CENTER FOR DRUG EVALUATION AND RESEARCH

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PROPRIETARY NAME REVIEW(S)

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Date:	July 20, 2010
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Subject:	Proprietary Name Review
Drug Name(s):	Cuvposa (Glycopyrrolate) Oral Solution 1 mg/5 mL
Application Type/Number:	NDA 022571
Applicant/Applicant:	Shionogi Pharma, Inc.
OSE RCM #:	2010-927

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EXECUTIVE SUMMARY

This review evaluates the acceptability of the proposed proprietary name Cuvposa from a safety and promotional perspective based on the product characteristics provided by Shionogi Pharma, Inc. DMEPA concludes the proposed proprietary name, Cuvposa, is acceptable. The Applicant will be notified by letter, and the proposed proprietary name must be re-evaluated 90 days prior to approval of the NDA.

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 responds to a request from Shionogi Pharma, Inc., dated April 28, 2010, for an assessment of the potential for confusion of the proposed proprietary name, Cuvposa, with other proprietary or established drug names in the usual practice settings. The Applicant submitted an external study conducted by (b) (4) in support of their proposed proprietary name. Shionogi also submitted labels and labeling for review as part of the original NDA application which are reviewed under separate cover (OSE Review # 2010-41).

1.2 REGULATORY HISTORY

In accordance with Section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act, Shionogi Pharma, Inc., submitted this New Drug Application for Glycopyrrolate Oral Solution 1 mg/5 mL on September 25, 2009. This NDA relies on the FDA's previous findings of safety and effectiveness for the listed drug Robinul (glycopyrrolate) Injection 0.2 mg/mL, via cross reference to NDA 017558, sponsored by Baxter Healthcare as well as Robinul (glycopyrrolate) Injection 0.2 mg/mL, via cross reference to NDA 014764, sponsored by A.H. Robins. Furthermore, Shionogi is the owner and sponsor of Robinul and Robinul Forte (glycopyrrolate) tablets 1 mg and 2 mg, NDA 012827. However, Shionogi only has rights to the proprietary name "Robinul" in connection with the tablet formulation. Glycopyrrolate is indicated for "treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients", and it received an orphan drug designation from FDA for this indication on June 9, 2006.

Shionogi previously requested a review of the proposed proprietary name, (b) (4) during IND review. DMEPA reviewed the proposed proprietary name, (b) (4) Shionogi subsequently withdrew the proposed proprietary name, (b) (4).

On December 10, 2009, Shionogi requested a review of the proprietary name (b) (4). (b) (4)

On April 20, 2010, Shionogi requested a review of the proprietary name (b) (4), but subsequently withdrew this request on April 28, 2010.

1.3 PRODUCT INFORMATION

Cuvposa is the proposed proprietary name for Glycopyrrolate Oral Solution (1 mg/5 mL). The Applicant is seeking approval for the treatment of (b) (4) (chronic (b) (4) severe) drooling in pediatric patients 3-16 years of age.

The usual dosage for this product varies widely from patient to patient. Doses are often initiated at approximately 0.01 – 0.02 mg/kg three times daily and titrated in increments of 0.02 mg/kg every 5-7 days. (b) (4) The maximum recommended dosage is 0.1 mg/kg three times daily.

Cuvposa will be supplied as 1 mg/5 mL, clear cherry-flavored oral solution in a 16 ounce bottle; (b) (4) A dosing device is not supplied with the product. Cuvposa should be stored at USP controlled room temperature, between 20ºC to 25ºC with excursions permitted to 15ºC to 30ºC. This product will not utilize a unique delivery system.

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 Cuvposa.

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 Cuvposa, 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 (7 letters), upstrokes (1, capital 'C'), downstrokes (1, lower case 'p'), cross strokes (none), and dotted letters (none). Additionally, several letters in Cuvposa 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 Cuvposa.

