

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

PROPRIETARY NAME REVIEW(S)



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

Date: February 26, 2009

To: Norman Stockbridge, MD Director,
Division of Cardiovascular and Renal Products

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Subject: Proprietary Name Review

Drug Name(s): Exforge HCT (Amlodipine, Valsartan, and Hydrochlorothiazide)
Tablets
5 mg/160 mg/12.5 mg; 10 mg/160 mg/12.5 mg;
5 mg/160 mg/25 mg; 10 mg/160 mg/25 mg; and
10 mg/320 mg/25 mg

Application Type/Number: NDA: 22-314

Applicant: Novartis

OSE RCM #: 2008-1346

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Exforge HCT, has some similarity to other proprietary and established drug names, but the findings of the Failure Mode and Effects Analysis (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 and Analysis does not object to the use of the proprietary name, Exforge HCT, for this product. The label and labeling review will be completed under separate cover in forthcoming review (OSE Review #: 2008-1945), however, at the time of completion of the proprietary name review, submission of carton labeling was still pending from the Applicant.

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 review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products, to evaluate the product for its potential to contribute to medication errors. The proposed name, Exforge HCT, is evaluated to determine if the name could potentially be confused with other proprietary or established drug names. Container labels, and insert labeling were also provided to be evaluated from a medications errors perspective and review comments will be provided under separate cover in a forthcoming review (OSE #: 2008-1945). To date, we have not received carton labeling from the Applicant to include in our label and labeling review.

1.2 REGULATORY HISTORY

The proprietary name, Exforge, was previously reviewed without objection by DMEPA in 2005 (OSE Consult #: 05-0313). Exforge (Amlodipine and Valsartan) was approved by FDA on June 7, 2007.

1.3 PRODUCT INFORMATION

Exforge HCT (Amlodipine, Valsartan, and Hydrochlorothiazide) is a combination tablet containing amlodipine, a dihydropyridine calcium channel blocker (DHP-CCB), valsartan, an angiotensin II receptor blocker (ARB), and hydrochlorothiazide a diuretic. It is indicated for add-on or switch therapy for patients not adequately controlled on an ARB/HCTZ, ARB/DHP-CCB, or DHP-CCB/HCTZ dual combination therapy.

Exforge HCT will be available as 5 mg/160 mg/12.5 mg; 10 mg/160 mg/12.5 mg; 5 mg/160 mg/25 mg; 10 mg/160 mg/25 mg; and 10 mg/320 mg/25 mg tablets. The usual adult dose is one tablet daily, but is not recommended for patients with severe renal impairment (creatinine clearance ≤ 30 mL/min). It will be supplied in bottles of 30 tablets and 90 tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis

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, Exforge HCT, and the proprietary and established names of drug products existing in the marketplace and those pending IND, BLA, NDA, and ANDA products currently under review by CDER.

For the proprietary name, Exforge HCT, DMEPA searches 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 Division of Medication Error Prevention and Analysis also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

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 2.1.4). The overall risk assessment is based on the findings of a Failure Mode 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 Prevention and Analysis 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 consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed name 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 use process, the Division of Medication Error Prevention and Analysis 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.³

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

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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.

For this review, particular consideration was given to drug names beginning with the letter 'E' 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.⁴⁵

To identify drug names that may look similar to Exforge HCT, the staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (10 letters, root name and suffix), upstrokes (5, capital letters 'E', 'H', 'C', 'T' and lower case letter 'f'), downstrokes (two, the letters 'f' and 'g'), cross-strokes (four, the letters 'x', 'f', 'H', and 'T'), and dotted letters (none). Additionally, several letters in Exforge HCT may be vulnerable to ambiguity when scripted, including the letter 'E' which may appear as the letters 'C', or the lowercase letters 'e', which may appear as a lower case 'i', or 'o' when scripted; and the letter 'g' which may appear as the letter 'j' or 'y'. As such, the staff also consider these alternate appearances when identifying drug names that may look similar to Exforge HCT. We also consider alternate interpretations and appearances of the modifier, 'HCT', to determine if misinterpretations may contribute to medication errors.

