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RESEARCH**

APPLICATION NUMBER:

204654Orig1s000

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
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: July 9, 2013

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

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Drug Name and Strength: Lo Minastrin Fe
(Norethindrone Acetate and Ethinyl Estradiol Chewable
Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate
Tablets)
1 mg/10 mcg and 10 mcg and 75 mg

Application Type/Number: NDA 204654

Applicant/Sponsor: Warner Chilcott

OSE RCM #: 2013-1522

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

CONTENTS

1	INTRODUCTION.....	1
1.1	Regulatory History	1
1.2	Product Information.....	1
2	RESULTS.....	2
2.1	Promotional Assessment	2
2.2	Safety Assessment.....	2
3	CONCLUSIONS.....	6
3.1	Comments to the Applicant.....	6
4	REFERENCES.....	7
	APPENDICES.....	10

1 INTRODUCTION

This review evaluates the proposed proprietary name, Lo Minastrin Fe, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

Warner Chilcott LLC submitted a request for proprietary name review for Lo Minastrin Fe (Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets) for NDA 204654 on June 27, 2013. The first proposed proprietary name, (b) (4) was found unacceptable in OSE Review #2013-860 dated June 12, 2013.

The New Drug Application for this product was submitted by the Applicant under Section 505(b)(1) on September 28, 2012. This NDA provides for a new method of administration for low dose oral contraception consisting of mint-flavored, chewable tablets. The proposed regimen is the same as the approved regimen for Lo Loestrin Fe (NDA 022501, approved October 21, 2010) by Applicant holder, Warner Chilcott LLC. The main difference with NDA 204654 is that the first 24 active tablets may be chewed before swallowing and followed with liquid (b) (4). Once approved, the Applicant plans to discontinue Lo Loestrin Fe.

Additionally, the Applicant submitted labels and labeling on June 27, 2013 which will be reviewed by DMEPA under a separate cover in OSE Review #2013-1-1.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 27, 2013 proprietary name submission.

- Active Ingredient: Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets and Ferrous Fumarate Tablets
- Indication of Use: Prevention of Pregnancy
- Route of Administration: Oral
- Dosage Form: Chewable Tablets and Tablets
- Strength: 1 mg/10 mcg, 10 mcg, and 75 mg
- Dose and Frequency: Take one tablet by mouth at the same time every day. The blue tablet may be (b) (4) chewed and swallowed. If the blue tablet is chewed, the patient should drink a full glass (8 ounces) of liquid immediately after swallowing. The white tablet and the brown tablet are swallowed.
- How Supplied: Carton of 5 blister cards; each blister card contains 24 blue, round (active) chewable tablets containing 1 mg norethindrone and 10 mcg ethinyl estradiol, 2 white hexagonal (active) tablets containing 10 mcg ethinyl estradiol, and 2 brown, round (non-hormonal placebo) tablets containing 75 mg ferrous fumarate.

- Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F)
- Container and Closure System: Primary packaging consists of unit-dose blisters consisting of (b) (4) blister film and an aluminum foil/vinyl heat-seal coated lidding. Secondary packaging consists of a rigid (b) (4) card bonded to the unit-dose blister, prescriber and patient package inserts, and (b) (4) board cartons.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Bone, Reproductive, and Urologic Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 *United States Adopted Names (USAN) SEARCH*

The June 28, 2013 search of the United States Adopted Name (USAN) stems did not identify that a USAN stem is present in the proposed proprietary name.

2.2.2 *Components of the Proposed Proprietary Name*

The proprietary name is comprised of the root name 'Minastrin' and the modifiers 'Lo' and 'Fe'. The Applicant indicated in their submission that a derivation of the proposed proprietary name has not been determined. They further indicate that the modifier 'Lo' denotes the low dose of estrogen in this product, and the modifier 'Fe' denotes the Ferrous Fumarate tablets (non-hormonal) provided to complete a 28-day cycle.

The Applicant did not provide data to support the use of these modifiers, nor provide data to support that these modifiers would not inadvertently introduce a source of error. However, the Applicant followed the same naming convention for the proposed name, Lo Minastrin Fe, as that of the reference listed drug, Lo Loestrin Fe.

The 'Fe' modifier in oral contraceptive products has consistently meant 75 mg of Ferrous Fumarate. The Applicant is proposing to use the modifier 'Fe' consistently with how it is used in the reference listed drug. Similarly, the 'Lo' modifier is used for other approved oral contraceptive products to represent lower estrogen content or lower estrogen and progestin content. The Applicant is proposing to use the modifier 'Lo' consistently with how it is used in the reference listed drug, and the amount of Ethinyl Estradiol in the proposed product, Lo Minastrin Fe is indeed less than that found in the Applicant's other proposed Minastrin product (i.e., Minastrin 24 Fe***) which is currently under review by the Agency. Additionally, DMEPA has previously reviewed and permitted the modifiers 'Lo' and 'Fe' into the marketplace in the past. Table 1 provides a comparison of Warner Chilcott's Loestrin product line as well as their new proposed products, Minastrin 24

Fe*** and Lo Minastrin Fe.