When searching to identify potential names that may sound similar to Cuvposa, the DMEPA staff search for names with similar number of syllables (three), stresses (CUV-po-sa, cuv-PO-sa, cuv-po-SA), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (see Appendix B). The Applicant's intended pronunciation (kuv-POE-suh) was also taken into consideration, as it was included in the Proprietary Name Review Request. Furthermore, 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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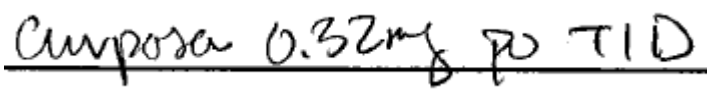
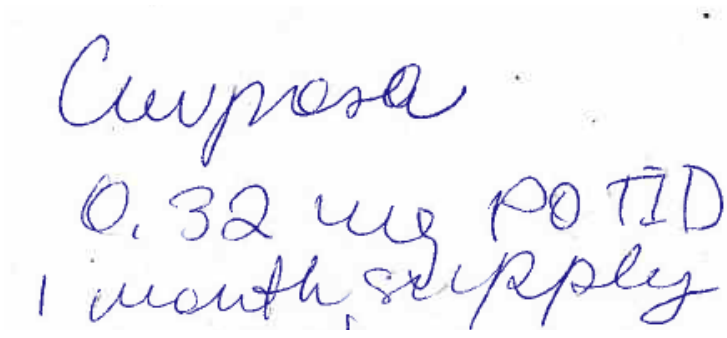
[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[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. Cuvposa Study (conducted on May 6, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: 	Cuvposa 0.32 mg by mouth three times daily
Outpatient Prescription: 	

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. 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 the proposed name, the Safety Evaluator compares the findings of their 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 DMEPA safety evaluator database searches yielded a total of 20 names as having some similarity to the name Cuvposa. However, one of the names, Compoz, is a Canadian drug name and will not be evaluated in this review. Thus, the safety evaluator searches of the database and information sources searched yielded a total of 19 names.

All 19 names were thought to look like Cuvposa by the DMEPA safety evaluators. These include Aczone, Ampyra, Avapro, Campral, Camptosar, Canasa, Cardura, Cavigen, Cimzia, Cipro, Crixivan, Cubicin, Embeda, Emtriva, (b) (4), Girosa, Lovaza, Loxapine, and Luveris.

Additionally, DMEPA safety evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of May 11, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the 19 names identified by DMEPA staff (see Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Cuvposa.

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

A total of 33 practitioners responded to the FDA prescription analysis studies. Only two of the practitioners interpreted the name correctly as "Cuvposa." Five practitioners misinterpreted the name Cuvposa as Cuposa in the verbal prescription study, omitting the 'v.' Cuposa is not an approved proprietary name. Eleven out of twelve practitioners misinterpreted the 'v' in Cuvposa as an 'r' in the inpatient prescription studies. Nine out of eleven practitioners misinterpreted the suffix '-osa' as '-resa' in the outpatient prescription studies. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL STUDY

The proprietary name risk assessment submitted by the Applicant found the name acceptable. They identified a total of 12 drug names thought to have some potential for confusion with the name Cuvposa: Canasa, Cefprozil, Cipro, Compazine, Copaxone, Cortisporin, Coumadin, Cuprimine, Cymbalta, Kariva, Kuvan, and Lupron. Two of the names, Canasa and Cipro, were identified in the database searches (see Section 3.1 above). The remaining 10 names will be added to the safety evaluator assessment.

3.5 SAFETY EVALUATOR RISK ASSESSMENT OF PROPOSED PROPRIETARY NAME

The primary Safety Evaluator identified 6 additional names which were thought to look similar to Cuvposa and represent a potential source of drug name confusion.

The names identified by the primary Safety Evaluator to have look-alike similarities are (b) (4) Ampriva[***], Anaprox, (b) (4) Compro, and Lamprene.

[***] This is proprietary and confidential information that should not be released to the public.

A total of 35 names were identified for their similarity to Cuvposa from the combined searches: 6 identified by the primary safety evaluator, 10 identified in the external prescription study, and 19 identified in section 3.1 above.

3.6 COMMENTS FROM THE DIVISION OF DERMATOLOGY AND DENTAL PRODUCTS (DDDP)

3.6.1 Initial Phase of Review

In a response to the OSE May 25, 2010, e-mail, the Division of Dermatology and Dental Products (DDDP) did not have any objections to the proposed proprietary name, Cuvposa.

