CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-562

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

Date:	February 24, 2010
To:	Donna Griebel, MD Director, Division of Gastroenterology Products
Through:	Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Carbaglu (Carglumic Acid) Tablets 200 mg
Application Type/Number:	NDA 022562
Applicant:	Orphan Europe, SARL
OSE RCM #:	2009-2140

CONTENTS

1 INTRODUCTION

This re-assessment of the proprietary name is written in response to the anticipated approval of NDA 022562 within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Carbaglu, acceptable in OSE Review #2009-1423, dated October 20, 2009. The Division of Gastroenterology Products did not have any concerns with the proposed name, Carbaglu during the previous review of the proposed name and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on August 18, 2009.

2 METHODS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 5) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We used the same search criteria outlined in OSE Review #2009-1423, dated October 20, 2009, for the proposed proprietary name, Carbaglu. None of Carbaglu's product characteristics have been altered since our previous review. Thus, we did not re-evaluate previous names of concern. Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

3 RESULTS

The searches of the databases did not result in any additional names thought to look or sound similar to Carbaglu and represent a potential source of drug name confusion.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of February 23, 2009.

4 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Carbaglu, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Carbaglu, for this product at this time.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Gastroenterology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

5 REFERENCES

1. Turner, T. OSE Review #2009-1423: Carbaglu Proprietary Name Review. October 20, 2009.

2. 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.

3. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

USAN Stems List contains all the recognized USAN stems.

4. Division of Medication Error Prevention and Analysis proprietary name 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22562	ORIG-1	ORPHAN EUROPE	CARBAGLU (CARGLUMIC ACID)

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

/s/

ZACHARY A OLESZCZUK
02/25/2010

DENISE P TOYER
02/25/2010

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:	October 20, 2009
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Kellie Taylor, Pharm.D., M.P.H., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Carbaglu (Carglumic Acid) Tablets 200 mg
Application Type/Number:	NDA 022562
Applicant:	Orphan Europe, SARL
OSE RCM #:	2009-1423

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

CONTENTS

EXECUTIVE SUMMARY

Carbaglu is the proposed proprietary name for Carglumic Acid Tablets. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Carbaglu, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from Orphan Europe, SARL dated July 30, 2009 for an assessment of the proposed proprietary name, Carbaglu, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. In addition, the Applicant submitted the results of their independent study in support of their proposed proprietary name.

The Applicant also submitted draft container labels, carton and insert labeling. The labels and labeling will be reviewed separately under OSE Review #2009-1642.

1.2 REGULATORY HISTORY

The NDA for Carbaglu (022562) was submitted on June 17, 2009. It has been granted orphan designation and fast track review status.

Carbaglu received European marketing authorization in 2003.

1.3 PRODUCT INFORMATION

Carbaglu (Carglumic acid) Tablets is proposed for the specific treatment of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS deficiency). The recommended initial dose is 100 to 250 mg/kg/day. It is recommended to divide the total dose into two to four doses to be given before meals or feedings. The tablets may be dispersed in a minimum of (b) (4) of water and ingested immediately or administered through a syringe via a nasogastric tube. Carbaglu will be available in a single strength dispersible tablet (200 mg). The white, elongated tablet contains three score marks and is engraved on one side. The product will be packaged as 5 or 60 tablets in a polypropylene bottle with a polyethylene cap and dessicant unit. Before opening, Carbaglu should be stored refrigerated. After first opening of the container, it should not be refrigerated or stored above 30˚C (86˚F). The container should be tightly closed in order to protect from moisture. The date of opening should be written on the tablet container, which should be discarded one month after first opening.

In their submission, the applicant indicates that there are not more than 10 patients with NAGS deficiency in the United States. Thus, the product will be dispensed to each doctor/patient individually.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2, and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Carbaglu.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'C' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Carbaglu, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (three, capital letter 'C', lower case 'b', and lower case 'l'), down strokes (one, lower case 'g'), cross strokes (none), and dotted letters (none). Additionally, some letters in Carbaglu may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Carbaglu.

