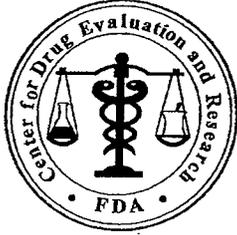


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-156

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: June 25, 2008

To: Norman Stockbridge, MD
Division of Cardiovascular & Renal Products

Thru: Kristina Arnwine, PharmD, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention

Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): Cleviprex (clevidipine butyrate) Injectable Emulsion
25 mg/50 mL and 50 mg/100 mL

Submission Number: N/A

Application Type/Number: NDA 22-156

Applicant/sponsor: The Medicines Company

OSE RCM #: 2008-538

CONTENTS

EXECUTIVE SUMMARY 2

1 BACKGROUND..... 2

 1.1 Introduction..... 2

 1.2 Regulatory History..... 2

 1.3 Product Information..... 2

2 METHODS AND MATERIALS 2

 2.1 Proprietary Name Risk Assessment..... 3

 2.2 Label and Labeling Risk Assessment 7

 2.2.1 Adverse Event Reporting System..... 8

3 RESULTS..... 8

 3.1 Proprietary Name Risk Assessment..... 8

 3.2 Label and Labeling Risk Assessment 9

 3.3 AERS Selection of Cases..... 9

4 DISCUSSION 9

5 CONCLUSIONS and Recommendations..... 10

 5.1 Comments To The Division..... 10

 5.2 Comments To The Applicant..... 11

6 REFERENCES..... 12

APPENDICES..... 13

**APPEARS THIS WAY
ON ORIGINAL**

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Cleviprex, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, The Division of Medication Error Prevention does not object to the use of the proprietary name, Cleviprex, for this product.

As part of a proprietary name review, the Division of Medication Error Prevention reviewed the container labels, carton and insert labeling and noted that improvements could be made to the carton and container labeling to decrease the potential for selection errors, to minimize confusion with dosing, and to increase readability of information presented on the labeling. The Medication Error Staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, The Division of Medication Error Prevention rescinds the Risk Assessment finding, and recommends that the name be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a consult from the Division of Cardiovascular and Renal Products to evaluate the Applicant's responses dated March 21, 2008 to the Division of Medication Error Prevention's comments on the carton and container labels for Cleviprex, and identify any outstanding areas of concern from a medication errors perspective. This review also contains the re-assessment of the proprietary name, Cleviprex, regarding potential name confusion with other proprietary or established names.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention completed an initial proprietary name, label and labeling review on December 20, 2007 (OSE Review #2007-1703). The Division of Medication Error Prevention had no objection to the proprietary name, Cleviprex. Comments with respect to the carton and container labels were forwarded to the Applicant on February 25, 2008. The Applicant provided a response to the Division of Medication Error Prevention's comments in the March 21, 2008 submission.

1.3 PRODUCT INFORMATION

Cleviprex is an injectable emulsion intended for intravenous use and should be titrated to achieve the desired blood pressure reduction. The proper dosing of Cleviprex is dependent on the severity of hypertension and the physiologic response of the patient. Cleviprex therapy is initiated at the dose of 2 mg/hour and titrated with the goal of blood pressure reduction. Infusion rates may be increased as tolerated at a rate of doubling increments every 1.5 minutes. Doses may be titrated as high as 32 mg/hour. The maximum duration of use is 72 hours. Cleviprex is available in 50 mL and 100 mL single use vials.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the medication error staff conducting a proprietary name risk assessment (see Proprietary Name Risk Assessment) and label, labeling, and or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The

primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The medication error staff defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Cleviprex, and the proprietary names of the drug products existing in the marketplace and those pending IND, NDA and ANDA products currently under review by the Agency.

For the proprietary name, Cleviprex, the medication error staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The medication error staff normally conducts internal CDER prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since the name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Cleviprex.

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 (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. (2) FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in 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. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since 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 drug name include, but are not limited to established name of the proposed product, the proposed indication, 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 process, the medication error 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.

