:</u> </p>	<p>Karbinal ER 120 mL 1 teaspoon by mouth every 12 hours</p>

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Karbinal ER

Total	25	34	27	
INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
CABENOL ER	0	1	0	1
CARBAMOL ER	0	1	0	1
CARBANOL ER	0	6	0	6
CARBENAL ER	0	1	0	1
CARBENAL ER 120MLS	0	1	0	1
CARBENOL ER	0	4	0	4
CARBINOL	0	1	0	1
CARBINOL ER	0	12	0	12
CARBONAL EL	0	1	0	1
CARBONAL ER	0	6	0	6
KALBINAL ER	1	0	0	1
KARBENAL ER	0	0	2	2
KARBENCEL ER	0	0	1	1
KARBENDEL ER	0	0	1	1
KARBINAL	2	0	0	2
KARBINAL ER	16	0	7	23
KARBINDEL ER	0	0	1	1
KARBINDL ER	0	0	3	3
KARBINDLER	0	0	1	1
KARBINOL ER	3	0	0	3
KARBUNAL	0	0	1	1

KARBUNDL ER	0	0	1	1
KARDINAL ER	0	0	1	1
KARSENCEL ER	0	0	1	1
KARSINAL ER	0	0	1	1
NARDERAL ER	0	0	1	1
NARDINAL	0	0	1	1
NARSUNDL ER	0	0	1	1
NASINAL ER	0	0	1	1
RAIBINAL ER	1	0	0	1
RARBINAL ER	2	0	0	2
XARDENALER	0	0	1	1
XNARBENAL ER	0	0	1	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to Karbinal ER	Failure preventions
1.	Karbinal	Carbinoxamine Maleate	Look and Sound	Name found on USPTO under the same Applicant. The name has not been submitted for review and there are no product characteristic found in common databases.
2.	(b) (4)	Carbinoxamine Maleate	Look and Sound	Proposed proprietary name found unacceptable by DMEPA via teleconference and resubmitted under Karbinal ER by the Applicant
3.	Karbinal ER	Carbinoxamine Maleate	Look and Sound	The name is the subject of this review

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

No.	Proposed name: Dosage Form(s): Karbinal ER (Carbinoxamine Maleate) Strength(s): 4 mg/5 mL Usual Dose: Adults: 7.5 mL to 20 mL every 12 hours Children: 3.75 mL to 15 mL every 12 hours	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
1.	Kedbumin (Albumin (human)) Injection, 12.5 g/50 mL <u>Usual dose:</u> 25 g to 100 g intravenously over 4 to 8 hours as necessary	<u>Orthographic:</u> The pair have similar beginning letter strings, 'Ka' and 'Ke' <u>Strength:</u> Both are single strength products	<u>Orthographic:</u> The ending letter strings, 'nal' vs. 'min' look different when scripted due to the upstroke letter 'l' in Karbinal. The infixes, 'rbi' vs. 'dbu' look different when scripted due to the double upstrokes, 'db' in Kedbumin. <u>Dose:</u> 3.75 mL to 20 mL or ¾ teaspoon to 4 teaspoons vs. 25 g to 100 g <u>Frequency:</u> Ever 12 hours vs. given once

No.	Proposed name: Dosage Form(s): Karbinal ER (Carbinoxamine Maleate) Strength(s): 4 mg/5 mL Usual Dose: Adults: 7.5 mL to 20 mL every 12 hours Children: 3.75 mL to 15 mL every 12 hours	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
2.	Hectorol (Doxercalciferol) Injection, 4 mcg/2 mL and 2 mcg/mL <u>Usual dose:</u> 4 mcg intravenously as a bolus dose three times weekly at the end of dialysis. May increase by 1 mcg to 2 mcg at 8 week intervals if needed	<u>Orthographic:</u> The pair have similar beginning letter strings, 'Ka' and 'He' and similar ending letter strings, 'nal' and 'rol' <u>Strength:</u> Both have a 4 (mg vs. mcg) strength	<u>Orthographic:</u> The infixes, 'rbi' vs. 'cto' look different when scripted due to the cross-stroke letter 't', in Hectorol <u>Dose:</u> 3.75 mL to 20 mL or ¾ teaspoon to 4 teaspoons vs. 4 mcg to 6 mcg <u>Frequency:</u> Ever 12 hours vs. three times a week
3.	Klebcil (Kanamycin a sulfate) Injection, 500 mg/vial and 1 g/vial Usual Dose: <i>Intramuscularly or Intravenously:</i> 7.5 mg/kg every 12 hours. <i>Intraperitoneal:</i> 500 mg diluted in 20 mL of sterile distilled water <i>Aerosol:</i> 250 mg 2 to 4 times a day	<u>Orthographic:</u> The pair have both start with the letter 'K' and have similar ending letter strings, 'nal' and 'cil'	<u>Orthographic:</u> Klebcil contains an upstroke letter 'l' after the letter 'K' which gives it a different shape than Karbinal ER. <u>Dose:</u> 3.75 mL to 20 mL or ¾ teaspoon to 4 teaspoons vs. 250 mg 500 mg <u>Route:</u> Oral vs. intramuscular, intravenous, intraperitoneal, or aerosol