When searching to identify potential names that may sound similar to Carbaglu, the DMEPA staff searches for names with similar number of syllables (three), stresses (CAR-ba-glu, car-BA-glu, or car-ba-GLU), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary. For example, 'C' may sound like 'K' or 'Q'. Likewise, 'b' may sound like 'p'; 'u' may sound like 'ue' or 'oo'. (Also see Appendix B).

The Applicant's intended pronunciation of the proprietary name is presented as (KARB'a'gloo). However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

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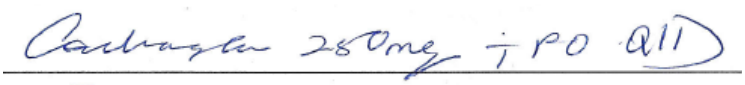
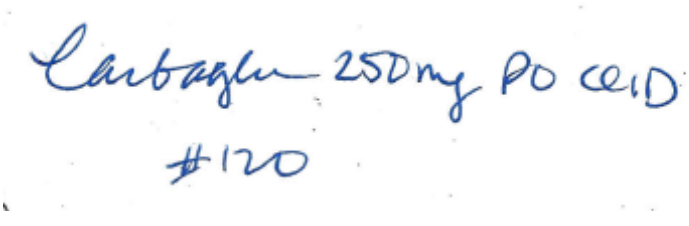
[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies.

Figure 1. Carbaglu Study

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: 	"Carbaglu 250 mg PO four times a day"
Outpatient Prescription: 	

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name, conducted by the Applicant. The Division of Medication Error Prevention and Analysis conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in DMEPA's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk associated with proposed name, the Safety Evaluator compares the findings of his/her overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 13 names as having some similarity to the name Carbaglu.

All 13 names were thought to look like Carbaglu. These include: Cardizem, Carbachol, Carbatrol, Carbilev, Carbidopa, Gardasil, Cerebyx, Acarbose, Carba-XP, Carbacot, Carbogel, Cafergot, and Colazal.

Our searches also revealed that the proposed name, Carbaglu, is trademarked in many foreign countries. We note from the applicant's website (www.orphan-europe.com) that Carbaglu, which contains Carglumic acid, is currently available in Europe.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of August 20, 2009.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Carbaglu.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

For the study conducted on August 31, 2009, a total of 28 practitioners responded. None of the responses overlap with an existing name. Ten of the participants interpreted the drug name correctly as "Carbaglu", with correct interpretation occurring in both the verbal and outpatient studies. The remainder of participants misinterpreted the drug name. The majority of misinterpretations in the written studies involved misinterpretation of the last syllable (Carbaglin, Carbagla, or Carbagler). In the verbal studies, all responses were misspelled phonetic variations of the proposed name, Carbaglu. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

In the external proposed proprietary name risk assessment, the Applicant conducted an independent search of two FDA electronic databases (Drugs@FDA and Orange Book), as well as the USAN website. The Applicant identified and evaluated a total of four names thought to have some potential for confusion with the name Carbaglu. The names are: Carbachol, Carbamazepine, Carbastat, and Carbatrol. Of the four names identified by the Applicant, three were also identified by DMEPA during the database searches: Carbachol, Carbastat, and Carbatrol. The remaining name (Carbamazepine) was evaluated as part of the Safety Evaluator Risk Assessment.

Additionally, the Applicant noted that the proposed name, Carbaglu, does not contain a USAN stem as of July 26, 2009.

The Applicant indicates "there is no possibility of medical error since the other drug products have totally different appearances and pharmacologic/therapeutic categories".

3.5 COMMENTS FROM THE DIVISION OF GASTROENTEROLOGY PRODUCTS (DGP)

DMEPA notified the Division of Gastroenterology Products via e-mail that we had no objections to the proposed proprietary name, Carbaglu, on September 18, 2009. Per e-mail correspondence, the Division of Gastroenterology Products on September 24, 2009 indicated that they concur with our assessment of the proposed proprietary name, Carbaglu.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in eight additional names which were thought to look or sound similar to Carbaglu and represent a potential source of drug name confusion.