3.6.2 Midpoint of Review

On June 2, 2010, DMEPA notified the Division of Dermatology and Dental Products via e-mail that we had objections to the proposed proprietary name, Cuvposa. Per e-mail correspondence from DDDP on June 7, 2010, they indicated that there were no reported concerns with our assessment of the proposed proprietary name, Cuvposa.

4 DISCUSSION

This proposed name, Cuvposa, was evaluated from a safety and promotional perspective. Furthermore, input from pertinent disciplines involved with the review of this application was considered accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA and the Division of Dermatology and Dental Products concurred with the findings of the promotional assessment.

4.2 SAFETY ASSESSMENT

In total, 35 names were evaluated by DMEPA. Twenty of the 35 names were eliminated for the following reasons (see Appendices D, E, and F): 18 of the 20 names lacked convincing orthographic and/or phonetic similarity to the proposed proprietary name Cuvposa, one name was a proposed proprietary name found unacceptable by DMEPA, and one name had limited available product characteristic information.

Failure mode and effect analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining 15 names and lead to medication errors. This analysis determined that the name similarity to Cuvposa was unlikely to result in medication errors with any of the 15 products for the reasons presented in Appendices G and H. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Cuvposa, is not promotional nor is it vulnerable to name confusion that can lead to medication errors. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Cuvposa, for this product at this time. Our analysis is consistent with the external risk assessment conducted by (b) (4) that was provided by the Applicant. The Applicant will be notified via letter.

5.1 COMMENTS TO THE APPLICANT

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

The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

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.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://csi.micromedex.com)

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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. This is a database which was created for the Division of Medication Error Prevention and Analysis, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

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

5. 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.

6. 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.

7. 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.

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

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. U.S. Patent and Trademark Office (http://www.uspto.gov)

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. 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.

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

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

13. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. 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.

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

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

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

A web-based searchable version of the Drug Information Handbook.

17. 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 search 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.

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 one.

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

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

[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.

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 (see Table 1 below for details). 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.

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-stokes 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 use 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 review 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 names.

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 handwriting and verbal communication of the name, inpatient medication orders and 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 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 their 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 their 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 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 Section one. 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?"***

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

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

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 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), Joint Commission on Accreditation of Hospitals (JCOAH), 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, Cuvposa	Scripted may appear as	Spoken may be interpreted as
Capital 'C'	A, l, O	K
lower case 'c'	a, o	k
lower case 'u'	a, ei, er, ie, m, n, o, re, v, w, y	any vowel
lower case 'v'	n, r, u	f
lower case 'p'	g, j, y, yn, ys	
lower case 'o'	a, e, re, ri,or u	any vowel
lower case 's'	a, g, n, o	
lower case 'a'	ce, ci, cl, e, o, or u	Any vowel

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
Curposa	Cievpresa	Couposa
Cuvposa	Cerpresa	Queuposa
Curposa	Curprosa	Cuposa
Curposa	Cuvpresa	Cuposa
Curposa	Cuvpresa	Cufposa
Aurposa	Cuvpresa	Kuposa
Curposa	Cuvpresa	Cuposa
Aurposa	Cuvposa	Cuposa
Curposa	Curpresa	Cuposa
Carposa	Curpresa	Kuposa
Curposa	Cuvpresa	
Curposa		

Appendix D: Drug names that lack convincing orthographic and/or phonetic similarities

Name	Similarity to Cuvposa
Camptosar	Look alike
Cefprozil	(b) (4)
Cimzia	Look alike
Cipro	(b) (4)
Compazine	(b) (4)
Cortisporin	(b) (4)
Coumadin	(b) (4)
Crixivan	Look alike

Cubicin	Look alike
Cuprimine	(b) (4)
Cymbalta	(b) (4)
Embeda	Look alike
Emtriva	Look alike
Girosa	Look alike
Kariva	(b) (4)
Kuvan	(b) (4)
Lupron	(b) (4)
Luveris	Look alike

Appendix E: Unapproved proprietary names

Proprietary Name	Similarity to Cuvposa	Status and Date
Ampriva*** (Dalfampridine)	Look alike	(b) (4) This drug was approved under the proprietary name Ampyra.