When searching to identify potential names that may look or sound similar to Exforge HCT, the Medication Error Prevention and Analysis staff search for names with similar number of syllables (2) in the root name and (3) in the suffix (HCT), stresses (EX-forge HCT or ex-FORGE HCT), and placement of vowel and consonant sounds. 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 staff were provided with the following information about the proposed product: the proposed proprietary name (Exforge HCT), the established name (amlodipine/valsartan/hydrochlorothiazide), proposed indication (hypertension), strength (5 mg/160 mg/12.5 mg; 5 mg/160 mg/25 mg; 10 mg/160 mg/12.5 mg; 10 mg/160 mg/25 mg; 10 mg/320 mg/25 mg), dose (one tablet), frequency of administration (daily), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Prevention and Analysis staff general take into consideration.

Lastly, DMEPA staff also consider 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 DMEPA staff provide 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, Exforge HCT, was provided to the medication error staff of the DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

databases to identify existing and proposed drug names that may sound-alike or look-alike to Exforge HCT using the criteria 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 Division of Medication Error Prevention and Analysis 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 Division of Medication Error Prevention and Analysis staff review the United States Adopted Names (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 and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Exforge HCT. 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 and Analysis (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the DMEPA 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.

2.1.1.3 CDER 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 Exforge HCT 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 a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Exforge HCT 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 prescriptions are optically scanned and one prescription is delivered to a random sample of 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 the medication error staff.

Figure 1: Exforge HCT Rx Study (conducted on September 16, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Rx #1:</u></p> <p style="text-align: center;">Exforge HCT 10/160/12.5 mg #30 1 tablet by mouth daily</p>	<p>Exforge HCT 10/160/12.5 mg One tablet by mouth daily #30</p>
<p><u>Inpatient Rx #2:</u></p> <p>Exforge HCT 10/160/12.5 mg 1 tablet by mouth daily</p>	

2.1.1.4 AERS Selection of Cases

DMEPA searched the Adverse Events Reporting System (AERS) database to identify postmarketing reports of medication errors associated with Exforge. AERS was searched as a combination product using the active ingredients 'amlodipine' and 'valsartan' and the verbatim terms 'amlo%' and 'vals%'. The MedDRA High Level Group Term (HLGT) 'Medication Errors' was used as the search criterion.

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the primary Safety Evaluator applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode 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.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis 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.

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

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 Exforge HCT convincing 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 Exforge HCT 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 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 and Analysis 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 and Analysis 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. The 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 name and another drug product.

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, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use of the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary 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 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission on Accreditation of Healthcare Organizations, and the Institute of Safe Medication Practices, 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, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, 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 Applicant, 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 Applicants 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, 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 limitations of the process).

If DMEPA 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. The Division of Medication Error Prevention and Analysis 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, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

This search identified 7 names as having some similarity to the name Exforge HCT.

Four names were thought to look like Exforge HCT, which include: Exjade, , Exflora, and Exgest LA, (which was misspelled on the EPD list of names as Exforge LA). Effexor was thought to sound like Exforge HCT, and the remaining two names, Exforge, and Exforj, were thought to look and sound similar to Exforge HCT. Exforge HCT and Exforge HCTZ were also identified however, these names were generated from the United States Patent and Trademark database as the trademarks for this product, and therefore were not included for review.

Additionally, the Division of Medication Error Prevention and Analysis did not identify any United States Adopted Names (USAN) stems in the name Exforge HCT, as of the last date searched on December 2, 2008.

b(4)

The modifier 'HCT', as an abbreviation has several meanings^{7,8} including: Hydrochlorothiazide, Hydrocortisone, Hematocrit, Head Computerized Tomography, Health Check Test, Heart-Circulation Training, Histamine Challenge Test, Historic Control Trial, Homocytotropic, Human Chorionic Thyrotropin, Human Calcitonin, and Hundred Count. Due to the fact that 'HCT' has a number of possible interpretations, it is included on the Institute of Safe Medication Practices (ISMP) list of Error-Prone Abbreviations, Symbols, and Dose Designations.⁹

3.1.2 CDER Prescription Analysis Studies

A total of 23 practitioners responded, and one of the responses overlapped with an existing proprietary drug name, Exforge. Approximately three-quarters of the participants (n = 18) interpreted the name correctly as 'Exforge HCT' with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the voice studies, with the modifier 'HCT' being interpreted as either 'HZT' or 'HCP'. One respondent in the outpatient study responded 'Exfarge HCT'. One respondent in the outpatient written study overlooked the modifier 'HCT' and interpreted the name as 'Exforge'. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.3 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), and did not identify any additional names thought to have orthographic or phonetic similarity to Exforge HCT and have the potential for confusion.