Seven names were identified to have look-alike similarities (Carbastat, Carbargal, Carbopol, Carbaryl, Carbocal, Cabergoline, and Carafate). The remaining name, Carbo Fuel, was identified to have look-alike and sound-alike similarities.

Additionally, the primary Safety Evaluator identified two medical abbreviations with look-alike and sound-alike similarities to Carbaglu: 'carb' which represents carbohydrate and 'glu' which represents glucose. However, these abbreviations are not typically used in prescribing and dispensing medications.

Accordingly, we evaluated a total of 22 names: 13 identified in Database and Information Sources (Section 3.1), one identified in the External Study (Section 3.4), and eight identified in this section by the primary Safety Evaluator.

4 DISCUSSION

Neither DDMAC nor the Review Division had concerns with the proposed name. DMEPA identified and evaluated 22 names for their potential similarity to the proposed name, Carbaglu. Four names lacked orthographic and/or phonetic similarity and were not evaluated further (see Appendix D).

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining 18 names and lead to medication errors. This analysis determined that the name similarity between Carbaglu and the identified names was unlikely to result in medication errors with any of the 18 products for the reasons presented in Appendices E through M. Additionally, no other sources of confusion were identified by DMEPA. This finding is consistent with and supported by an independent risk assessment of the proprietary name conducted and submitted by the Applicant.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Carbaglu, is not vulnerable to name confusion that could lead to medication errors, nor is it promotional. Our assessment is supported by the findings of the independent study conducted and submitted by the Applicant. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Carbaglu, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

If you have further questions or need clarifications, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Carbaglu, and have concluded that it is acceptable.

Carbaglu will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

6 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. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

5. Division of Medication Error Prevention and Analysis proprietary name 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. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

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 potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. 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. [3]

For the proposed proprietary name, DMEPA staff conducts searches of a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment 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 focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [4] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. 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.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the 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. Because drug name confusion can occur at any point in the medication use process, DMEPA staff 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.[5] DMEPA provides the product characteristics considered for this review in Section 1.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly, and even dissimilarly, spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such 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 are in Table 1 below. In addition, the DMEPA staff 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. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[5] 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**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 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, the DMEPA staff also 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 staff conducts searches of 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 using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff 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, the DMEPA staff 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.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. 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). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed name.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of 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 Analysis 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 handwritten and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written; each consists 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 the 123 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 send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for its comments or concerns with the proposed proprietary name and 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 or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys its decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

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, conducts a Failure Mode and Effects Analysis, and provides an overall 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.[6] 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 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 Section 1. 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, prescription studies, and 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?"***

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. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses 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.

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 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

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

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.

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 is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to 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 Applicant 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. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission (TJC), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug 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 a preventable source of medication error that, in many instances, the Agency and/or Applicant 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. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant 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 Applicants 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. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Carbaglu	Scripted may appear as	Spoken may be interpreted as
Capital 'C'	'A', 'G', 'L', or 'E'	K, Q
Lower case 'a'	'o', 'u', 'c', 'ce', or 'ci'	o, u, i
Lower case 'r'	'n', 'v', 'u', 'x', or 't'	
Lower case 'b'	'v', 'l', 'li', or 't'	p
Lower case 'g'	'q', 'j' , 'z', 'p', or 's'	
Lower case 'l'	'e', 't', or 'i'	
Lower case 'u'	'a', 'o', 'n', 'v', or 'y'	ue, oo

Appendix C: Carbaglu Prescription Study Responses (conducted August 31, 2009)

Inpatient Medication Order	Voice Prescription	Outpatient Prescription
Carbagla	Carbaglu	Carbagler
Carbagla	Carbaglu	Carbaglin
Carbagla	Carbaglu	Carbaglin
Carbagla	Carbaglu	Carbaglin
Carbagla	Carbaglue	Carbaglin
Carbagler	Carbaglute	Carbaglu
Carbaglin	Carbiglue	Carbaglu
	Carpaglue	Carbaglu
	Carpaglue	Carbaglu
	Karpaglu	Carbaglu
		Carbaglu