No.	Proposed name: Dosage Form(s): Karbinal ER (Carbinoxamine Maleate) Strength(s): 4 mg/5 mL Usual Dose: Adults: 7.5 mL to 20 mL every 12 hours Children: 3.75 mL to 15 mL every 12 hours	Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
4.	Restoril (Temazepam) Capsules, 7.5 mg, 15 mg, 22.5 mg, 30 mg <u>Usual dose:</u> 1 capsule by mouth at bedtime	<u>Orthographic:</u> The pair have similar beginning letter strings, 'Ka' and 'Re' and similar ending letter strings, 'nal' and 'ril' <u>Route:</u> Both oral <u>Dose:</u> 15 mL and 15 mg	<u>Orthographic:</u> The infixes, 'rbi' vs. 'sto' may look different when scripted due to the cross-stroke letter 't' in Restoril.
5.	Resperal DM (Brompheniramine Maleate, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide) Elixir, 1 mg/15 mg/5 mg per 5 mL <u>Usual dose:</u> 2 (10 mL) to 4 (20 mL) teaspoonfuls by mouth every 4 to 6 hours	<u>Orthographic:</u> The pair have similar beginning letter strings, 'Ka' and 'Re' and have similar ending letter strings, 'nal' and 'ral' <u>Strength:</u> Both are single strength products <u>Route:</u> Both oral	<u>Orthographic:</u> The infixes, 'rbi' vs. 'spe' look different when scripted due to upstroke letter 'b' in Karbinal and the downstroke letter 'p' in Resperal. The modifiers, 'ER' vs. 'DM' look different when scripted. <u>Frequency:</u> Ever 12 hours vs. every 4 to 6 hours

Appendix F: Currently marketed products with “ER” modifier and their corresponding immediate-release products with frequency of administration.

Immediate-release product	Frequency	Extended-release product	Frequency
Depakote	two to three times daily	Depakote ER	once daily
Flagyl	three times daily	Flagyl ER	once daily
Razadyne	twice daily	Razadyne ER (formerly Reminyl ER)	once daily
Ultram	four times daily	Ultram ER	once daily
Dynahist ER does not have a corresponding immediate-release product		Dynahist ER	twice daily
Entex ER does not have a corresponding immediate-release product		Entex ER	twice daily
TriTuss ER does not have a corresponding immediate-release product		TriTuss ER	twice daily
Tussionex does not have a corresponding immediate-release product		Tussionex	twice daily
Opana	every 4 to 6 hours	Opana ER	twice daily
Albuterol tablets	three to four times daily	VoSpire ER	twice daily
Methylphenidate tablets	two to three times daily	Metadate ER	three times daily
Methylphenidate tablets	two to three times daily	Methylin ER	three times daily

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/s/

LUBNA A MERCHANT
01/02/2013

KELLIE A TAYLOR
01/02/2013

CAROL A HOLQUIST
01/02/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: November 15, 2011

Reviewer: Chi-Ming (Alice) Tu, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Karbinal ER (Carbinoxamine Maleate) Extended-release
Oral Suspension, 4 mg/5 mL

Application Type/Number: NDA 022556

Applicant/sponsor: Tris Pharma Inc

OSE RCM #: 2011-3192

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Karbinal ER, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension is the subject of a 505(b)(2) application. The name Karbinal ER is the third proposed proprietary name for this product, submitted by the Applicant on August 19, 2011.

The first proposed proprietary name, (b) (4) was found unacceptable by DMEPA in OSE Review #2011-429, dated March 18, 2011, because of promotional concern that the suffix (b) (4) suggests that the drug can be used in all (b) (4) patients but this product is contraindicated in patients less than two years old. The alternate name, (b) (4) was also found unacceptable because of the same promotional concern.

The second proposed proprietary name, (b) (4) was found unacceptable because this extended release formulation of carbinoxamine maleate product is dosed twice daily but the proposed modifier (b) (4) usually denotes (b) (4) daily dosing (e.g. (b) (4) already marketed by the Applicant is dosed once daily). Our concern was communicated to the Applicant on a teleconference, dated August 18, 2011; and subsequently the Applicant withdrew the name (b) (4) on August 19, 2011.

On October 7, 2011 this Application received a Complete Response letter for NDA 022556 from the Agency.

