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**PROPRIETARY NAME REVIEW(S)**

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**Department of Health and Human Services  
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**Subject:** Proprietary Name, Label and Labeling Review for TriLipix

**Drug Name(s):** TriLipix (Fenofibric acid) Delayed-released capsules

**Application Type/Number:** NDA 22-224

**Applicant:** Abbott Laboratories

**OSE RCM #:** 2008-841

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

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## **EXECUTIVE SUMMARY**

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

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton labeling and container labels introduces vulnerability to confusion that could lead to medication errors. Specifically, we are concerned with the capitalization of the letter 'L' in the proprietary name and the use of color and the layout of the sample carton labels. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review was written in response to a request from the Division of Metabolism and Endocrinology Products (HFD-510), for assessment of the product for its potential to contribute to medication errors. The proposed proprietary name, TriLipix, is evaluated to determine if the name could be potentially confused with other proprietary or established drug names.

Additionally, the container labels, carton, and insert labeling were provided for evaluation to identify areas that could lead to medication errors.

### **1.2 REGULATORY HISTORY**

The Division of Medication Error Prevention and Analysis previously reviewed the proposed proprietary name, Trilipix, for this product as IND 70,345 in OSE review # 2007-959, dated February 5, 2008. Our analysis at that time found the name did not appear to be vulnerable to name confusion leading to medication errors. However, in the current presentation, the applicant proposes to use a capitalized 'L' in the proprietary name which differs from the proposed name analysis in the previous review. In addition, the established name has changed to fenofibric acid from choline fenofibrate.

### **1.3 PRODUCT INFORMATION**

TriLipix (fenofibric acid) delayed release capsules are indicated for hypercholesterolemia/ mixed dyslipidemia and hypertriglyceridemia. It is available as 45 mg and 135 mg capsules containing four and twelve enteric coated minitablets, respectively. The usual dose of 135 mg will be taken orally as a single daily dose. The 45 mg dose is intended for patients with moderate renal impairment. Both strength will be available in bottles of 90 capsules as well as professional samples containing seven or 28 capsules.

## **2 METHODS AND MATERIALS**

This section consists of two sections which describe the methods and materials used by the medication error prevention staff conducting a proprietary name risk assessment (see 2.1

Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The medication error prevention 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.<sup>1</sup>

## 2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, TriLipix, the medication error prevention staff 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). Our Division also conducts internal CDER prescription analysis studies, and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (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.<sup>2</sup> 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 medication error prevention staff uses our clinical expertise 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

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

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

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 medication error prevention 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.<sup>3</sup>

### **2.1.1 Search Criteria**

The medication error prevention staff considers 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 'T' 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.<sup>45</sup>

To identify drug names that may look similar to Trilipix, 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 (eight letters), upstrokes (one, Capital 'L' or lower case 'l'), downstrokes (one, lower case 'p'), cross-strokes (one, lower case 'x'), and dotted letters (three, lower case 'i'). Additionally, several letters in TriLipix may be vulnerable to ambiguity when scripted, including the letter 'T' may appear as 'F,' 'L' or 'Z'; lower case 'i' may appear as a lower case 'e;' capital 'L' may appear as 'T' or 'Z;' lower case 'l' may appear as a lower case 'b', 'd' or 'e'; lower case 'p' may appear as 'f'; lower case 'x' may appear as 'n,' 'r,' or 'v'; and '-ipi-' may appear as '-yn' or '-ys-'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to TriLipix.

When searching to identify potential names that may sound similar to TriLipix, the medication error prevention staff searches for names with similar number of syllables (three), stresses (tri-LI-pix or TRI-li-pix), and placement of vowel and consonant sounds. Additionally, several letters in TriLipix are prone to misinterpretation when spoken, including the letter 'T' misinterpreted as a 'D' and the letter 'x' misinterpreted as 'cks,' 'cs,' or 'ks.'

The staff also considers 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 prevention staff were provided with the following information about the proposed product: the proposed proprietary name (TriLipix or Trilipix), the established name (fenofibric acid), proposed indication (hypercholesterolemia/ mixed dyslipidemia and hypertriglyceridemia), strength (45 mg, and 135 mg), dose (135 mg daily, dose decrease to 45 mg based on renal function), frequency of administration (daily), route (oral) and dosage form of

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

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

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

the product (capsule). Appendix A provides a more detailed listing of the product characteristics the Staff generally takes into consideration.