Appendix D: Names lacking convincing look-alike or sound-alike similarities with Carbaglu

Proprietary Name	Source
Carbidopa	EPD
Cerebyx	EPD
Colazal	EPD
Carbamazepine	Applicant's independent search

Appendix E: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Carbaglu	Country	Description
Carbargal	Look/Sound	Venezuela	Activated charcoal and simethicone
Carbocal	Look	Spain	Calcium carbonate

Appendix F: Product that is not currently marketed in the U.S.

Proprietary Name	Similarity to Carbaglu	Description	Date Discontinued
Carbastat	Look	(carbachol) intraocular solution; 0.01% ANDA 073677 RLD (Miostat) currently available	6/11/2007

Appendix G: Natural Medicine Product (which is not dispensed pursuant to a prescription)

Proprietary Name	Similarity to Carbaglu	Description	Use
Carbo Fuel Complex Carbohydrate Peak Performance Energy Drink **Discontinued by manufacturer**	Look/Sound	Carbohydrates, Vitamin b1, Vitamin B2, Vitamin B3, Vitamin B6, Pantothenic Acid, Biotin, potassium, Magnesium, Yeast-Free GTF Chromium, Inosine, L-Carnitine, CoQ10, Lipoic Acid, Pantetheine, Pyridoxine-Alpha-Ketoglutarate, Soluble Potassium, Citrates, Aspartates, Fumarates, Malates, Alpha-Ketoglutarates	Nutritional supplement

Appendix H: Product for which no information could be found in the standard databases listed in Section 6

Proprietary Name	Similarity to Carbaglu	Description	Source
Carbacot	Look	Search retrieved monographs for methocarbamol; no product characteristics were identified in any of the standard references	Facts and Comparisons

Appendix I: Products with different context of use than Carbaglu

Proprietary Name	Similarity to Carbaglu	Description
Carbogel	Look	Carbopol gel in a water base; for use with water-soluble active ingredients in topical gel (pharmaceutical compounding)
Carbopol	Look	Carbomer; used in pharmaceutical manufacturing as suspending agents, gel bases, emulsifiers, and binding agents in tablets
Carbaryl	Look	Carbamate insecticide; used as a 0.5% or 1% lotion or shampoo in the treatment of head and pubic pediculosis (Carbaryl lotion BP 2009) ; also used as a topical ectoparasiticide in veterinary practice and as an agricultural, horticultural, and household insecticide (foreign product – identified in Martindale)

Appendix J: Products with no overlap in strength or dose

Carbaglu **(carglumic acid)**		**Dispersible Tablets:** **200 mg** **the tablets may be dispersed in a minimum o (b) (4) of water and ingested immediately or administered through a syringe via a nasogastric tube**	**The recommended initial dose is 100 to 250 mg/kg/day; it is recommended to divide the total daily dose into 2 to 4 doses to be given before meals or feedings**
Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength**	**Usual Dose (if applicable)**
Cardizem (diltiazem HCl)	Look	**Cardizem tablets**: 30 mg, 60 mg, 90 mg, 120 mg **Cardizem CD** (extended release capsules) : 120 mg, 180 mg, 240 mg, 300 mg, 360 mg **Cardizem LA** (extended release tablets): 120 mg, 180 mg, 240 mg, 300 mg, 360 mg, 420 mg **Cardizem SR** (extended release capsules): 60 mg, 90 mg, 120 mg, 180 mg **Discontinued – generics available** **Cardizem Injection** (b) (4) **Discontinued - generics available**	**Cardizem**: Initially, 30 mg orally 3 or 4 times a day, gradually increasing dosage at 1 or 2 day intervals up to 480 mg per day **Cardizem CD and LA**: Initially, 120 to 240 mg orally once daily. The usual dose range is 240 to 360 mg orally once daily, however, some patients require 480 mg orally once daily. **Cardizem SR**: Initially, 60 to 120 mg orally twice daily. Increase dose if necessary. The usual dosage range during clinical studies was 120 to 180 mg orally twice daily. Maximum dosage is 360 mg per day. **Cardizem Injection**: Bolus: Initially, 0.25 mg/kg (20 mg is a typical dose) administered as an IV bolus over 2 minutes. If necessary, a second bolus dose of 0.35 mg/kg (25 mg is a typical dose) administered as above. Infusion: 10 mg/hr IV infusion started immediately following the IV bolus. Do not exceed 15 mg/hr. Should not be administered for longer than 24 hours.