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

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

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.^{2,3}

To identify drug names that may look similar to Cleviprex the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), upstrokes (two, capital letter 'C' and lower case letter 'l'), down strokes (one, lower case letter 'p'), cross-strokes (one, lower case 'x') and dotted letters (one, lower case 'i'). Additionally, several letters in Cleviprex may be vulnerable to ambiguity when scripted, including the capital letter 'C' may appear as capital 'L', 'D' and the combination of 'Cl' as 'A'; lower case 'c' may look like lower case 'o' or 'l'; lower case 'l' has the potential to resemble 'f', 'd', 'h', or 't'; lower case 'e' may look like lower case 'i', 'o', or 'l'; lower case letter 'v' may appear as lower case 'n', 's', 'r', 'b' or 'a'; lower case 'i' may appear as lower case 'e'; lower case 'p' may appear as lower case 'g' or 'q'; lower case 'r' may resemble a lower case 'm', 'v', 's', or 'a'; and lower case 'x' may appear as lower case 't', 'f', or 'k'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Cleviprex.

When searching to identify potential names that may sound similar to Cleviprex, the Medication Error Staff search for names with similar number of syllables (3), stresses (CLEV-i-prex or Clev-i-PREX), and placement of vowel and consonant sounds. In addition, several letters in Cleviprex may be subject to interpretation when spoken, including the letter 'C' may be interpreted as 'S', 'i' may be interpreted as either an 'a' or 'e', 'p' may be interpreted as 'b'; 'e' may be interpreted as 'a'. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the medication error staff were provided with the following information about the proposed product: the proposed proprietary name (Cleviprex), the established name (clevidipine emulsion for injection), proposed indication strength (0.5 mg/mL), how supplied (50 mL and 100 mL single use vials), dose (2 mg per hour, titrated for response), frequency of administration (varies per response), route of administration (intravenous), and dosage form (injectable emulsion). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

Lastly, the medication error staff also considers the potential for the proposed 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. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Cleviprex, was provided to the medication error staff to conduct a search of the internet, several standard published drug product references texts and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Cleviprex using the criteria

² Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

³ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the medication error 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 medication error staff reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention to gather CDER professional opinions on the safety of the product and the proprietary name, Cleviprex. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of The Division of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The pooled results of the medication error staff were presented 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 Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk 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.⁴ When applying FMEA to assess the risk of a proposed proprietary name, the medication error staff seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and 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 look- or sound-alike 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 Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. 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 evaluation, and studies, and identifies potential failure modes by asking: "Is the name Cleviprex 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 Cleviprex to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to

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

the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated 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 ultimately not be a source of medication errors in the usual practice setting, the name is eliminated 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 that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. 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 trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The Division of Medication Error Prevention 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)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. 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.

In the event that The Division of Medication Error Prevention objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention will not object to the use of the proprietary name. If any of these conditions are met, then The Division of Medication Error Prevention will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the Division of Medication Error Prevention contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, The Division of Medication Error Prevention 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 limitations of the process).

If The Division of Medication Error Prevention objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for The Division of Medication Error to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so The Division of Medication Error Prevention may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors⁵ to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

On March 28, 2008 the Applicant submitted the following labels for our review:

- Container Label: 50 mL, 100 mL (Appendix F)
- Carton Labeling: 50 mL, 100 mL (Appendix G)
- Package Insert Labeling (no image)

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Additionally, we compared the revised labeling to the previously reviewed carton and container labels that were evaluated in OSE Review 2007-1703, dated December 20, 2007.

2.2.1 ADVERSE EVENT REPORTING SYSTEM

The FDA Adverse Event Reporting System (AERS) was searched on May 22, 2008 to assess errors associated with Diprivan injectable emulsion due to product similarities between Cleviprex and Diprivan injectable emulsion (e.g. time limits after spiking) and the context of its use (limited duration of use in acute settings). The AERS search was conducted using the active ingredient 'propofol' and the trade name 'Diprivan' and the search terms included; accidental overdose (PT), maladministrations (HLT), medication errors due to accidental exposures (HLT), medication errors nec (HLT), medication monitoring errors (HLT), multiple drug overdose (PT), multiple drug overdose accidental (PT), overdose (PT), and pharmaceutical product complaint (PT).