1.2 PRODUCT INFORMATION

Karbinal ER (Carbinoxamine Maleate) Extended-release Oral Suspension, 4 mg/5 mL, is an antihistamine with anticholinergic and sedative properties. The proposed indication is 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
- Dermatographism
- As therapy for anaphylactic reaction adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled
- Amelioration of the severity of allergic reaction to blood or plasma

The recommended (b) (4) dosage is (b) (4) (6 to 16 mg) administered orally every 12 hours, and (b) (4) (0.2 to 0.4 mg/kg/day) administered orally every 12 hours in (b) (4). Karbinal ER will be supplied in (b) (4). (b) (4) The product should be stored at room temperature (25°C).

2 RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall evaluation.

2.2.1 *United States Adopted Names (USAN) SEARCH*

The United States Adopted Name (USAN) stem search conducted on October 7, 2011, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 *Components of the Proposed Proprietary Name*

The proposed proprietary name contains two components: 1) the proposed root name, Karbinal, and 2) a modifier, ER. The Applicant stated that the derivation of the proposed proprietary name, Karbinal ER, is (b) (4) .” Additionally, the modifier “ER” is intended to mean “extended release.”

Our evaluation of the modifier found that “ER” adequately represents the extended-release property of this product. In addition, the modifier has been used with products administered once or twice daily. Because the modifier has been in use on the market, the “ER” modifier can provide an indication to healthcare practitioners that this is an extended-release product, which differs from the currently marketed immediate-release Carbinoxamine products.

Although there is no product currently marketed with just the root name Karbinal, there is also precedence for products marketed with a root name plus a modifier when there is no product marketed by the root name alone such as Dynahist ER, Entex ER, and TriTuss ER (See Appendix G). Because there are Carbinoxamine immediate-release products marketed and this is the first extended-release product it will be important to differentiate this extended-release from the immediate-release (See Section 2.2.6.3).

Thus, we find the use of the modifier “ER” in the proposed name Karbinal ER appropriate for this product.

2.2.4 *FDA Name Simulation Studies*

Forty-two practitioners participated in DMEPA's prescription studies, with no response overlapping with currently marketed drug names. Eleven of the 42 respondents interpreted the name correctly as “Karbinal ER.” One respondent interpreted the root name “Karbinal” correctly but dropped the modifier “ER” from the response in the

inpatient study. In the voice study, common misinterpretations include the first letter “K” as “C” by all respondents (n=17), the fifth letter “i” as “a” (n=6), and the seventh letter “a” as “o” (n=14). In the written prescriptions, common misinterpretations included the fifth letter “i” as “u” (n=10). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE August 24, 2011 e-mail, the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) stated that the “Karbinal ER proprietary name is redundant in repeating ER if ER is suppose to indicate extended release.” We will discuss DPARP’s comment in Section 2.2.6.3.

2.2.6 Failure Mode and Effects Analysis of the Proposed Name

Karbinal ER is the first extended-release product for Carbinoxamine Maleate. Therefore, we evaluated the potential for name confusion between similar names and the proposed name, the potential medication errors within the Carbinoxamine product line, and the need for a modifier in the proposed name.

2.2.6.1 Failure Mode and Effects Analysis of Similar Names

Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Karbinal ER (see Appendix B). These names were identified by the primary reviewer, the Expert Panel Discussion (EPD), FDA name simulation studies, or other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD and Other Disciplines)

Look Similar		Sound Similar		Look and Sound Similar	
Name	Source	Name	Source	Name	Source
Clozaril	EPD	Adderall XR	EPD	Carbatrol	EPD
Colazal	EPD	(b) (4)	EPD	Cardinol	Primary reviewer
Depakote ER	EPD	Carmol	EPD	Kalbitor	EPD
Fiorinal	EPD	Cartrol	EPD		
Kaletra	EPD	Carvedilol	EPD		
Kalexate	EPD	Harmonyl	Primary reviewer		
(b) (4)	EPD	Isopto Carbachol	EPD		
Kantrex	EPD	Karbinone	Primary reviewer		
Karbozyme	EPD				
(b) (4)	EPD				
(b) (4)	EPD				
Karidium	EPD				

Look Similar		Sound Similar		Look and Sound Similar	
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Karigel N	EPD				
Kariva	EPD				
(b) (4)	Primary reviewer				
Kelnor 1/35	EPD				
Keppra XR	EPD				
Keratol 40	EPD				
Kerledex	EPD				
Kerlone	EPD				
Ketocal	Primary reviewer				
Kombiglyze	EPD				
Kondremul	EPD				
Lactinol	Primary reviewer				
Limbrel	Primary reviewer				
Marinol	Primary reviewer				
Metadate	EPD				
Metharbital	EPD				
Profenal	EPD				
Rabavert	EPD				
Rebetol	EPD				
Razadyne	EPD				
Rhinall	EPD				
RhinoFlex	EPD				
Robinul	EPD				
Rosanil	EPD				
(b) (4)	EPD				
Ridenol	EPD				
Robaxisal	EPD				
Xalatan	EPD				
Xenical	EPD				
(b) (4)	EPD				

Our analysis of the 53 names contained in Table 1 considered the information obtained in the previous sections along with the product characteristics. We determined the 53 names will not pose a risk for confusion as described in Appendix D through F.