Table 1: Loestrin (Marketed) and Minastrin (Proposed) Product Line Comparison								
Product Name	Lo Loestrin Fe	Lo Minastrin Fe***	Loestrin 24 Fe	Minastrin 24 Fe***	Loestrin Fe 1/20	Loestrin Fe 1.5/30	Loestrin 21 1/20	Loestrin 21 1.5/30
Combination tablets Norethindrone acetate (NA) and Ethinyl estradiol (EE)	NA 1 mg/EE 10 mcg (24 tablets)	NA 1 mg/EE 10 mcg (24 Chewable tablets)	NA 1 mg/EE 20 mcg (24 tablets)	NA 1 mg/EE 20 mcg (24 Chewable tablets)	NA 1 mg/EE 20 mcg (21 tablets)	NA 1.5 mg/EE 30 mcg (21 tablets)	NA 1 mg/EE 20 mcg (21 tablets)	NA 1.5 mg/EE 30 mcg (21 tablets)
Ethinyl estradiol (EE) tablets	EE 10 mcg (2 tablets)	EE 10 mcg (2 tablets)						
Ferrous fumarate tablets	FF 75 mg (2 tablets)	FF 75 mg (2 tablets)	FF 75 mg (4 tablets)	FF 75 mg (4 tablets)	FF 75 mg (7 tablets)	FF 75 mg (7 tablets)		
Monthly estrogen content	(b) (4)							

DMEPA conducted a search of the FDA Adverse Event Reporting System (FAERS) on July 2, 2013 to identify potential problems with the nomenclature of the Loestrin product line. This search identified the same number of relevant cases related to the Loestrin product line that were identified in OSE Review #2009-2349 dated January 19, 2010 (Lo Loestrin Fe Proprietary Name Review), OSE Review #2012-1408, 2012-1409 dated March 21, 2013 (b)(4) Proprietary Name Review), and OSE Review #2013-1 dated May 21, 2013 (b)(4) Label, Label, and Packaging Review). All of these cases were wrong drug errors and included eight reports of confusion between the strengths of the Loestrin Fe products (i.e., Loestrin Fe 1/20, which are represented by numerical modifiers (e.g. 1/20 and 1.5/30), and two reports of confusion between Loestrin Fe 24 and Lo Loestrin Fe. No cases of confusion between Loestrin Fe and the non-iron containing Loestrin products were identified, which helps to support the safety of the “Fe” modifier. No additional cases of wrong drug errors have been reported since July 9, 2012. See Appendix G for a list of the case numbers retrieved from the July 2, 2013 FAERS search.

In our assessment of the modifiers ‘Lo’ and ‘Fe’, we also considered the possibility of these modifiers being omitted from prescriptions or medication orders. The results of our written prescription studies identified three participants who omitted the ‘Fe’ modifier on the medication order. However, none of the participants omitted the ‘Lo’ modifier. This

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can be attributed to the fact that based on post-marketing reports of medication errors resulting from practitioners dropping the modifier ‘Lo’ when it appears at the end of the name, DMEPA now recommends incorporating the modifier ‘Lo’ at the beginning of the name or within the name. The name submitted by the Applicant follows this recommendation which should help prevent the modifier ‘Lo’ from being overlooked when included on a prescription. Therefore, even if the modifier ‘Fe’ is omitted from a prescription order that is intended for Lo Minastrin Fe, the presence of the modifier ‘Lo’ can help differentiate this product from the other Minastrin products (i.e., Minastrin 24 Fe***).

Although confusion between products with similar root names but differing modifiers (i.e., Lo Minastrin Fe and Minastrin 24 Fe^{***}) is a possibility, the Applicant is proposing to use the modifiers ‘Lo’ and ‘Fe’ in the proposed product, Lo Minastrin Fe, as they are consistently used in the oral contraceptive marketplace. Additionally, adequate differentiation of the labels and labeling associated with the Minastrin products may help minimize confusion, especially if the (b) (4)

(b) (4) Thus, in consideration of the total data available, DMEPA does not object to the use of the modifiers, ‘Lo’ and ‘Fe’.