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The search of the internet and information sources (see Section 7 References) identified twenty nine names as having some similarity to the name Cleviprex.

Eighteen names were previously evaluated in the OSE review (#2007-1703). The eleven names not previously reviewed are: Aerovent, Aeropep, Clindamax, Clemex, Avonex, Comvax, OraPred, Aurodex, Mifiprex, Altoprev and Calcijex. All eleven names were thought to look like Cleviprex.

The proposed proprietary name, Cleviprex, does not contain a USAN stem as of the last date searched, May 1, 2008.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the medication error staff (see section 3.1.1. above), and noted no additional names.

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

3.1.3 Safety Evaluator Risk Assessment

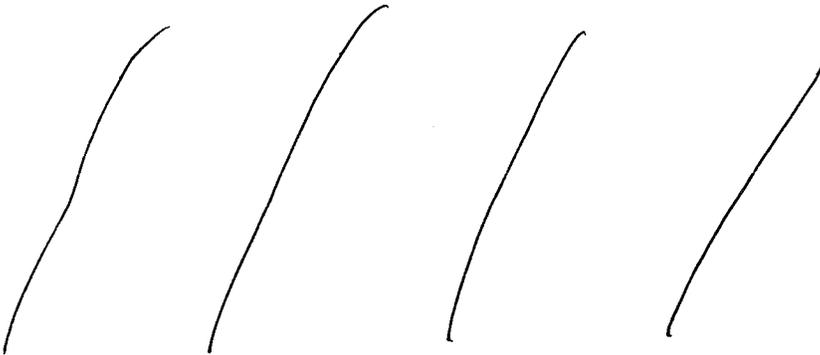
The primary safety evaluator, affording careful evaluation to drug names beginning with the letters 'C', 'D', and 'A', conducted independent searches which did not identify any additional names. As such, a total of eleven names were reviewed for look alike similarity to Cleviprex.

The names Aeropep and Clemex were determined to be orthographically dissimilar to Cleviprex. In addition, these names pertain to lab equipment, lab analysis or a medical device, and therefore would not be utilized in the context of prescribing or dispensing.

For nine of the names (Aurodex, Avonex, Calcijex, Mifeprex, OraPred, Comvax, Clindamax, Aerovent, and Altoprev), FMEA determined that medication errors were unlikely because they do not overlap in strength, dosage, and/or route of administration with Cleviprex (See Appendix D).

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the revised container labels, carton and insert labeling the Division of Medication Error Prevention identified several areas of vulnerability that could lead to medication errors.



3.3 AERS SELECTION OF CASES

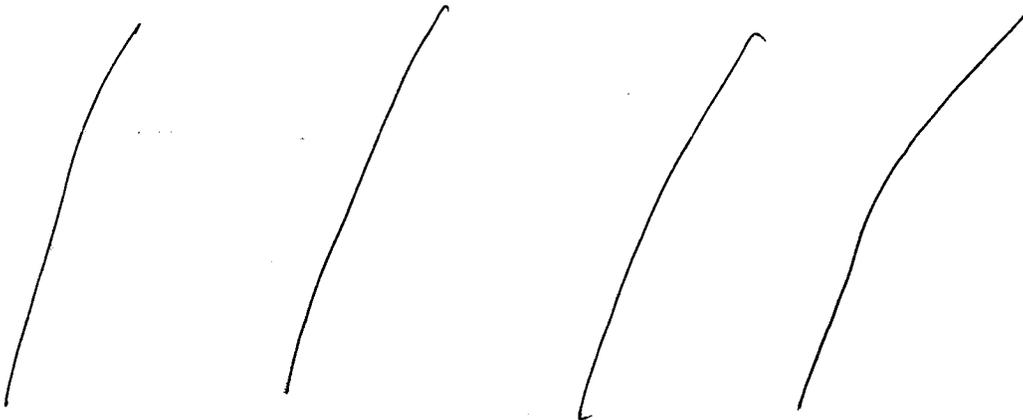
The Diprivan search yielded one hundred seventy eight cases, of which five were applicable to the Cleviprex labels and labeling. The 4 cases involved re-use of spiked vials or improper storage which resulted in adverse reactions (see Appendix J). Two reviews (#00-0217 and #03-0135) had been conducted previously with regards to errors associated with Diprivan labels and labeling in which recommendations were made to revise labels/labeling regarding prompt use after opening and discarding within specified time limit. These findings will be used in our assessment of the Cleviprex label and labeling.