DMEPA communicated our midpoint findings to the Division of Pulmonary, Allergy and Rheumatology Products via e-mail on November 7, 2011. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Pulmonary and Allergy Products and Rheumatology on November 7, 2011, they stated no additional concerns with the proposed proprietary name, Karbinal ER.

2.2.6.2 Failure Mode and Effects Analysis of Errors with Marketed Carbinoxamine Products

The currently marketed formulations of immediate-release Carbinoxamine Maleate Oral Solution and the proposed Karbinal ER Extended-release Oral Suspension are available in the same single strength, 4 mg/5 mL. Therefore, the overlapping product characteristics (i.e. same active ingredient, strength, liquid dosage forms, and oral route of administration) and that liquid dosage forms are often prescribed in “# mL” pose a risk of confusion and wrong drug medication errors between the immediate-release product and this extended-release product.

In addition, the proposed Karbinal ER has a dosing frequency of every 12 hours, while immediate-release Carbinoxamine Maleate Oral Solution products have a dosing frequency of three to four times daily (every 6 to 8 hours). Because of the different frequency of administration, confusion between the immediate-release product and this extended-release product may lead to underdose or overdose medication errors. Although underdose errors may only result in lack of therapeutic effect, overdose of carbinoxamine may result in serious adverse events such as hallucination, convulsion, or death.

Ideally, a different strength for the extended-release formulation would help differentiate it from the immediate release formulations and reduce the risk for wrong drug dispensing errors. However, since both formulations are single strength products, the strength may be omitted from prescriptions and the risk of product confusion due to the overlapping product characteristics may still occur. Thus, this risk of product confusion should be mitigated via adequate naming, labels and labeling. Our comments and recommendations for labels and labeling were addressed in OSE Review #2011-169, dated August 29, 2011. Additionally, the frequency of “every 12 hours” for the extended-release product should be considered for printing on the principal display panel of the labels and labeling.

2.2.6.3 Evaluation of the Need for a Modifier in the Proposed Name

The Applicant proposed to differentiate this extended-release product from the currently marketed Carbinoxamine products by using the modifier “ER” as a part of the proprietary name, Karbinal ER. Although the “ER” modifier is appropriate for this product as discussed in Section 2.2.2, the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) stated that the use of the modifier “ER” in the proprietary name appears redundant. In addition, DPARP indicated that none of the currently marketed

Carbinoxamine Maleate immediate release products are marketed with the proprietary name Karbinal. Thus, we evaluated the need for a modifier in naming this product.

Proprietary name options for this proposed extended-release product are 1) Karbinal, without the modifier; or 2) Karbinal ER, as proposed by the Applicant.

A proprietary name without a modifier, Karbinal, does not provide any reminder to healthcare practitioners that this is an extended-release product that differs from the currently marketed immediate-release Carbinoxamine products approved for dosing every 6 to 8 hours. Therefore, the use of a meaningful modifier such as “ER” may help reduce the risk of product confusion and likelihood of error if the product is marketed as Karbinal ER in light of the overlapping product characteristics between the extended release and immediate release formulations.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective. The Applicant will be notified of this conclusion via a letter.

The proposed proprietary name, Karbinal ER, must be re-reviewed upon submission of the NDA and 90 days before approval of the NDA 022556.

If you have further questions or need clarifications, please contact Nichelle Rashid, OSE project manager, at 301-796-3904.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Karbinal ER, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your August 19, 2011 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

4 REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO***
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***Electronic online version of the FDA Orange Book***
(<http://www.fda.gov/cder/ob/default.htm>)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)
USPTO provides information regarding patent and trademarks.
9. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)
Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.
10. ***Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at*** (www.thomson-thomson.com)
The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.
11. ***Natural Medicines Comprehensive Databases*** (www.naturaldatabase.com)
Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.
12. ***Access Medicine*** (www.accessmedicine.com)
Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.
13. ***USAN Stems*** (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)
USAN Stems List contains all the recognized USAN stems.
14. ***Red Book Pharmacy's Fundamental Reference***
Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.
15. ***Lexi-Comp*** (www.lexi.com)
Lexi-Comp is a web-based searchable version of the Drug Information Handbook.
16. ***Medical Abbreviations Book***
Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by DDMAC. DDMAC evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. DDMAC provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.² The product characteristics considered for this review appears in Appendix B1 of this review.