Carbilev (carbidopa/levodopa) (b) (4) RLD is Sinemet	Look	Tablets for Oral Suspension: 10 mg/100 mg; 25 mg/100 mg; 25 mg/250 mg	The recommended initial dose is one 25 mg/100 mg tablet orally 3 times per day. Dosage may be increased by one tablet every day or every other day, as necessary, until a maximum of 8 tablets per day is reached. If the 10 mg/100 mg tablet is used, the dosage may be started with one tablet 3 or 4 times a day. Dosage may be increased by one tablet every day or every other day until a total of 8 tablets is reached.
Acarbose (active ingredient in Precose; generic acarbose also available)	Look	Tablets: 25 mg, 50 mg, 100 mg	**Initial Dosage:** The recommended starting dosage is 25 mg given orally three times daily at the start (with the first bite) of each main meal. However, some patients may benefit from more gradual dose titration to minimize gastrointestinal side effects. This may be achieved by initiating treatment at 25 mg once per day and subsequently increasing the frequency of administration to achieve 25 mg three times daily. **Maintenance Dosage:** Once a 25 mg three times daily dosage regimen is reached, dosage should be adjusted at 4 to 8 week intervals based on one-hour postprandial glucose or glycosylated hemoglobin levels, and on tolerance. The maintenance dose ranges from 50 mg three times daily to 100 mg three times daily

Appendix K: Products with no overlap in dose or frequency

Carbaglu **(carglumic acid)**		**Dispersible Tablets:** **200 mg**	**The recommended initial dose is 100 to 250 mg/kg/day; it is recommended to divide the total daily dose into 2 to 4 doses to be given before meals or feedings; the tablets may be dispersed in a minimum of (b) (4) of water and ingested immediately or administered through a syringe via a nasogastric tube**
Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength**	**Usual Dose/Frequency**
Carba-XP (carbetapentane citrate and guaifenesin)	Look	Oral solution: carbetapentane citrate 20 mg/5 mL and guaifenesin 100 mg/5 mL	5 mL to 10 mL orally every 4 to 6 hours (maximum dose of carbetapentane is 240 mg per day; maximum dose of guaifenesin is 2400 mg per day)
Cafergot (caffeine/ergotamine tartrate)	Look	Tablets : 100 mg/1 mg Rectal suppository : 100 mg/2 mg (**Discontinued- generics available**)	Oral: 1 to 2 tablets orally at the first sign of an attack. Then, 1 to 2 tablets orally after 30 minutes, if needed. Do not exceed 6 tablets for one attack or per 24 hours or 10 tablets per week Rectal: Initially, 1 suppository per rectum; repeat initial dose in 1 hour if necessary; maximum dose of 2 suppositories per attack; do not exceed 5 suppositories per week
Cabergoline (active ingredient in Dostinex) **Dostinex discontinued; generics available**	Look	Tablets : 0.5 mg	The recommended dosage for initiation of therapy is 0.25 mg twice a week. Dosage may be increased by 0.25 mg twice weekly up to a dosage of 1 mg twice a week according to the patient's serum prolactin level.