Lastly, the medication error prevention 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 prevention 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, TriLipix, was provided to the medication error prevention staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to F 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 medication error prevention 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 prevention 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 medication error prevention staff to gather CDER professional opinions on the safety of the product and the proprietary name, TriLipix. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the 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 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 TriLipix or Trilipix 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 124 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 TriLipix or Trilipix 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 124 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. Trilipix Study (conducted on June 26, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Prescription:</u></p> <p><i>Trilipix 45mg #60</i> <i>1 tablet daily</i></p>	<p>TriLipix 45 mg number sixty Take one tablet by mouth daily.</p>
<p><u>Inpatient Medication Order:</u></p> <p><del><i>Trilipix 45 mg</i></del> <del><i>1 tab by mouth daily</i></del></p>	

### 2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, 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.<sup>6</sup> When applying FMEA to assess the risk of a proposed proprietary name, the medication error prevention 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

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

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 TriLipix or Trilipix 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 TriLipix 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 medication error prevention staff 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 medication error prevention staff 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 medication error prevention staff identifies 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 another drug product.

In the event that the medication error prevention staff 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 medication error prevention staff will not object to the use of the proprietary name. If any of these conditions are met, then our division 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, and the Institute for Safe Medication Practices, that 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 medication error prevention staff 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 Applicant'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 medication error prevention staff believes that post-approval efforts at reducing name confusion 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 medication error prevention staff 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. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for the medication error prevention staff 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 we may be able to provide the Applicant 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 errors.<sup>7</sup>

Because the medication error prevention staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. Our Division uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on December 7, 2007 the following labels and labeling for the medication error prevention staff review (see Appendix I, J, K, L, M, and N

- Retail Container: 45 mg and 135 mg
- Sample Carton: 45 mg (7 capsule package, 28 capsule package, 8 X 7 capsule package); 135 mg (7 capsule package, 28 capsule package, 8 X 7 capsule package)
- Sample Blister Labels: 45 mg (7 capsule blister); 135 mg (7 capsule blister)
- Prescribing Information (no image)

## **3 RESULTS**

### **3.1 PROPRIETARY NAME RISK ASSESSMENT**

#### **3.1.1 Database and Information Sources**

The medication error prevention staff conducted a search of the internet, several standard published databases and information sources (see Section 6 References) for existing drug names which sound-alike or look-alike to TriLipix to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, 33 names were identified as having some similarity to the name TriLipix or Trilipix.

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<sup>7</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Twenty-eight of the 33 names that were thought to look like TriLipix, which include: Aricept, Avalide, Lupron, Lutera, Relpax, Salpax, Taclonex, Thioplex \_\_\_\_\_, Triaprin, Trichlorex, Triglide, Trilafon, Trileptal, \_\_\_\_\_ Arlisate, Trilitron, TriLyte, Trimpex \_\_\_\_\_ Trisenox, Tritec, \_\_\_\_\_, and \_\_\_\_\_ Two names, Tri-Hist and Trymex, were thought to sound like TriLipix. Three additional names (Tri-Legest 21, Trilipix, and Tri-Luma) were thought to look and sound similar to TriLipix.

b(4)

A search of the United States Adopted Name stem list on July 20, 2008 identified USAN stem '-tril.' The USAN stem '-tril' refers to endopeptidase inhibitor establish names. However, the identified stem is an ending stem, and in TriLipix, this group of letters appears at the beginning of the name and thus does not represent a stem.

### 3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the medication error prevention staff (see section 3.1.1. above), and noted no additional names thought to have orthographic or phonetic similarity to Trilipix. The Expert Panel also questioned whether the capitalized 'L' in the name could contribute to name confusion with names beginning with 'L'. The Expert Panel recommended that independent searches consider the potential for confusion with drug names beginning with this letter.

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 CDER Prescription Analysis Studies

A total of 27 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About two-thirds of the participants (n=17) interpreted the name correctly as "Trilipix," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The misinterpretations occurring in the phonetic prescription study resulted with the middle 'i' in TriLipix reported as 'a' by two respondents. One respondent placed the letter 'a' before 'l' and one placed it after the 'l.' In the written prescription studies, three respondents to the outpatient prescription omitted the first 'i' in the name, however the first letter 'i' in this writing sample does lack a prominence. The second letter 'i' was misinterpreted as 'u' and 'e' by one respondent each; the 'x' was misinterpreted as 'n' by one respondent, 's' by two respondents, and 'sc' by one respondent See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

It is noted that neither of the sample prescriptions utilized the capital 'L' when writing the proposed proprietary name, TriLipix. None of the four respondents to the verbal prescription capitalized the 'l' in their response.

### 3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified one additional name, Lipitor, thought to look or sound similar to TriLipix and thus had the potential for confusion with the proposed name. Careful evaluation was afforded to drug names beginning with the letters 'L' in

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

accordance with the Expert Panel's recommendations. As such, a total of 34 names were analyzed to determine if the drug names could be confused with TriLipix and if the drug name confusion would likely result in a medication error.