Appendix F: Names which have limited product characteristic information

Proprietary Name	Similarity to Cuvposa	Comments
(b) (4)	Look alike	Name found in US Patent and Trademark search, but no active ingredients listed. More detailed product characteristics could not be found in Micromedex, Lexi-Comp, Drugs@FDA, Clinical Pharmacology On-line, Redbook, Natural Medicines Database, Stat-Ref, or DARRTS.

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

Appendix G: Products with orthographic, phonetic and/or multiple differentiating product characteristics minimize the risk for medication errors

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
Aczone (Dapsone) Gel	Look alike	5%	Apply a pea sized amount in a thin layer to the acne affected areas twice daily.	Route of Administration: *Oral vs. topical* Dosage Form: *Oral Solution vs. Gel* Usual Dose: *0.01 to 0.1 mg/kg vs. pea-sized amount* Strength: *1 mg/5 mL vs. 5%* Frequency: *Three times daily vs. twice daily*
[redacted]				(b) (4)
Anaprox (Naproxen Sodium) Tablet	Look alike	275 mg	275 mg to 550 mg by mouth twice daily	Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is much lower than the dose used for Anaprox.* Strength: *1 mg/5 mL vs. 275 mg or 550 mg* Frequency: *Three times daily vs. twice daily*

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

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
Campral (Acamprosate Calcium) Tablet, Delayed Release	Look alike	333 mg	Two-333mg tablets by mouth three times a day	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix '–posa' in Cuvposa does not look like the suffix '–pral' in Campral due to an upstroke 'l' in Campral.* Strength: *1 mg/5 mL vs. 333 mg* Patient Population: *Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Campral has not been established in children.*
Canasa (Mesalamine) Suppository	Look alike	1000 mg	One-1000mg suppository rectally once daily at bedtime	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, Cuvposa contains a downstroke 'p,' whereas Canasa contains no downstrokes.* Route of Administration: *Oral vs. rectal* Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is much lower than the 1000 mg dose used for Canasa. Additionally, Canasa may be ordered as a dose of 'one suppository,' which would help to further differentiate it from Cuvposa.* Frequency: *Three times daily vs. once daily at bedtime*

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
Cardura (Doxazosin Mesylate) Tablet	Look alike	1 mg, 2 mg, 4 mg, 8 mg	The dose is individualized for each patient. Anywhere from 1 mg to 16 mg daily at bedtime can be prescribed.	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, Cardura contains an upstroke 'd,' whereas Cuvposa contains no upstrokes. Additionally, Cuvposa contains a downstroke 'p,' whereas Cardura contains no downstrokes.* Frequency: *Three times daily vs. once daily at bedtime* Patient Population: *Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Cardura has not been established in children.*
Cavigen Capsule (This dietary supplement contains lyophilized fish roe and ginkgo biloba leaf extract)	Look alike	NA	Take one capsule three times daily after meals for 4-8 weeks, then decrease to one capsule once or twice daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix '–osa' in Cuvposa does not look like the suffix '–en' in Cavigen. Additionally, the downstroke 'p' in Cuvposa has a placement within the name that differs from the placement of the downstroke 'g' in Cavigen.* Patient Population: *Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas Cavigen is for use in adult males with erectile dysfunction.* Marketing: *Cuvposa will be marketed as an Rx only product whereas Cavigen is an over-the-counter dietary supplement not likely to be written as a prescription*

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
[redacted]				(b) (4)
Compro (Prochlorperazine) Suppository	Look alike	25 mg	Insert one-25 mg suppository rectally twice daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix '–osa' in Cuvposa does not look like the suffix '–ro' in Compro.* Route of Administration: *Oral vs. rectal* Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is lower than the dose for Compro. Additionally, Compro may be ordered in a dose of 'one suppository' which helps to further distinguish it from Cuvposa.* Frequency: *Three times daily vs. twice daily*