Appendix L: Single Strength Products with Differentiating Product Characteristics

Product name with potential for confusion	Similarity to Product Name	Strength	Usual Dose	Other Differentiating Product Characteristics
Carbaglu (carglumic acid)		**Dispersible Tablets: 200 mg**	**The recommended initial dose is 100 to 250 mg/kg/day; it is recommended to divide the total daily dose into 2 to 4 doses to be given before meals or feedings; the tablets may be dispersed in a minimum of (b) (4) mL of water and ingested immediately or administered through a syringe via a nasogastric tube**	
Carbachol (active ingredient in: Miostat; Carbastat) **Carbastat discontinued** **Generic Carbachol discontinued**	Look	Miostat intraocular solution: 0.01%	No more than one-half milliliter should be gently instilled into the anterior chamber for the production of satisfactory miosis. It may be instilled before or after securing sutures. Miosis is usually maximal within two to five minutes after application	**Dosage form:** Intraocular solution vs. dispersible tablet **Route of administration:** Intraocular injection vs. oral **Dose:** No more than 0.5 mL vs. 100 to 250 mg/kg/day **Frequency of administration:** During procedure vs. divided into 2 to 4 doses to be given before meals or feedings **Setting of use:** Administered by healthcare practitioner vs. outpatient use
Gardasil Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant	Look	Suspension for intramuscular injection: 0.5 mL	0.5 mL via intramuscular injection at the following schedule: 0, 2 months, 6 months	**Dosage form:** Suspension for injection vs. dispersible tablet **Route of administration:** Intramuscular injection vs. oral **Dose:** 0.5 mL vs. 100 to 250 mg/kg/day **Frequency of administration:** At 0, 2 months, 6 months vs. divided into 2 to 4 doses to be given before meals or feedings **Setting of use:** Administered by healthcare practitioner vs. outpatient use

Appendix M: Products with overlap in strength, frequency, or dosage form

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Carbaglu (carglumic acid)	**Dispersible tablets: 200 mg**	**The recommended initial dose is 100 to 250 mg/kg/day; it is recommended to divide the total daily dose into 2 to 4 doses to be given before meals or feedings; the tablets may be dispersed in a minimum of (b) (4) of water and ingested immediately or administered through a syringe via a nasogastric tube**
Carbatrol (carbamazepine) extended-release capsules 100 mg, 200 mg, 300 mg	Overlapping strength (200 mg) Overlapping frequency (2 times per day) Orthographic similarity (same beginning letters 'Carba')	The orthographic differences in the names help to distinguish between them. Although the names share the same beginning letters ('Carba'), the downstroke of the letter 'g' in Carbaglu differentiates it from Carbatrol, which has the upstroke of the letter 't' in the same position. Finally, the ending letters of the names ('lu' vs. 'rol') do not look similar. The risk of medication errors is further reduced by the fact that these products have different dosage regimens. The usual initial dose of Carbatrol for the treatment of epilepsy is 200 mg orally twice daily and may be increased to 400 mg to 600 mg twice daily. Carbaglu is individually dosed based on the patient's weight (100 to 250 mg/kg/day) divided into 2 to 4 doses. Each dose will be calculated in terms of milligrams and may consist of multiple tablets and/or fractions of tablets.
Carafate (sucralfate) Tablets: 1 gram (in practice the tablets may be dispersed in 10 mL of water to create a suspension) Oral Suspension: 1 gram/10 mL	Overlapping dosage form (dispersible tablets) Overlapping frequency (2 to 4 times per day) Orthographic similarity (similar beginning letters 'Carba' vs. 'Caraf')	The orthographic differences in the names help to distinguish between them. Although the beginning letters of the names may look similar when scripted ('Carba' vs. 'Caraf''), the downstroke of the letter 'g' in Carbaglu differentiates it from Carafate. The risk of medication errors is further reduced by the fact that these products have different dosage regimens. The usual dose of Carafate for an active duodenal ulcer is 1 gram orally 4 times per day. Maintenance therapy is 1 gram orally twice a day. Carbaglu is individually dosed based on the patient's weight (100 to 250 mg/kg/day) divided into 2 to 4 doses. Each dose will be calculated in terms of milligrams and may consist of multiple tablets and/or fractions of tablets.

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