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
	Similar spelling	Identical prefix	• Names may appear similar

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Look-alike		Identical infix Identical suffix Length of the name Overlapping product characteristics	in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and

Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary

name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.³ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix B1 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

practice setting? And Are there any components of the name that may function as a source of error beyond sound/look-alike”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug

product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

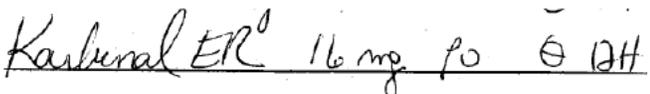
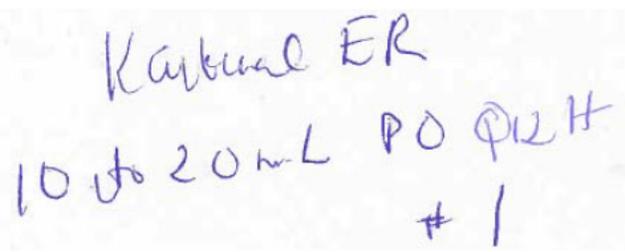
Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Karbinal ER	Scripted May Appear as	Spoken May Be Interpreted as
K	H, R, X	G
k	h, x, lc	c, g
a	Any vowel	Any vowel
r	n, u, v	l
b	d, h	p
i	Any vowel	Any vowel
n	m, r, u, v	m
l	e, h, t	r
E	A, F	Any vowel
R	K, P, n, u, v	l

Appendix C: Prescription Simulation Samples and Results

Figure 1. Karbinal ER Study (Conducted on September 6, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> 	<p>Karbinal ER Take 10 to 20 mL by mouth every 12 hours Dispense 1 bottle</p>
<p><u>Outpatient Prescription:</u></p> 	

FDA Prescription Simulation Responses (n=42)

INPATIENT (n=12)	VOICE (n=17)	OUTPATIENT (n=13)
KARBENAL ER (1)	CARBANOL ER (6)	KAIBIVAN ER (1)
KARBINAL (1)	CARBINAR ER (1)	KARBINAL ER (2)
KARBINAL ER (9)	CARBINOL ER (8)	KARBUAL ER (6)
KARBUNAL ER (1)	CARBONAL ER (2)	KARBUCAL ER (1)
		KARBUNAL ER (2)
		KAYBIVAL ER (1)

Appendix D: Names lacking orthographic similarity to Karbinal ER

Product name with potential for confusion	Similarity to Karbinal ER	Product name with potential for confusion	Similarity to Karbinal ER	Product name with potential for confusion	Similarity to Karbinal ER
Adderall XR	Sound	Kariva	Look	Metharbital	Look
Carmol	Sound	Karigel N	Look	Rabavert	Look
Cartrol	Sound	(b) (4)	Look	Razadyne	Look
Carvedilol	Sound	Kaletra	Look	Rhinall	Look
Clozaril	Look	(b) (4)	Look	RhinoFlex	Look
Colazal	Look	Kantrex	Look	Xalatan	Look
Depakote ER	Look	Keppra XR	Look	(b) (4)	Look
Kalexate	Look	Kombiglyze	Look		
Karbozyme	Look	Metadate ER	Look		

Appendix E: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Karbinal ER	Failure preventions
(b) (4)	Unknown	Sound	The name was identified in POCA (RxNorm), but no further drug information can be found from Clinical Pharmacology, Drug@FDA, Facts & Comparison and Lexi-Comp.
Cardinol	propranolol	Look and Sound	This name was identified in POCA, but was found to be a foreign drug name for propranolol in New Zealand per Lexi-Comp.
Harmony1	deserpidine	Sound	Per Drugs@FDA, brand name product is discontinued and no generic version exists. DARRTS search for NDA 10796 found application is in “withdrawn FR effective” status since 3/13/2009.
Karbinone	Unknown	Sound	This name was identified in Saegis with an “expired” status. No further drug information can be found from Clinical Pharmacology, Drug@FDA, Facts & Comparison and Lexi-Comp.
(b) (4)	artichoke	Look	This name was identified in Natural Medicines Comprehensive Database as “artichoke (also known as: (b) (4) When searching for a commercial product on the Database, however, (b) (4) was not found.
Ridenol	Acetaminophen	Look	This name was identified in Clinical Pharmacology, but no further drug information can be found from Clinical Pharmacology, Drug@FDA, Facts & Comparison and Lexi-Comp.
Robaxisal	aspirin 325 mg/ methocarbamol 400 mg	Look	This name was identified in Clinical Pharmacology, which lists the product as off market. Per Drugs@FDA, the brand name product is discontinued,