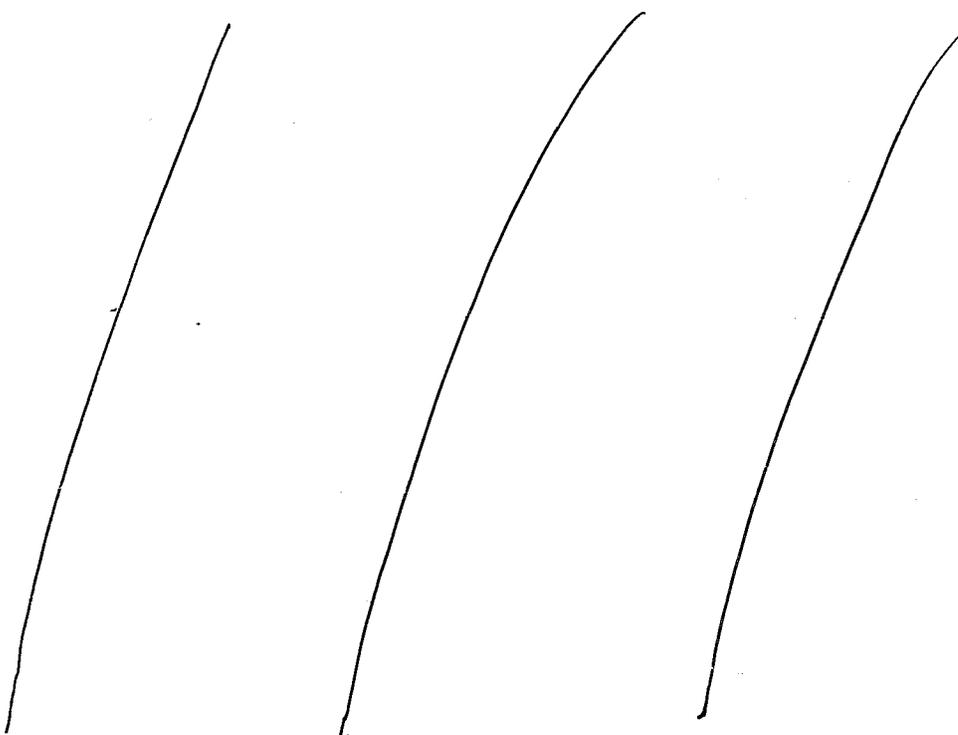
4 DISCUSSION

4.1 PROPRIETARY RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Cleviprex, has some similarity to other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

4.2 LABEL AND LABELING REVIEW





5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Cleviprex, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Cleviprex, for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention has no objections to the use of the proprietary name Cleviprex for this product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.

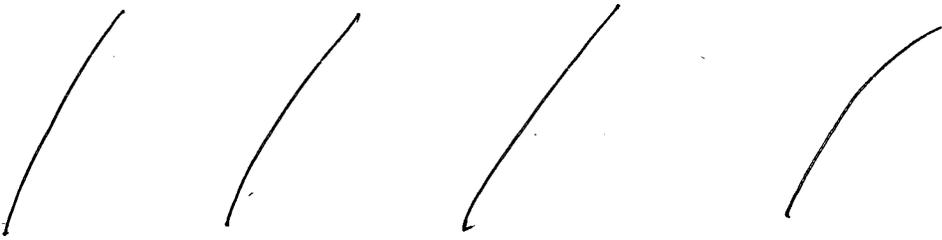
If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, OSE project manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

- A. The Division of Medication Error Prevention has no objections to the use of the proprietary name Cleviprex for this product. If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review.
- B. Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention has identified the following areas of needed improvement.