Five of the 34 identified names were determined to lack sufficient orthographic and/or phonetic similarity to TriLipix to present a risk of confusion. These names include: Avalide, Lupron, Lutera, Taclonex and Trilisa odoratissima. (Appendix C)

All of the remaining 29 names were determined to have some orthographic and/or phonetic similarity to TriLipix, and thus determined to present some risk of confusion. Failure mode and effect analysis was then applied to determine if the potential name, TriLipix, could potentially be confused with any of the 29 names and lead to medication errors.

This analysis determined that the name similarity between TriLipix and the identified names was unlikely to result in medication errors for 29 products. The name, Trilipix, was identified as the previously reviewed name for this product and could not result in a medication error. Four names (Salpax, \_\_\_\_\_ and Tritec) have been withdrawn from the market and have no generic equivalent. (Appendix D) Four names (Triaprin, Trichlorex, Trilitron, and Trymex) were branded generic products which have been withdrawn from the market. (Appendix E) One name, \_\_\_\_\_, was a proposed proprietary name for a product which was later approved with a different name. (Appendix F).

b(4)

For 16 of the 29 names (Aricept, Thioplex, \_\_\_\_\_, Triglide, Tri-Hist, Tri-Legest, Trileptal, Trilisate, Tri-Luma, TriLyte, Trimpex, \_\_\_\_\_) the Failure mode and effect analysis determined that medication errors were unlikely due to minimal orthographic and/or phonetic similarity to TriLipix as well as they do not overlap in strength or dosage with TriLipix. (Appendix G)

b(4)

Three names having some numerical overlap in strength with TriLipix include: Relpax, Trilafon, and Lipitor. However, analysis of the failure modes of these three products did not determine the effect of these similarities to result in medication errors in the usual practice setting. (See Appendix H.)

### 3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the container label and carton labeling, the Division of Medication Error Prevention notes several vulnerabilities that may contribute to medication errors.

The presentation of the proprietary name includes a capitalized 'L' throughout the labels and labeling for this product.

#### 3.2.1 Sample Carton Labeling (45 mg and 135 mg)

The proposed proprietary name appears in two colors of font.

The NDC number and the net quantity appear in small white font on a colored background which is difficult to read.

The net quantity appears directly beneath and in close proximity to the strength of the capsules.

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

## **4 DISCUSSION**

### **4.1 PROPRIETARY NAME RISK ASSESSMENT**

The results of the Proprietary Name Risk Assessment found that the proposed name, TriLipix, 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.

We believe that the capitalization of the letter 'L' in the proposed name, TriLipix, will vary in practice. In fact, all the participants in the verbal prescription study failed to capitalize the letter 'L' in Trilipix. Phonetically, "Trilipix" is identical to "TriLipix." The writing samples used in the prescription studies also lacked this capitalization. In addition, an independent proprietary name risk assessment submitted by the Applicant finding the name 'Trilipix' unlikely to be confused with existing names was reviewed in OSE review # 2007-959. However, we note the name reviewed in the independent risk assessment also lacked the capitalized 'L.' Therefore, the proposed names, Trilipix and TriLipix, were simultaneously reviewed with and without the capitalization of the letter 'l' (TriLipix/Trilipix).

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the Medication Error Prevention Staff believes that these limitations are sufficiently minimized by the use of an Expert Panel, and the CDER Prescription Studies that involved 124 CDER practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings.

### **4.2 LABELS AND LABELING RISK ASSESSMENT**

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed carton and container labels appears to be vulnerable to confusion that could lead to medication errors.

#### ***4.2.1 Use of a Capitalized 'L'***

We note the Applicant has chosen to capitalize the 'L' in the name TriLipix. The capitalized 'L' appears throughout the labels and labeling. The use of capitalization highlights one letter in the name and may be misconstrued as Tall Man lettering. Tall Man lettering involves highlighting the dissimilar letters in an established or proprietary name to aid in distinguishing between two names that are similar. In addition, the use of Tall Man lettering is generally reserved to distinguish specific pairs of known look-alike medication names. The use of Tall Man lettering primarily addresses the potential risk from a selection error between known look-alike medication names. The Office of Generic Drugs has compiled a list of 16 generic pairs which

must utilize Tall Man lettering.<sup>8</sup> The list is used consistently throughout the generic manufacturers. We are also concerned that arbitrary use of Tall Man lettering has the potential to decrease its effectiveness to distinguish similar name pairs by making this tool more commonplace. Although the Applicant may not intend to use Tall Man lettering, by highlighting the capital 'L' in TriLipix, we believe this interpretation is possible and could be avoided with the use of standard upper/lower case presentation of the name.