			but a generic aspirin 325 mg/methocarbamol 400 mg product is still marketed by Stevens J. However, the aspirin 325 mg/methocarbamol 400 mg product marketed by Stevens J does not have a therapeutic equivalent code in the Orange Book. Google search for the company Stevens J, with terms “Stevens J” and “Stevens J pharmaceutical” could not locate the company website. No further drug information can be found for this product.
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Appendix F: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Fiorinal (butalbital, aspirin, and caffeine)	Look	Tablet: 50 mg/ 325 mg/ 40 mg Capsule: 50 mg/ 325 mg/ 40 mg	1 to 2 tablets or capsules by mouth every 4 hours, not to exceed 6 tablets or capsules per day	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 to 2 tablets/capsules Frequency: every 12 hours vs. every 4 hours Orthographic differences: Karbinal ER contains an upstroke “b” in the middle of the name that is not seen in Fiorinal.
Karidium (sodium fluoride drops)	Look	Liquid: 1.95 mg/mL	6 months to 3 years of age: 550 mcg by mouth daily 3 to 6 years of age: 1.1 mg by mouth daily 6 years and older: 2.2 mg by mouth daily	Frequency: every 12 hours vs. daily Orthographic differences: Karbinal ER contains an upstroke “l” at the end of the name that is not seen in Karidium. Other: Karidium is available in two different dosage forms so either the specific strength or the dosage form is needed on a prescription for dispensing, thus providing orthographic differentiation from Karbinal ER.
		Tablet: 1 mg	No dosing information found in Clinical Pharmacology, Drug Facts & Comparison, Lexi-Comp, and Micromedex.	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. # tablets Orthographic differences: same as above. Other: same as above.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
(b) (4) (pentetate calcium trisodium)	Look	Injection: 1 g/5 mL	1 g intravenous push over three to four minutes once daily, or 1 g intravenous infusion after dilution in 100 to 250 mL of suitable diluent once daily, or 1 g inhaled via nebulized inhalation after dilution once daily	Route of administration: by mouth vs. intravenously Frequency: every 12 hours vs. once daily Dosage form: oral suspension vs. injection Orthographic differences: There is a two letter space between the upstrokes “K” and “b” in Karbinal ER vs. one letter space between “K” and “I” in (b) (4) Frequency: every 12 hours vs. once daily Orthographic differences: same as above.
Kelnor 1/35 (ethinyl estradiol and ethynodiol diacetate)	Look	Tablet: 0.035 mg/1 mg	1 tablet by mouth once daily (21 active then 7 inactive)	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 tablet Frequency: every 12 hours vs. once daily Orthographic differences: Karbinal ER contains an upstroke “l” at the end of the name that is not seen in Kelnor 1/35. In addition, Karbinal ER contains the modifier ER, which is not orthographically similar to the modifier 1/35 in Kelnor 1/35.
Keratol 40 (urea) Brand name product discontinued but generic equivalents available.	Look	Cream: 40% Gel: 40% Lotion: 40%	Apply topically 1 to 3 times daily	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. “thin layer” Route of administration: by mouth vs. topically Frequency: every 12 hours vs. 3 times daily Dosage form: oral suspension vs. cream, gel or lotion Orthographic differences: There is a three letter space between the upstrokes “b” and “l” in Karbinal ER vs. one letter space between “t” and “l” in Keratol.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Kerledex (betaxolol HCl/ chlorthalidone) Brand name product is discontinued and no generic version exists, but NDA application is still in approved status.	Look	Tablet: 5 mg/12.5 mg and 10 mg/12.5 mg	Take 1 tablet by mouth once daily	Strength: 4mg/5mL (single strength) vs. 5 mg/12.5 mg and 10 mg/12.5 mg (multiple strength) Orthographic differences: Karbinal ER contains an upstroke “l” at the end of the name that is not seen in Kerledex.
Kerlone (betaxolol)	Look	Tablet: 10 mg (scored) and 20 mg	5 mg by mouth once daily, may increase every 2 weeks up to a maximum of 20 mg per day	Strength: 4mg/5mL (single strength) vs. 10 mg and 20 mg (multiple strength) Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. # tablets Frequency: every 12 hours vs. once daily Orthographic differences: Karbinal ER contains an upstroke “l” at the end of the name that is not seen in Kerlone.
Kondremul (mineral oil) Over-the-counter product	Look	Micoremsulsion: 2.5 ml/5 mL	Adult: 30 to 75 mL orally per day Child 6 to 12 years of age: 10 to 25 mL per day	Frequency: every 12 hours vs. once daily Orthographic differences: There is a three letter space between the upstrokes “b” and “l” in Karbinal ER vs. a four letter space (including the wide in shape letter “m”) between “d” and “l” in Kondremul.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Ketocal 3:1 Ketocal 4:1	Look	Nutritional Powder	Intake to be determined by a medical professional and is based on patient's age, weight and medical condition. No specific dosage and administration can be found on Google search for Ketocal (search date July 15, 2011) and NaturalMedine.	Orthographic differences: The orthographic similarity between the name pair stems from the root name Karbinal and Ketocal. The risk of name confusion is reduced by the modifier "ER" in Karbinal ER and modifiers "3:1" and "4:1" in Ketocal 3:1 or Ketocal 4:1. If the modifiers are left off when scripted, the likelihood of medication error between Karbinal ER and Ketocal is rare because Karbinal is a prescription drug product while Ketocal is a medical food when ketogenic diet is indicated.
Lactinol Lactinol-E Lactinol HX (lactic acid) Over-the-counter product	Look	Lotion: 10% Cream: 10%	Apply to affected areas topically twice daily	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. "thin layer" Route of administration: by mouth vs. topically Dosage form: oral suspension vs. cream or lotion
Limbrel 250 (flavocoxid) Limbrel 500 (flavocoxid)	Look	Capsule: 250 mg and 500 mg	250 or 500 mg by mouth every 12 hours	Strength: 4mg/5mL (single strength) vs. 250 mg and 500 mg (multiple strength) Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 capsule Orthographic differences: Karbinal ER contains the modifier ER, which is not orthographically similar to the modifier 250 or 500 in Limbrel 250 or Limbrel 500. Also, the dotted letter "i" is in the fifth position of the name Karbinal ER vs. in the second position of the name Limbrel 250 or Limbrel 500.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Marinol (droenabinol)	Look	Capsule: 2.5 mg, 5 mg and 10 mg	<u>Antiemetic</u> : 5 mg/m ² by mouth 1 to 3 hours before chemotherapy, then give 5 mg/m ² /dose every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day. Maximum of 15 mg/m ² /dose. <u>Appetite stimulant (AIDS-related)</u> : initiate 2.5 mg by mouth twice daily, titrate up to a maximum of 20 mg per day.	Strength: 4mg/5mL (single strength) vs. 2.5 mg, 5 mg and 10 mg (multiple strength) Orthographic differences: Karbinal ER contains an upstroke letter “b” that is not seen in Marinol. In addition, the first letter “M” in Marinol is orthographically different from the first letter “K” in Karbinal ER.
Profenal (Suprofen) Brand name product is discontinued and no generic version exists, but NDA application is still in approved status.	Look	Solution, ophthalmic: 2.5 mL	Instill two drops in the conjunctival sac at three, two and one hour prior to surgery. Two drops may be instilled into the conjunctival sac every four hours the day preceding surgery.	Orthographic differences: Profenal contains a cross-stroke letter “f” that is not seen in Karbinal ER. Suprofen was once marketed under the name Profenal by Alcon Laboratories, Inc. but stopped marketing this NSAID ophthalmic drop because it has high discontinuation rate from users due to gastrointestinal side effects.
Rebetol (ribavirin)	Look	Capsule: 200 mg Solution, oral: 40 mg/mL	Adult weighing less than or equal to 75 kg, or children weighing greater than 61 kg: 400 mg in the morning, then 600 mg in the evening Adult weighing greater than 75 kg: 600 mg in the morning, then 600 mg in the evening Children less than 61 kg: 15 mg/kg/day in 2 divided doses	Orthographic differences: Rebetol contains 4 upstroke letters in the root name (R, b, t, and l) vs. Karbinal ER contains 3 upstroke letter in the root name (K, b, l) plus a modifier that is not seen in Rebetol. Other: Rebetol is available in two different dosage forms so either the specific strength or the dosage form is needed on a prescription for dispensing, thus providing orthographic differentiation from Karbinal ER.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Robinul Robinul Forte (glycopyrrolate)	Look	Solution for injection: 0.2 mg/mL (Robinul only)	<u>Anesthesia, or reserve neuromuscular blocking agents</u> 4 mcg/kg intramuscular injection 30 to 60 minutes before procedure 0.1 mg intravenous injection repeat as needed at 2 to 3 minute intervals	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 0.2 mg (1 mL, based on an average adult weight of 72 kg) Route of administration: by mouth vs. intramuscular or intravenous injection Frequency: every 12 hours vs. one time before procedure then as needed Dosage form: oral suspension vs. solution for injection Orthographic differences: There is a two letter space between the upstrokes “K” and “b” in Karbinal ER vs. a one letter space between “R” and “b” in Robinul.
		Tablet: 1 mg (Robinul only)	<u>Peptic ulcer, adjunctive therapy</u> 1 tablet by mouth three times daily	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 tablet Frequency: every 12 hours vs. three times daily Orthographic differences: same as above.
		Tablet: 2 mg (Robinul Forte only)	<u>Peptic ulcer, adjunctive therapy</u> 1 tablet by mouth two to three times daily at equally spaced intervals	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 tablet Orthographic differences: Karbinal ER contains the modifier ER, which is not seen in Robinul. Additionally, the orthographic similarity between the name pair stems from the root name Karbinal and Robinul Forte. The risk of name confusion is reduced by the modifier “ER” in Karbinal ER and modifier “forte” in Robinul Forte.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Rosanil (sulfur and sulfacetamide)	Look	Cleanser, topical: 5%/10%	Wash affected area topically once to twice daily	Route of administration: by mouth vs. topical Dosage form: oral suspension vs. cleanser Orthographic differences: Karbinal ER contains an upstroke letter “b” in the middle of the name that is not seen in Rosanil.
(b) (4) (b) (morphine) Brand discontinued but generic equivalents available	Look	Oral Solution: 20 mg/mL	10 to 30 mg by mouth every 4 hours as needed in adults, 0.15 to 0.2 mg/kg by mouth every 3 to 4 hour hours as needed in children 6 months or older and weighs less than 50 kg	Frequency: every 12 hours vs. every 3 to 4 hours as needed Orthographic differences: Karbinal ER contains an upstroke letter “b” in the middle of the name that is not seen in (b) (4)
Xenical (orlistat)	Look	Capsule: 120 mg	1 tablet by mouth three times daily with each main meal containing fat (during or up to 1 hour after the meal); omit dose if meal is occasionally missed or contains no fat	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 capsule Frequency: every 12 hours vs. three times daily with each main meal containing fat Orthographic differences: Karbinal ER contains an additional upstroke letter “b” in the name that is not seen in Xenical.