[Redacted content]



6 REFERENCES

1. Review of Safety Applications

OSE Review # 2007-1703, September 5, 2007 (Cleviprex Name Review)

OSE Review # 19-627/S-039, September 15, 2000 (Diprivan Label Review)

2. Micromedex Integrated Index (<http://weblern/>)

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 DMETS, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)

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

5. AMF Decision Support System [DSS]

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

6. Division of Medication Errors and Technical Support proprietary name consultation requests

This is a list of proposed and pending names that is generated by DMETS 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. United States Patent and Trademark Office <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (<http://weblern/>)

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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (<http://weblern/>)

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

13. Stat!Ref (<http://weblern/>)

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.pharmacist.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:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEDP also compare the spelling of the

proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine 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* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their 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), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEDP will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, DMEDP also considers a variety of pronunciations that could occur in the English language.

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	<ul style="list-style-type: none"> Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics 	<p>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</p> <p>Names may look similar when scripted and lead to drug name confusion in written communication</p>
	Orthographic similarity	<ul style="list-style-type: none"> Similar spelling Length of the name Upstrokes Down strokes 	Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
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

Appendix B: Product is device

Proprietary Name	Similarity to Cleviprex	Product
Aeropep	Look	Inhalation spacer

Appendix C: Identified product name not on market.

Proprietary Name	Similarity to Cleviprex	
Clemex	Look	

***** Of note, Clemex is also lab equipment *****

Appendix D: Products with no numerical overlap in strength and/or routes of administration

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Cleviprex (clevidipine emulsion) for injection		50 mg and 100 mg single use vial	2 mg per hour and titrated for response, up to 32 mg per hour
Aurodex (antipyrine and benzocaine)	Look	54 mg/14 mg/ mL Otic solution	Fill ear canal with solution every one or 2 hours for pain or 3 times daily to soften earwax
Avonex (interferon beta 1A)	Look	30 mcg/ mL vial	30 mcg injected intramuscularly once a week
Mifeprex (mifepristone)	Look	200 mg oral tablet	600 mg in a single dose on day one Followed by 400 mcg of misoprostol on day three
OraPred (prednisolone sodium phosphate)	Look	EQ 15 mg base/ 5 mL Oral solution	1.67 mL to 20 mL (5 to 60 mg prednisolone base) per day depending on indication
Comvax (Haemophilus influenzae type b and Hepatitis B vaccine)	Look	0.5 mL vial	0.5 mL subcutaneously given in 3 separate doses ideally at 2, 4, and 12-15 months of age
Clindamax (clindamycin)	Look	2 % vaginal cream	1 applicatorful (5 grams) intravaginally at bedtime for 3 or 7 days
Aerovent (ipratropium bromide)	Look	20 mcg inhaler	1-2 inhalations four times daily as needed
Altoprev (lovastatin)	Look	10 mg, 20 mg, 40 mg, and 60 mg extended release oral tablets	10-60 mg/day in a single dose

Appendix E: Potential confusing name with numerical overlap in strength or dose

<p>Cleviprex (clevipidine emulsion) for injection</p>	<p>50 mg and 100 mg single use vial</p>	<p>2 mg per hour infusion and titrated for response up to 32 mg per hour</p>
<p>Failure Mode: Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Effects</p>
<p>Calcijex (calcitriol) Solution of injection 1 mcg/ mL 2 mcg/ mL</p>	<p>Orthographic similarity (names begin with 'C', have 2 upstrokes in similar position; 1 down stroke in a similar position; names are similar length; names share 'ex' ending)</p> <p>Phonetic similarity (names begin with hard 'C', both are three syllables, both end in 'ex', stresses can be put on similar syllables</p> <p>Similar doses 2 mcg and 2 mg</p>	<p>Orthographic difference (upstrokes spaced differently, different number of letters, " could provide another dot or cross-stroke)</p> <p>Phonetic difference ('n' separating 'I' and 'c', 'I' starts third syllable, 'a' in second syllable, 'pr' and 'j')</p> <p>Dose of calcitriol is given three times weekly subcutaneously, patient is usually on dialysis.</p>