#### ***4.2.2 The Use of Color on the Sample Carton Labeling***

On the professional Sample Carton labeling the Applicant presents the proprietary name in two colors. The first three letters 'Tri' are in light blue font while last five letters 'Lipix' are in the purple font. The Division of Medication Error Prevention and Analysis believes the use of more than one color in the name of a drug product makes it more difficult to read.

The color field in the upper right corner of the primary display panel contains several important pieces of information. The strengths are the most prominent and readable information in this field. In addition, the NDC number and the net quantity appear in this field but in much smaller print. In fact, we find the small white font difficult to read in its current presentation. It is of our opinion that healthcare providers may confuse the number of capsules they are supplying patients as they will be unable to read the printed net quantity on the carton.

Additionally, the strength and the net quantity appear above one another in this field. Although we the net quantity is much smaller than the strength, this size make it difficult to read as previously discussed. We believe that the layout and space on the label provide a means to better separate these often confused numbers on the carton labeling.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The Proprietary Name Risk Assessment findings indicate that the proposed name, TriLipix, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the medication error prevention staff does not object to the use of the proprietary name, TriLipix, 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 medication error prevention staff rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If 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.

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

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<sup>8</sup> <http://www.fda.gov/CDER/Drug/MedErrors/nameDiff.htm>

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

## **5.1 COMMENTS TO THE DIVISION**

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, project manager, at 301-796-0675.

## **5.2 COMMENTS TO THE APPLICANT**

### ***5.2.1 Proprietary Name Assessment***

The Proprietary Name Risk Assessment findings indicate that the proposed name, TriLipix, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the medication error prevention staff does not object to the use of the proprietary name, TriLipix, 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 medication error prevention staff rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If 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.

We believe that the capitalization of the letter 'L' in the proposed name, TriLipix, will vary in practice. In fact, all the responders to the verbal prescription study failed to capitalize the letter 'L' in Trilipix. The writing samples also lacked this capitalization. Thus, our analysis evaluated the proposed name as Trilipix and TriLipix.

Additionally, we believe the presentation of the name in two colors with 'Lipix' in the more dominant purple color disrupts the continuity and thereby decreases the readability of the name. We offer the recommendations below for consideration.

### ***5.2.2 Labels and Labeling Assessment***

#### **5.2.2.1 Retail Container Labels (45 mg and 135 mg)**

1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.

#### **5.2.2.2 Sample Blister Labels**

1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.

### 5.2.2.3 Sample Carton Labeling (45 mg and 135 mg)

1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.
2. Present the proprietary name, TriLipix, in one color.
3. Improve the readability of the NDC number and the net quantity.

### 5.2.2.4 Insert Labeling

1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.

## 6 REFERENCES

### 6.1 REVIEWS

1. *OSE review #2007-959, Proprietary Name Review Trilipix, Abate, R, February 5, 2008.*

### 6.2 DATABASES

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

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

2. *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 medication error prevention staff, FDA.

3. *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.

4. *AMF Decision Support System [DSS]*

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

5. *Division of Medication Error Prevention proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the medication error prevention staff from the Access database/tracking system.

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

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

**7. *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.

**8. *US Patent and Trademark Office location*** (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

**9. *Clinical Pharmacology Online*** ([www.clinicalpharmacology-ip.com](http://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.

**10. *Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at***  
***([www.thomson-thomson.com](http://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.

**11. *Natural Medicines Comprehensive Databases*** ([www.naturaldatabase.com](http://www.naturaldatabase.com))

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

**12. *Stat!Ref*** ([www.statref.com](http://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.

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

List contains all the recognized USAN stems.

**14. *Red Book Pharmacy's Fundamental Reference***

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

**15. *Lexi-Comp*** ([www.lexi.com](http://www.lexi.com))

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

**16. *Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

## APPENDICES

### Appendix A:

The medication error prevention staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The medication error prevention staff also compares 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 prevention staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* 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 prevention 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. "I" 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 prevention staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the medication error prevention staff 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 medication error prevention staff 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"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>

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

**Appendix B:**

**CDER Prescription Study Responses**

	Trilipix	Trilipix
Trilipix	Trilipix	Trilipix
Trilipix	Trilipix	Trilipin
Trilipix	Trilapix	Trilipisc
Trilipix	Trilipix	Trilipix
Trilipix		Trilepis
		Trilipix

		Trilipix

**Appendix C: Proprietary names with minimal orthographic similarity**

Proprietary Name	Similarity to Trilipix
Avalide	Look
Lupron	Look
	Look
Taclonex	Look
Trilisa odoratissima	Look