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Carbatrol (carbamazepine)	Sound	Capsule, extended release: 100, 200 and 300 mg	<u>Epilepsy</u> Adult and children over 12 years of age: 200 mg by mouth twice daily, titrate up by 200 mg/day. Usual maintenance dose is 400 to 600 mg by mouth twice daily Children under 12 years of age: 35 mg/kg daily divided in 2 doses <u>Trigeminal neuralgia</u> 200 mg by mouth twice daily, titrate up by 200 mg/day as needed to achieve freedom from pain	Strength: 4mg/5mL (single strength) vs. 100, 200 and 300 mg (multiple strength) Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 capsule Phonetic differences: The ending sound “-nal” in Karbinal ER provides phonetic differences from the sound “-trol” in Carbatrol.
Isopto Carbachol (carbachol)	Sound	Solution, ophthalmic: 1.5% and 3%	<u>Glaucoma</u> Instill 1 to 2 drops in affected eye up to three times daily <u>Ophthalmic surgery (miosis)</u> Instill 0.5 mL into the anterior chamber eye before or after securing sutures.	Strength: 4mg/5mL (single strength) vs. 1.5% and 3% (multiple strength) Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 1 to 2 drops Route of administration: by mouth vs. ophthalmic instillation Dosage form: oral suspension vs. ophthalmic solution