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
Copaxone (Glatiramer Acetate) Injection	Look alike	20 mg/ syringe	Inject 20 mg subcutaneous injection once daily	Route of Administration: *Oral vs. subcutaneous injection* Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is lower than the dose used for Copaxone.* Strength: *1 mg/5 mL vs. 20 mg/syringe* Frequency: *Three times daily vs. once daily*
Lamprene (Clofazimine) Soft Gelatin Capsules	Look alike	50 mg	Take 100 mg by mouth once daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix '–osa' in Cuvposa does not look like the suffix '–rene' in Lamprene.* Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is much lower than the dose for Lamprene.* Frequency: *Three times daily vs. once daily*
Lovaza (Omega-3-acid ethyl esters) Capsule	Look alike	1 gram	Take 4 grams daily as a single dose, or 2 grams twice daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix –posa in Cuvposa does not look like the suffix –aza in Lovaza. Additionally, the placement of the downstroke 'z' in Lovaza differs from the placement of the downstroke 'p' in Cuvposa. When scripted, the 'z' in Lovaza may or may not be scripted as a downstroke.* Usual Dose: *Cuvposa will likely be ordered in a dose by 'mg' or 'mL' of solution, whereas Lovaza will likely be ordered by number of capsules or grams.*

Product name with potential for confusion	Similarity to Cuvposa	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Cuvposa (Glycopyrrolate) Oral Solution	**N/A**	**1 mg/5 mL**	**0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients**	**N/A**
				Patient Population: *Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Lovaza has not been established in children.*
Loxapine (Loxapine Succinate) Capsule	Look alike	5 mg, 10 mg, 25 mg, 50 mg	Start with 10 mg twice daily then titrate up to effect. Loxapine is usually given in divided doses two to four times a day. Daily dosage should be adjusted to the individual patient's needs based on severity of symptoms.	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the infix '–uv-' in Cuvposa does not look like the infix '-oxa-' in Loxapine. The placement of the downstroke in Loxapine also differs from the placement of the downstroke in Cuvposa.* Strength: *1 mg/5 mL vs. 5 mg, 10 mg, 25 mg, or 50 mg* Patient Population: *Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Loxapine has not been established in children.*
Avapro (Irbesartan) Tablet	Look alike	75 mg, 150 mg, 300 mg	Take 150 mg to 300 mg by mouth once daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *When scripted, the suffix '–osa' in Cuvposa does not look like the suffix '–ro' in Avapro.* Usual Dose: *Cuvposa 0.1 mg/kg will not likely exceed a 10 mg dose (for children 3-16 years), which is lower than the dose for Avapro.* Strength: *1 mg/5 mL vs. 75 mg, 150 mg, or 300 mg* Frequency: *Three times daily vs. once daily*

Appendix H: Potentially confusing names with orthographic and multiple differentiating product characteristics that decrease the risk of medication error

Proposed Name: **Cuvposa (Glycopyrrolate) Oral Solution**	**Strength:** **1 mg/5 mL**	**Usual Dose and Administration:** **0.01 to 0.1 mg/kg three times a day (TID) in pediatric patients (3 – 16 years old)**
Failure Mode: Name confusion	**Causes (can be multiple)**	**Prevention of Failure Mode**
Ampyra (Dalfampridine) Extended Release Tablet **Strengths:** 10 mg **Usual Dose and Administration:** 10 mg by mouth twice daily	**Orthographic Similarities:** The Prefix Amp- can look like the prefix Cuv- when scripted. **Overlap in Dose:** May have overlap in 10 mg dose	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. **Rationale:** When scripted, Cuvposa contains only one downstroke ('p') whereas Ampyra contains two downstrokes ('p' and 'y') next to each other. The suffix –yra in Ampyra does not look like the suffix –osa in Cuvposa when scripted. Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Ampyra has not been established in patients younger than 18 years of age. These two products are also dosed with differing frequencies. Ampyra is administered twice daily, whereas Cuvposa is administered three times a day. Cuvposa is seeking an indication of pathologic (chronic moderate to severe) drooling in pediatric patients, which will largely target cerebral palsy patients. In order for there to be a dose overlap of 10 mg, a cerebral palsy pediatric patient would have to weigh 100 kg and receive a dose on the high end of the dosing range at 0.1 mg/kg. Due to the large dosing range proposed for this drug along with the target patient population, it is unlikely that many patients will meet these specific parameters. Additionally, Cuvposa will be approved for use in pediatric patients age 3 – 16, whereas the safety and effectiveness of Ampyra in patients younger than 18 years of age have not been established.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22571	ORIG-1	SHIONOGI PHARMA INC	GLYCOPYRROLATE ORAL SOLUTION

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