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

In addition, the Division stated in an electronic mail message dated 12/02/08, that they have no objections to the proposed proprietary name, Exforge HCT.

3.1.4 AERS Selection of Cases

Our search of AERS did not identify any medication errors associated with Exforge as of 10/03/2008.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified one additional name, Exfozyme, thought to look similar to Exforge HCT and represent a potential source of drug name confusion. Careful evaluation was afforded to drug names beginning with the letter 'E' in accordance with the Expert Panel's recommendations. As such, a total of 8 names were analyzed to determine if the drug names could be confused with Exforge HCT and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Exforge HCT, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Exforge HCT, could potentially be confused with any of the 8 names and lead to medication errors. The findings of our assessment of the name similarity between Exforge HCT and Exforge are discussed in section 4.1. Overall, our analysis determined that the similarity between Exforge HCT and the 8 identified names was unlikely to result in medication errors (see Appendices C through F).

4 DISCUSSION

4.1 PROPRIETARY NAME

Exforge HCT will be an extension of the Exforge product line, and therefore may cause confusion within the product line. However, our FMEA found that the different product characteristics will help to minimize the risk of medication errors within the product line. Typically, when modifiers are omitted or overlooked, it may lead to medication errors. In this case, Exforge HCT contains three active ingredients and will be available in five different strengths (5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, and 10 mg/ 320 mg/25 mg). The multiple product strengths make it necessary for prescribers to include the strengths of all three components, amlodipine, valsartan, and hydrochlorothiazide, to ensure that patients receive the correct dose. Therefore, if a prescriber omitted the modifier, 'HCT', or the modifier is overlooked when interpreting the name, the presence of the three strengths on the prescription, would help to prevent the wrong product, Exforge, from being dispensed. Additionally, we evaluated the similarity of Exforge HCT to other marketed products and those in the pipeline. The FMEA indicates that the proposed name does not appear to be vulnerable to confusion.

4.1.1 Use of 'HCT' as a Modifier

Our FMEA also evaluated the potential for medication errors to occur due to misinterpretation of the modifier, 'HCT', including the potential for 'HCT' to resemble any numbers, dosing instructions or medical abbreviations other than Hydrochlorothiazide as previously listed in section 3.1.1. The results of our FMEA determined that 'HCT' does not resemble any numbers or dosing instructions and that these alternate interpretations should not result in either product or dosing confusion due to the different context of use 'HCT' will have as part of the proprietary name.

DMEPA acknowledges that the abbreviation 'HCT' appears on the Institute of Safe Medication Practices (ISMP) list of Error-Prone Abbreviations, Symbols, and Dose Designations due to the fact that 'HCT' can represent multiple medical terms and its incorrect interpretation has contributed to medication errors. Typically, in accordance with our agreement with ISMP not to approve proprietary names which contain error-prone abbreviations, DMEPA would object to the use of the modifier 'HCT' for the proposed proprietary name, Exforge HCT. However, 'HCT' has previously been approved as a modifier for combination antihypertensive products. There are currently 9 approved antihypertensive products marketed with 'HCT' in conjunction with different proprietary root names. Our review of postmarketing reports did not establish that misinterpretation of the 'HCT' modifier perpetuates the medication errors that caused this modifier to be designated as a dangerous abbreviation. Therefore, DMEPA, does not object to the use of the proprietary name, Exforge HCT, for this product.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Exforge HCT, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Exforge HCT, for this product. 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 and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

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 Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, at 301-796-1332.

6.2 COMMENTS TO THE APPLICANT

1. We have completed our review of the proposed proprietary name, Exforge HCT, and have concluded that it is acceptable.
2. Exforge HCT will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following re-review, we will notify you.
3. If any of the proposed product characteristics are altered prior to approval of the of the marketing application, the proprietary name should be resubmitted for review.