Product name with potential for confusion	Similarity to Karbinal ER	Dosage Form/ Strength	Usual Dose (if applicable)	Name confusion is prevented by the stated product characteristics and/or orthographic/phonetic differences as described
Karbinal ER (carbinoxamine maleate, USP)	n/a	4 mg/5 mL Oral suspension	Adult: 6 to 16 mg by mouth every 12 hours Child: 0.2 to 0.4 mg/kg/day: 3 to 12 mg by mouth every 12 hours	n/a
Kalbitor (ecallantide)	Look and Sound	Solution for injection, 10 mg/mL	<u>Acute attacks of hereditary angioedema</u> 30 mg subcutaneous injection once, may repeat an additional 30 mg within 24 hours	Dose: 3 to 16 mg (3.75 mL to 20 mL) vs. 30 mg Route of administration: by mouth vs. intravenous injection Frequency: every 12 hours vs. once, may repeat an additional 30 mg within 24 hours Dosage form: oral suspension vs. solution for injection Orthographic differences: Karbinal ER contains an upstroke letter “l” at the end of the name, which is not seen in Kalbitor; whereas Kalbitor contains an additional upstroke letter “l” in the middle of the name that is not seen in Karbinal ER. Phonetic differences: The ending sound “-nal” in Karbinal ER provides phonetic differences from the sound “-tor” in Kalbitor.

Appendix G: Currently marketed products with “ER” modifier and their corresponding immediate-release products with frequency of administration.

Immediate-release product	Frequency	Extended-release product	Frequency
Depakote	two to three times daily	Depakote ER	once daily
Flagyl	three times daily	Flagyl ER	once daily
Razadyne	twice daily	Razadyne ER (formerly Reminyl ER)	once daily
Ultram	four times daily	Ultram ER	once daily
Dynahist ER does not have a corresponding immediate-release product		Dynahist ER	twice daily
Entex ER does not have a corresponding immediate-release product		Entex ER	twice daily
TriTuss ER does not have a corresponding immediate-release product		TriTuss ER	twice daily
Opana	every 4 to 6 hours	Opana ER	twice daily
Albuterol tablets	three to four times daily	VoSpire ER	twice daily
Methylphenidate tablets	two to three times daily	Metadate ER	three times daily
Methylphenidate tablets	two to three times daily	Methylin ER	three times daily

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/s/

CHI-MING TU
11/15/2011

CAROL A HOLQUIST
11/16/2011

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

Date: March 18, 2011

Application Type/Number: NDA 022556

Through: Carlos M. Mena-Grillasca, RPh, Team Leader
Division of Medication Error Prevention and Analysis (DMEPA)

From: Chi-Ming Tu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name: (b) (4) (Carbinoxamine extended-release) Oral Suspension
4 mg/5 mL

Applicant/Sponsor: Tris Pharma Inc.

OSE RCM #: 2011-429

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