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Draft Labeling

Deliberative Process

Appendix J: AERS Cases

<u>AERS date</u> <u>ISR #</u>	<u>Brief Summary of AERS Report</u>
06/01/1999 3290781-5	Physician used a vial which had been opened 4 days earlier and not discarded
06/2007 5391363-1	Physician drew up remaining amount from vial that had been used on previous patient.
08/26/1998 3189865-1	Physician used open vial that may have been stored in the refrigerator
02/16/1994 1680071	Physician administered diprivan that was left over from the previous procedure

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Anne Crandall
6/25/2008 12:17:34 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/25/2008 12:47:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/25/2008 12:51:13 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22; Mail Stop 4447)

DATE RECEIVED: 8/6/07	DESIRED COMPLETION DATE: 10/8/07	OSE REVIEW #: 2007-1703
DATE OF DOCUMENT: 7/2/07	PDUFA DATE: 1/2/08	

TO: Norman Stockbridge, MD
Director, Division of Cardiovascular and Renal Products
HFD-110

THROUGH: Kellie Taylor, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Cleviprex (Clevidipine Emulsion) for Injection 0.5 mg/mL	SPONSOR: The Medicines Company
NDA #: 22-156	

RECOMMENDATIONS:

1. DMETS has no objections the use of the proprietary name, Cleviprex. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Cleviprex, acceptable from a promotional perspective.
4. DMETS recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (the Project Manager assigned to the LNC), and the assigned ONDQA Chemist regarding the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence forwarded to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, Project Manager, at 301-796-0558.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: September 5, 2007
NDA #: 22-156
NAME OF DRUG: **Cleviprex**
(Clevidipine Emulsion) for Injection
0.5 mg/mL
NDA SPONSOR: The Medicines Company

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Cardiovascular and Renal Products, for an assessment of the proprietary names "Cleviprex" regarding potential name confusion with other proprietary or established drug names. Carton, container, and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Cleviprex (clevidipine) is a dihydropyridine calcium channel blocker indicated for _____ when the use of oral therapy is not feasible or not desirable. Cleviprex is an emulsion intended for intravenous use. It should be titrated to achieve the desired blood pressure reduction. Dosages must be individualized depending on the severity of hypertension and the response of the patient. Patients may be monitored with a blood pressure cuff on an arterial line.

Initiation of Cleviprex via intravenous infusion should begin at 2 mg/hour and titrated to achieve the desired reduction in blood pressure. Steady-state arterial blood concentrations are reached within 2 minutes. The infusion rate may be increased as tolerated, in doubling increments (i.e., 2 mg/hr to 4 mg/hr, 4 mg/hr to 8 mg/hr, 8 mg/hr to 16 mg/hr, and 16 mg/hr to 32 mg/hr) every 1.5 minutes. Most patients will achieve desired therapeutic response at doses of up to 16 mg/hr. The rate of infusion should be adjusted as needed to maintain blood pressure within the desired target range. Cleviprex can be discontinued or titrated to maintain blood pressure to the desired effect while appropriate oral therapy is established. If treatment includes transfer to an oral anti-hypertensive agent, _____, and continue to monitor blood pressure until the desired effect is achieved. No dosage adjustment is required for patients with underlying cardiac, hepatic or renal impairment.

Cleviprex appears as a milky white liquid emulsion and will be supplied in sterile, pre-mixed, ready-to-use, 50 mL and 100 mL single-use vials at a concentration of 0.5 mg/mL. Cleviprex should be refrigerated and protected from light until administration. It may be transferred to room temperature for a period not to exceed 2 months. Cleviprex should not be re-refrigerated after it has been at room temperature. Once the vial stopper is punctured, Cleviprex should be used within 2 hours, and any unused portions should be discarded.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference textsⁱⁱ as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to Cleviprex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. The Saegis^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Cleviprex. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name, Cleviprex.
2. The Expert Panel identified 15 proprietary names that were thought to have the potential for confusion with Cleviprex. The names are as follows: Aciphex, Aleve, Anaprox, Clofarex, Clinitek, Clomiphene, Clonopin, Clivarine, Clearprex, Clofibrate, Clobevate Gel, Celebrex, Clarinex, Codeprex, and Divalproex. Upon independent analysis, three additional names, Clorpres, _____, and Prevpac were identified as names that may be potentially confused with Cleviprex.