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**Appendix D: Products withdrawn from the market with no generic equivalent product available**

Proprietary Name	Similarity to Trilipix	Year product withdrawn by the Applicant
Salpix	Look	1994
	Look	Date unknown
	Look	1972
Tritec	Look	1999

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**Appendix E: Products Branded generic products withdrawn from the market**

Proprietary Name	Similarity to Trilipix	Year product withdrawn by the Applicant
Triaprin	Look	2001
Trichlorex	Look	2005

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

Trilitron	Look	2001
Trymex	Sound	1990

**Appendix F:** Proposed proprietary names for products approved with another name.

Proprietary Name	Similarity to Trilipix
_____	Look

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**Appendix G:** Products with no numerical overlap in strength or dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Trilipix (Fenofibric acid)		45 mg and 135 mg capsules	Usual dose: 1 capsule daily
Aricept	Look	5 mg and 10 mg	10 mg (one tablet) by mouth daily.
Thioplex (discontinued with generic available)	Look	15 mg	0.3 to 0.4 mg/kg intravenously weekly.
_____	Look	0.025%, 0.05%, and 0.1%	Apply daily to affected area.
_____	Look	365.4 mg/30 mg/16 mg	Two capsules by mouth every four hours.
Triglide	Look	50 mg and 160 mg	160 mg (one tablet) by mouth daily.
_____	Sound	5 mg/2 mg/12.5 mg per 5 mL	One teaspoonful by mouth every 12 hours.
Tri-Legest	Look and Sound	21 and Fe (suffixes)	One tablet by mouth daily.
Trileptal®	Look	150 mg, 300 mg and 600 mg	One tablet twice daily.
_____	Look	500 mg, 750 mg, and 1000 mg	One to two tablets twice or three times daily.
Tri-Luma	Look and Sound	0.01%/4%/0.05%	Apply to affected area daily.
TriLyte®	Look	one gallon container	One gallon once as directed.
Trimex®	Look	100 mg	One tablet twice daily or 2 tablets daily.
_____	Look		0.5 ml as a 5-dose series in infants and

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

(vaccine)			children 6 weeks to 7 years of age.
Trisenox	Look	10 mg/10 mL	0.15 mg/kg intravenous infusion daily.
—	Look	25 mg/175 mg/12.5 mg per 5 mL	One to two teaspoonful (5-10 mL) by mouth every four to six hours
⌈ ⌋	Look		One mL intramuscularly at zero, one and six months.

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**Appendix H: Potential confusing name with similarity in strength or dose**

Failure Mode: Name confusion	Causes	Effects
Trilipix (Fenofibric acid)	45 mg and 135 mg capsules	Usual dose: 1 capsule daily
Relpax (Eletriptan HBr) 20 mg and 40 mg tablets	Orthographic similarity: 'el' appears similar to 'il' and ending three letters may appear similar 'pax' vs. 'pix.' numerically similar strengths (40 vs. 45) Dose is one oral solid.	Orthographic differences in the names reduce the risk of medication errors in the usual practice settings. <i>Rationale:</i> Orthographic difference stem from the fact TriLipix begins with 'T' vs. 'R' and also contains eight letters providing additional length to the name. The usual dose of Trilipix is 135 mg daily. The directions for use for Relpax are to take at the onset of headache and may repeat in two hours. As this is lengthy, it may also be written "Take as directed"
Trilafon® (perphenazine) 2 mg, 4 mg, 8 mg, and 16 mg tablets (withdrawn from the market with generic equivalents available)	Orthographic similarities, Tril-, 'p' may resemble 'f', same length. Dose is one oral solid. Prescribers continue to use proprietary names when writing orders for generic equivalents after the original product has been withdrawn from the market. Numerically similar strengths (45 mg vs. 4 mg)	Orthographic differences in the names reduce the risk of medication errors in the usual practice settings. The strengths of the products minimize the risk of medication error in the usual practice settings. <i>Rationale:</i> The risk of medication errors is reduced by the orthographic differences in the names. Trilipix contains an 'i' at the fifth and seventh positions and ends with an 'x' compared to Trilafon. The strengths of Trilafon (perphenazine) are 2 mg, 4 mg, 8 mg, and 16 mg minimized the risk of medication errors as these differ from the strengths of Trilipix. The usual frequency of administration for perphenazine is three times daily.