7 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. *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 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:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis 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 led 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 (i.e. "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, the Division of Medication Error Prevention will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis 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	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		<p>Cross-strokes</p> <p>Dotted letters</p> <p>Ambiguity introduced by scripting letters</p> <p>Overlapping product characteristics</p>	
Sound-alike	Phonetic similarity	<p>Identical prefix</p> <p>Identical infix</p> <p>Identical suffix</p> <p>Number of syllables</p> <p>Stresses</p> <p>Placement of vowel sounds</p> <p>Placement of consonant sounds</p> <p>Overlapping product characteristics</p>	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: CDER Prescription Study Responses

Outpatient Prescription	Inpatient Prescription	Verbal Order
Exforge HCT	Exforge HCT	Exforge HCP
Exfarge HCT	Exforge HCT	Exforge HCP
Exforge HCT	Exforge HCT	Exforge HCT
Exforge HCT	Exforge HCT	Exforge HZT
Exforge	Exforge HCT	Exforge HCT or HZT
Exforge HCT	Exforge HCT	Exforge HCT
Exforge HCT	Exforge HCT	Exforge HCT
Exforge HCT		Exforge HCT
Exforge HCT		Exforge HCT
		Exforge HCT

Appendix C: Proprietary names with orthographic similarity to Exforge HCT but are discontinued and no longer marketed or have been withdrawn

Proprietary Name	Similarity to Exforge HCT	Status
Exgest LA (guaifenesin/phenylpropanolamine)	Look-alike	Discontinued
_____	Look-alike	Withdrawn

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Appendix D: Foreign proprietary names with similar orthographic characteristics with Exforge HCT

Proprietary Name (established name)	Country	Similarity to Exforge HCT
Exforj	Switzerland	Look-alike and sound-alike
Exflora	France and Switzerland	Look-alike

Appendix D: Proprietary names for over-the-counter products with no overlapping product characteristics

Proprietary Name (established name)	Strength/Dosage Form	Usual adult dose
Exforge HCT (amlodipidine/valsartan/ hydrochlorothiazide)	5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg tablets	One tablet by mouth once a day
Exfozyme (multiple ingredients)	NA	Apply to face for 10 to 15 minutes once or twice a week

Appendix E: Proprietary names for prescription drugs with orthographic similarity to Exforge HCT with numerical overlap in strength and/or dose

Proprietary Name (established name)	Strength/Dosage Form	Usual adult dose
Exforge HCT (amlodipidine/valsartan/ hydrochlorothiazide)	5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg tablets	One tablet by mouth once a day
Exjade (deferasirox)	125 mg, 250 mg, and 500 mg Tablet for Oral Suspension	20 mg/kg/day; doses should be calculated to the nearest whole tablet
Effexor (venlafaxine)	25 mg, 37.5 mg, 50 mg, 75 mg tablets	Starting dose is 75 mg/day in two to three divided doses and may be increased up to 150 mg/day.

Appendix F: Proprietary Names with substantial overlapping product characteristics and orthographic/phonetic similarity to Exforge HCT

<p>Exforge HCT (amlodipine/valsartan/ hydrochlorothiazide)</p>	<p>5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg tablets</p>	<p>One tablet by mouth once a day</p>
<p>Failure Mode: Name confusion</p>	<p>Causes (could be multiple)</p>	<p>Effects</p>
<p>Exforge (amlodipine/valsartan)</p>	<p>Overlapping established names amlodipine/valsartan vs amlodipine/valsartan/hydrochlorothiazide</p> <p>Overlapping strengths 5 mg/160 mg, 10 mg/160 mg 5 mg/320 mg, 10 mg/320 mg vs 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/12.5 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg</p> <p>Overlapping dosage forms: tablets</p>	<p>Wrong Drug</p> <p>Despite overlapping root names and product characteristics, the product difference and prescribing practices will help minimize the potential for confusion that could lead to medication errors.</p> <p><i>Rationale:</i> Exforge HCT has three active ingredients and will be available in five strengths. Even if the modifier 'HCT' were omitted, or overlooked, the strengths of all three active ingredients would help to ensure patients receive the correct dose.</p>

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