ⁱ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

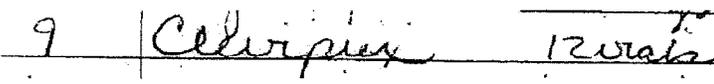
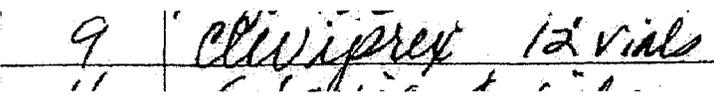
^{vi} Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

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

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Cleviprex 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. Each set of studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two pharmacy requisition orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Cleviprex (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were 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 sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Requisition #1:</p> 	<p>Cleviprex Dispense 12 vials to Same Day Surgery Clinic</p>
<p>Requisition #2:</p> 	

2. Results:

One participant in the verbal prescription study interpreted the proposed proprietary name as "Previpax", which is phonetically similar to the currently marketed product, Prevpac. See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Cleviprex", a total of 18 names were identified as having similar sound and/or appearance to Cleviprex. These names include: Aciphex, Aleve, Anaprox, Clofarex, Clinitek, Clomiphene, Clonopin, Clivarine, Clearprex, Clofibrate, Clobevate Gel, Celebrex, Clarinex, Codeprex, Clorpres, Divalproex, _____, and Prevpac.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, one respondent from the verbal prescription study interpreted the name as "Previpax". This name may sound similar to the currently marketed drug product, Prevpac. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Cleviprex.

Upon further analysis of these 18 names, 15 proprietary names (Aleve, Anaprox, Clofarex, Clinitek, Clomiphene, Clonopin, Clivarine, Clearprex, Clofibrate, Clobevate Gel, Celebrex, Clarinex,

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

The "Aci" in Aciphex may resemble the "Cle" in Cleviprex when scripted. The endings ("-phex" vs. "prex") may also appear similar if the "h" is not prominent. However, Aciphex may appear shorter in length as it contains seven letters as opposed to the nine letters in Cleviprex. Additionally, the "v" in Cleviprex may provide some distinction of the name.

Aciphex
Cleviprex

Aciphex and Cleviprex may potentially overlap at a dose of 20 mg. However, Aciphex is dosed in milligrams (mg) and Cleviprex is dosed in milligrams/hour (mg/hr). Additional differentiating product characteristics include product strength (20 mg vs. 0.5 mg/mL), indication of use (gastric ulcers and hypersecretory conditions vs. _____ route of administration (oral vs. intravenous), frequency of administration (4-8 weeks or continuously vs. continuous infusion of to 72 hours), and dosage form (delayed-release tablets vs. emulsion).

Although Aciphex and Cleviprex share similar orthographic characteristics, the aforementioned differentiating product characteristics (strength, indication of use, route of administration, frequency of administration, and dosage form) may help to minimize the potential for confusion between these two drug products.

2. Prevpac was identified from the verbal prescription study as a name that may sound similar to the proposed proprietary name, Cleviprex. In the verbal prescription study, a participant interpreted the name, Cleviprex as "Previpax".

Prevpac is indicated for the eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence. Prevpac is a packaging configuration that contains Prevacid (30 mg capsules), Amoxicillin (500 mg tablets), and Clarithromycin (500 mg tablets). The dose is prevacid 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg administered together twice daily for 10 to 14 days.

Prevpac and Cleviprex may sound similar as they both contain the "ev" sound in the middle of the name. Both names also have a "p" sound at the beginning of the last syllable of each name. Although Prevpac and Cleviprex share some phonetic similarities, the names are also phonetically different. Prevpac contains two syllables whereas Cleviprex contains three syllables. Additionally, the endings are different ("pac" vs. "prex"). Furthermore, there are several differentiating product characteristics such as, route of administration (oral vs. intravenous), frequency of administration (twice daily vs. continuous infusion), duration of treatment (10 to 14 days vs. up to 72 hours), and dosage form (tablets/capsules vs. emulsion).

Although the findings from the verbal prescription study (Previpax) identified that Cleviprex may sound similar to Prevpac, the differentiating product characteristics between this name pair may help to minimize the risk of confusion between Prevpac and Cleviprex.