<p><b>Lipitor</b> (atorvastatin calcium) 10 mg, 20 mg, 40 mg, and 80 mg tablets</p>	<p><b>Orthographic similarity:</b> Both names contain "Lipi-" and this grouping is followed by a letter which contains a cross stroke 'x' vs. 't.'</p> <p><b>Phonetic similarity:</b> Both names contain three syllables, the names share one same syllable 'lip' and the syllable following contains 'i'.</p> <p><b>Numerically similar strengths</b> (45 mg vs. 40 mg)</p> <p><b>Same frequency of administration.</b> (once daily)</p> <p><b>Both are oral solid dosage forms.</b> (capsule vs. tablet)</p> <p><b>Same patient population</b> (TriLipix is indicated for use with a HMG CoA reductase inhibitor)</p>	<p><b>Orthographic and phonetic differences in the names reduce the risk of medication errors in the usual practice settings.</b></p> <p><i>Rationale:</i></p> <p>The orthographic and phonetic differences stem from the "Tri" prior to 'Lipi-' in TriLipix as well as the '-or' ending in Lipitor. Orthographic difference is provided when the name TriLipix is written with a lower case 'l' as in the prescription study. It is unlikely that prescribers or other healthcare practitioners will stop writing in midstroke to write a capital 'L.'</p> <p>The numerically similar strengths have phonetic differences if given in a verbal prescription.</p>
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**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:** September 15, 2008

**To:** Julie Golden, MD/Medical Officer  
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**From:** Vicky Borders-Hemphill, Pharm.D., LCDR USPHS  
Drug Use Analyst  
Division of Epidemiology  
Office of Surveillance and Epidemiology

**Subject:** Concurrency Analysis VOCON: fenofibrate concurrency with HMG CoA Reductase Inhibitors

**Drug Name(s):** Antara®/Lofibra®/Fenoglide®/Lipofen®/Tricor®/Triglide® (fenofibrate), Mevacor®/Altoprev® (lovastatin), Baycol® (cerivastatin), Crestor® (rosuvastatin), Lescol®/Lescol® XL (fluvastatin), Lipitor® (atorvastatin), Pravachol® (pravastatin), Zocor® (simvastatin)

**Application Type/Number:** NDA 22-224

**Applicant/sponsor:** Abbott Laboratories

**OSE RCM #:** 2008-1344

\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\*

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## EXECUTIVE SUMMARY

The Division of Metabolism and Endocrinology Products (DMEP) is reviewing an NDA for Trilipix Delayed Release Capsules (NDA 22-224), a fenofibric acid compound with clinical data supporting an indication for co-administration with a statin, HMG CoA Reductase Inhibitor. Current labeling for fenofibrate discourages concomitant use with a statin due to rhabdomyolysis risk. DMEP requested an estimate of the amount of concurrent use of any statin with any fenofibrate and a separate analysis of any statin with Tricor<sup>®</sup>, a fenofibrate, over the last 5 years.

We examined the annual number of patients who filled a prescription for a fenofibrate concurrent with a statin/HMG CoA Reductase Inhibitor (USC 32110) during the years 2002-2007. We conducted a concurrency analysis utilizing the Verispan, Vector One<sup>®</sup>: Concurrency (VOCON) tool.

Please note. Data from VOCON are unprojected patient counts and may not be generalizable to all US patients.

- Overall, approximately \_\_\_\_\_ of patients who filled a prescription for a fenofibrate (denominator) concurrently filled a prescription for an HMG CoA Reductase Inhibitor per year of this review.
- Overall, approximately \_\_\_\_\_ of patients who filled a prescription for an HMG CoA Reductase Inhibitor (denominator) concurrently filled a prescription for a fenofibrate per year of this review.
- For each year studie \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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## 1 INTRODUCTION

The sponsor submitted an NDA for Trilipix Delayed Release Capsules (fenofibric acid), NDA 22-224, in December 2007 for use in combination with statins for mixed dyslipidemia or as monotherapy for mixed dyslipidemia, primary hypercholesterolemia, or hypertriglyceridemia. The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated with rhabdomyolysis, markedly elevated creatine kinase levels, and myoglobinuria, leading to acute renal failure. In the WARNINGS section of the label of currently marketed fenofibrates, avoidance of combined use with an HMG CoA Reductase Inhibitor, unless the benefit outweighs the increased risk, is recommended. DMEP requested an estimation of concurrent use between fenofibrates and HMG CoA Reductase Inhibitors to assist in the review of this NDA.

## 2 METHODS AND MATERIALS

### 2.1 INTRODUCTION

Using the currently available data resources, this review describes the concurrency between fenofibrates (including Antara<sup>®</sup>/Lofibra<sup>®</sup>/Fenoglide<sup>®</sup>/Lipofen<sup>®</sup>/ Tricor<sup>®</sup>/ Triglide<sup>®</sup>, fenofibrate generic) grouped or separately and HMG CoA Reductase Inhibitors (USC 32110). Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

## 2.2 DATA SOURCES USED

Using the VOCON tool, we queried for concurrent use of fenofibrates with the HMG CoA Reductase Inhibitor Class (USC 32110). An episode of concurrency is identified when a prescription in the Base group (including Antara<sup>®</sup>/Lofibra<sup>®</sup>/Fenoglide<sup>®</sup>/Lipofen<sup>®</sup>/Tricor<sup>®</sup>/Triglide<sup>®</sup>, fenofibrate generic) overlaps with the days supply for a dispensed prescription in the Concurrent group HMG CoA Reductase Inhibitor (USC 32110). The days supply is calculated by adding the number of *therapy days* to the time of prescription dispensing. A grace period of 50% is allowed for the days supply time window to adjust for delays in prescription filling. Thus, the total days of therapy for a claim with 30 days supply would be 45 days when including the 50% grace period. The number of *therapy days* is estimated by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day.

## 2.3 PRODUCTS INCLUDED

Twelve sets of reports were generated from concurrency scenarios that were set up using a 50% grace period of overlapping days supply concurrency method. Analyses included six calendar years from 2002 through 2007. Data were analyzed for concurrency between fenofibrates and the HMG CoA Reductase Inhibitor Class (USC 32110).

## 3 RESULTS

### 3.1 OVERALL CONCURRENCY BETWEEN FENOFIBRATES AND HMG COA REDUCTASE INHIBITOR CLASS (USC 32110)

In 2007, in this sample of patients, more than \_\_\_\_\_ patients filled a prescription for a fenofibrate and nearly \_\_\_\_\_ patients filled a prescription for an HMG CoA Reductase Inhibitor. *Table 1 (see Appendix 2)* shows the overall concurrency between fenofibrates and the HMG CoA Reductase Inhibitor class (USC 32110) by year from 2002 through 2007.

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Overall, approximately \_\_\_\_\_ of patients who filled a prescription for a fenofibrate concurrently filled a prescription for an HMG CoA Reductase Inhibitor per year of this review. When determining the proportionality based on the number of HMG CoA Reductase Inhibitor patients, the proportion of patients filling a prescription for HMG CoA Reductase Inhibitor (denominator) concurrently with a prescription for a fenofibrate \_\_\_\_\_ is substantially less because far fewer patients filled a fenofibrate prescription, comparatively.

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### 3.2 CONCURRENCY BETWEEN FENOFIBRATES BRANDS AND HMG COA REDUCTASE INHIBITOR CLASS (USC 32110)

For each year studied, there were a greater absolute number of concurrent patients filling a prescription for Tricor<sup>®</sup> with a prescription for an HMG CoA Reductase Inhibitor when compared to the other brands of fenofibrate (*see Table 1 in Appendix 2*). Although Antara<sup>®</sup> was approved in November 2004 and Triglide<sup>®</sup> was approved in May 2005.

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## 4 DISCUSSION

The findings from this consult should be interpreted in the context of the known limitations of the databases used. When examining fill sequence, several assumptions are made: (1) that a patient is

taking the prescription(s) as recommended; and (2) the days supply for a prescription is recorded to reflect how the patient is actually taking the prescription.

Verispan's Vector One<sup>®</sup>: Concurrency does not capture data from mail order pharmacies. Mail order pharmacies typically dispense chronic use meds in larger quantities than retail pharmacies. We therefore believe that the omission of mail order may underestimate the days of concurrent therapy. Although the concurrency data presented in this review are all based on analysis of unprojected patient counts and they cannot be generalized to the national level, the Verispan database is capturing a very large sample representing roughly half the retail prescription volume in the U.S.

## 5 CONCLUSIONS

Based on this analysis of a sample of patients from 2002 through 2007, overall, fenofibrates have a substantial percentage of concurrency ~~with HMG CoA Reductase Inhibitors.~~

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## APPENDICES

### APPENDIX 1: DATABASE DESCRIPTIONS

#### *Verispan, LLC: Vector One®: Concurrency (VOCON)*

Data used in VOCON is derived from Verispan's Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims annually, representing over 160 million unique patients. Vector One® receives approximately half the of retail prescriptions dispensed nationwide. Verispan obtains all prescriptions from approximately one-third of the reporting stores and a significant sample of prescriptions from the remaining stores.

VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using four scenarios. These scenarios are (in order of most to least restrictive): Same day fills, overlapping days supply, overlapping days supply with % grace period, fills during the same time period.

The VOCON module provides unprojected patients counts. Nationwide projections are not available.