3. Clorpres was identified as a name with similar appearance to Cleviprex when scripted. Clorpres is a combination tablet that contains clonidine and chlorthalidone. It is indicated for the treatment of hypertension, but it is not indicated for initial therapy. Clorpres is dosed once or twice daily from a minimum dose of 0.1 mg clonidine plus 15 mg chlorthalidone to a maximum dose of 0.6 mg clonidine plus 30 mg chlorthalidone.

The beginning of Clorpres and Cleviprex may look similar when scripted ("Clor" vs. "Clev"). Additionally, the endings may appear similar, ("pres" vs. "prex") although the cross of the "x" may help to distinguish the endings. Cleviprex is longer than Clorpres, which may also help to

differentiate the names.

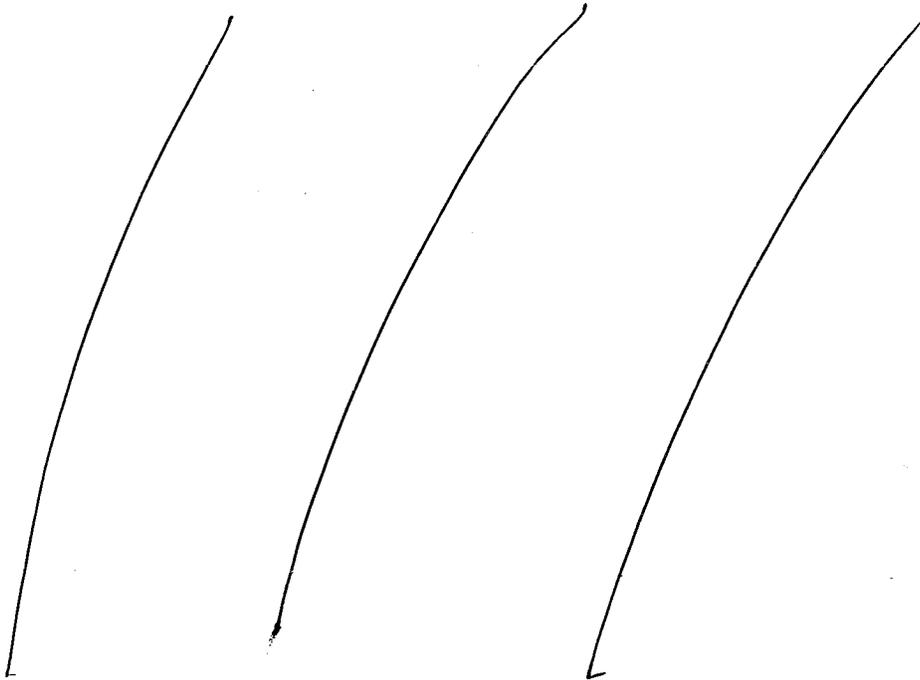
Clorpres
Cleviprex

Clorpres _____ indicated for the treatment of hypertension. However, Clorpres is available in three strengths (0.1 mg/15 mg, 0.2 mg/15 mg, and 0.3 mg/15 mg). Since the chlorthalidone strength is constant, Clorpres may be prescribed by the clonidine strength (0.1 mg, 0.2 mg, 0.3 mg) compared to Cleviprex 0.5 mg/mL. Although Clorpres and Cleviprex may share a similar numerical dose (0.2 mg vs. 2 mg/hr to 32 mg/hr), the directions for use on prescriptions for Clorpres may help to distinguish between Clorpres and Cleviprex. Despite the product similarities, Clorpres and Cleviprex differ in route of administration (oral vs. intravenous), dosage form (tablets vs. emulsion), and frequency of administration (once or twice daily vs. continuous infusion). Additionally, the duration of use for Clorpres is continuous whereas Cleviprex is only administered up to 72 hours.

Although Clorpres and Cleviprex _____ and have orthographic similarities, the directions for use for Cleviprex, including route of administration and frequency and/or duration of treatment may help to distinguish between the two drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS evaluated the container labels, carton and insert labeling applying the principles of human factors and using failure modes effects analysis, and have identified the following areas of improvement to minimize potential user error.



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