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

Date: October 2, 2008

To: Mary Parks, M.D., Director  
**Division of Metabolism and Endocrinology Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management**

From: Nancy Carothers, RN, BA  
Patient Product Information Specialist  
**Patient Labeling and Education Team  
Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Trilipix™ (fenofibric acid) Delayed-Release Capsules

Application Type/Number: NDA 22-224

Applicant/sponsor: Abbott Laboratories

OSE RCM #: 2008-1433

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## 1 INTRODUCTION

Abbot Laboratories submitted a new Drug Application (NDA 22-224) for TriLipix™ Delayed Release Capsules (fenofibric acid) on December 7, 2007. On February 12, 2008 FDA sent an Agency Filing Communication requesting additional CMC and Clinical Statistics information. The sponsor provided a partial response to these requests on April 10, 2008. This response included changes to the proposed labeling, which include using “fenofibric acid” as the established name and using the dosage form name, “delayed release capsule,” on all labeling. The tradename will also be changed from TriLipix to Trilipix and the new tradename is used for this review. The review assignment for the Trilipix™ Package Insert (PI) and Patient Package Insert (PPI) was received in DRISK on September 10, 2008. The PDUFA date is October 7, 2008.

The Division of Metabolism and Endocrinology Products requested that the Patient Labeling and Education Team review the Patient Package Insert for this product. This review was written in response to that request.

## 2 MATERIAL REVIEWED

- Trilipix™ (fenofibric acid) PI submitted by the Sponsor on April 10, 2008 and further revised by the RD throughout the current review cycle.
- Trilipix™ (fenofibric acid) PPI submitted by the Sponsor on April 10, 2008 and further revised by the RD throughout the current review cycle.

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.0 and a Flesch Reading Ease score of 52.8%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). Our revised PPI has a Flesch Kinkaid grade level of 8.1 and a Flesch Reading Ease score of 57.9%.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible,
- made the PPI consistent with the PI,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information

more accessible for patients with low vision. We have reformatted the PPI document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are **bolded, underlined and italicized**.

We are providing the review division a marked-up and clean copy of the revised PPI.

We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

- At this time, we are submitting a review of the sponsor's proposed PPI. We have discussed with DMEP whether or not Trilipix meets the criteria to require a Medication Guide, and agree that it does. While we support the idea of a Medication Guide for this product, the PI does not contain strong enough language or warnings, such as a boxed or bolded warning, about an increased risk of muscle toxicity when fenofibrate is used in combination with a statin, particularly at high doses. We believe that if this risk information is to be conveyed in a Medication Guide, the label would need to be modified or strengthened to support the language in the MG. The PI does say that Trilipix is not recommended for use in combination with the maximum dose of statins, and it lists serious side effects that must be reported right away. If the language in the PI is strengthened and if it is decided that a Medication Guide will enhance the safe and effective use of this drug, we will amend this review. In addition, we suggest that if a Medication Guide is developed for Trilipix, then a Medication Guide should be developed for the class of drugs (fenofibrates), because we have information to suggest that there is significant concomitant use of fenofibrates with statins.
- In the section, "What should I tell my healthcare provider before taking Trilipix?" we have added, "cholesterol-lowering agents" because Trilipix is often co-administered with statins. We also added "bile acid sequestrants" because the Drug Interactions (7.2) section states that Trilipix must be taken one hour before or 4 to 6 hours after taking bile acid sequestrants to ensure that Trilipix is fully absorbed.
- The PI states that Trilipix should be used during pregnancy only if the "benefit justifies the potential risk to the fetus" (8.1). It is not known if Trilipix will harm the fetus or pass into breast milk, (8.3) and patients should choose whether to breastfeed or take Trilipix. This information has been added to the PPI in the section, "Tell your healthcare provider if you:"
- The statement \_\_\_\_\_ was in the, "Who should not take Trilipix?" section of the original PPI. The statement has been deleted because it may be confusing to patients. This statement is telling patients not to take these two medicines together, but the PI (See 8.1) says that statins are contraindicated and Trilipix is not recommended for pregnant or breastfeeding patients. If the statement must be retained it should be

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in the section instructing patients on what to tell their healthcare provider before taking Trilipix.

- Trilipix is a delayed release capsule and tampering with capsules can be relatively easy. For these two reasons, patients should be told not to alter the capsule in any way (“Do not break, crush, dissolve, or chew Trilipix capsules before swallowing.”) This instruction has been added to the PPI and should be added to the PI’s Patient Counseling section. The PI and PPI must be consistent.
- Trilipix may cause serious side effects, and these should be listed first, before common or less serious side effects.
- The sponsor uses the term “doctor,” in the proposed PPI. We recommend using the term “healthcare provider” because other healthcare professionals, such as nurse practitioners and physician’s assistants, may provide primary care and patient counseling (about medicines) to some patients.
- We have added the following statement to the end of the section, “What are the possible side effects of Trilipix?”:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Trilipix, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

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