2.2.3 FDA Name Simulation Studies

Thirty-two practitioners participated in DMEPA’s prescription studies. The interpretations did not overlap with any currently marketed products nor did the misinterpretations sound or look similar to any currently marketed products or any products in the pipeline. Thirteen out of thirty-two prescription study participants interpreted the name correctly as Lo Minastrin Fe (9 outpatient and 4 inpatient participants). All ten voice prescription study participants misinterpreted the modifier ‘Lo’. The misinterpretations included the following: ‘Blo’, ‘Blu’, ‘Bo’, and ‘Bul’. Other misinterpretations included confusing the second position vowel ‘i’ as ‘e’, the fourth position vowel ‘a’ as ‘e’, ‘i’, and ‘u’, and the eighth position vowel ‘i’ as ‘a’, ‘i’, ‘o’, ‘u’, ‘e’, and ‘ai’, in the root name Minastrin in the voice and inpatient prescription studies. Three inpatient prescription study participants omitted the ‘Fe’ modifier. We have considered these variations including those related to the modifier ‘Lo’ in our look-alike and sound-alike searches and analysis (see Appendix B). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, July 5, 2013 e-mail, the Division of Bone, Reproductive, and Urologic Products, (DBRUP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Lo Minastrin Fe. Table 2 lists the names

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with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Lo Minastrin Fe identified by the primary reviewer and the Expert Panel Discussion (EPD), which were not previously identified and evaluated in OSE Review #2013-1490. Since our evaluation found that none of the product characteristics have changed, we did not re-evaluate the previously identified names. See Appendix F for a list of these names.

Table 2: Collective List of Potentially Similar Names (DMEPA and EPD)					
Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Loma Asthma	EPD	Lomustine	EPD	Lovastatin	EPD
Look and Sound Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
(b) (4)	EPD	(b) (4)	EPD		

Our analysis of the five names contained in Table 2 considered the information obtained in the previous sections along with their product characteristics. We determined none of the five names will pose a risk for confusion as described in Appendices D through E.

2.2.6 Communication of DMEPA’s Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Bone, Reproductive, and Urologic Products via e-mail on July 8, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Bone, Reproductive, and Urologic Products on July 9, 2013, they stated no additional concerns with the proposed proprietary name, Lo Minastrin Fe.

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3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Marcus Cato, OSE project manager, at 301-796-3903.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Lo Minastrin Fe, and have concluded that this name is acceptable.

The proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The results are subject to change. If any of the proposed product characteristics as stated in your June 27, 2013 submission are altered, the name must be resubmitted for review.

4 REFERENCES

OSE Review #2013-1490, Minastrin 24 Fe Proprietary Name Review, Siahpoushan, M., July 1, 2013.

OSE Review #2013-1, (b) (4) Label, Labeling, and Packaging Review, Park, A., Siahpoushan, M., May 21, 2013

OSE Review #2012-78/2012-79, 2012-65/2012-66, 2012-110/2012-111, 2012-1408/2012/1409, (b) (4) Proprietary name, Label, Labeling, and Packaging Review, Brody, S., March 21, 2013.

OSE Review #2009-2349, Lo Loestrin Fe Proprietary Name Review, Turner, T., January 19, 2010.

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

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

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. *Drug Facts and Comparisons, online version, St. Louis, MO* (<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. *FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]*

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. *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.

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

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

7. *U.S. Patent and Trademark Office* (<http://www.uspto.gov>)

USPTO provides information regarding patent and trademarks.

8. *Clinical Pharmacology Online* (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. *Natural Medicines Comprehensive Databases* (www.naturaldatabase.com)

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

10. *Access Medicine* (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison’s Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman’s The Pharmacologic Basis of Therapeutics.

11. *USAN Stems* (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

12. *Red Book* (www.thomsonhc.com/home/dispatch)

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

13. *Lexi-Comp* (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

14. *Medical Abbreviations* (www.medilexicon.com)

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

15. CVS/Pharmacy (www.CVS.com)

This database contains commonly used over the counter products not usually identified in other databases.

16. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

17. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

18. Dogpile (www.dogpile.com)

Dogpile is a [Metasearch](#) engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

19. Natural Standard (<http://www.naturalstandard.com>)

Natural Standard is a resource that aggregates and synthesizes data on complementary and alternative medicine.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.²

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
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/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the

safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA 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, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically

scanned and one prescription is delivered to a random sample of 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.³ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product

³ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. 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, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Lo Minastrin Fe	Scripted May Appear as	Spoken May Be Interpreted as
Capital 'L'	J, I, C, Z, T, S	W, B
Lower case 'l'	b, e, s, A, P, l, t, c	w, b
Lower case 'o'	a, c, e, u	Oh
Capital 'M'	Ss, W, N, V	N, B
Lower case 'm'	n, nn, rn, v, w, wi, vi, ve, onc, z	n, b
Lower case 'i'	e, l	Any vowel
Lower case 'n'	M, u, x, r, h, s	dn, gn, kn, mn, pn, m
Lower case 'a'	'el', 'd', 'o', 'n', 'u'	Any vowel
Lower case 's'	G, 5, g, n, i	X
Lower case 't'	r, f, x, A	D
Lower case 'r'	s, n, e, ,v	Wr
Capital 'F'	T, J, L, Z, I, P, E	PF, PH
Lower case 'f'	t, x, j, b, z, l	
Lower case 'e'	a, i, l, o, u, P, c	Any vowel
Modifier 'Fe'	'Fc' or modifier could be omitted during prescribing	Se, may be inadvertently omitted
Letter Strings		
Lo	b, k, h, 10	Bo, Blo. May be misinterpreted as quantity or may be inadveretently omitted.
Mi	Vi, W	Me, Ma
In	Ur, m,	m, d
Tr	B	Ter
Ri	u, v	
In	Ur, ui, w	im, id

Appendix C: Prescription Simulation Samples and Results

Figure 1. Lo Minastrin Fe Study (Conducted on 7/3/13)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u> <i>Lo Minastrin Fe 1 tab po once daily </i></p>	<p>Lo Minastrin Fe 1 tab po qd # 1 pack</p>
<p><u>Outpatient Prescription:</u> <i>Lo Minastrin Fe 1 tab po qd #1 pack</i></p>	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

191 People Received Study
32 People Responded

Study Name: Lo Minastrin Fe

Total	10	10	12	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
BLOMENESTRAN FE	0	1	0	1
BLOMENISTRAN FE	0	1	0	1
BLOMINISTRAN FE	0	1	0	1
BLUMENISTRAN FE	0	1	0	1
BOMENESTRAN FE	0	1	0	1
BOMINESTRAN FE	0	1	0	1
BOMINESTRAND FE	0	1	0	1
BOMINISTRAN FE	0	2	0	2
BULMINISTRAN FE	0	1	0	1
LO MINASTRIN FE	7	0	1	8
LO MINASTRON FE	0	0	1	1
LO MINUSTRUM	0	0	1	1
LOMINASTRAN FE	0	0	1	1
LOMINASTREN FE	0	0	1	1
LOMINASTRIM FE	1	0	0	1
LOMINASTRIN FE	2	0	3	5
LOMINASTRUM FE	0	0	1	1
LOMINISTRAIM	0	0	1	1
LOMINSASTUM FE	0	0	1	1
LOMINSTRIM	0	0	1	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Proprietary Name	Active Ingredient	Similarity to Lo Minastrin Fe	Failure preventions
1.	Loma Asthma	N/A	Look	Name identified in the Redbook on line database and described as a homeopathic agent. Unable to find product characteristics in commonly used drug databases. (b) (4)
2.	(b) (4)			
3.	(b) (4)			

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Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

No.	<p>Proposed name: Lo Minastrin Fe (Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets)</p> <p>Dosage Form: Tablets</p> <p>Strength(s): 1 mg/10 mcg and 10 mcg and 75 mg</p> <p>Usual Dose: One tablet orally once daily.</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
1.	<p>Lovastatin (Established name for Mevacor) Tablets 20 mg, 40 mg</p> <p>Usual Dose: The usual recommended dose is 20 mg once a day with the evening meal. The dosing range is 10 mg to 80 mg in a single or two divided dose.</p>	<p>Orthographic: If the modifier 'Fe' is omitted from Lo Minastrin Fe, both names begin with 'Lo', share similar scripted letter strings '-nast-' vs. '-vast-', and the ending letter string '-in'.</p> <p>Route of Administration: Oral</p> <p>Dosage form: Tablets</p> <p>Possible Overlap in the Frequency: Once daily</p> <p>Usual Dose: One tablet</p>	<p>Orthographic: The eighth position upstroke 't' in Lovastatin provides a different shape for this name which can help differentiate Lo Minastrin Fe and Lovastatin when scripted. Additionally, if included, the modifier 'Fe' in Lo Minastrin Fe can also help differentiate the two names orthographically.</p> <p>Strength: Single strength vs. multiple strengths (20 mg or 40 mg) with no overlap between the strengths.</p>

No.	<p>Proposed name: Lo Minastrin Fe (Norethindrone Acetate and Ethinyl Estradiol Chewable Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate Tablets)</p> <p>Dosage Form: Tablets</p> <p>Strength(s): 1 mg/10 mcg and 10 mcg and 75 mg</p> <p>Usual Dose: One tablet orally once daily.</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
2.	<p>Lomustine (Established name for CeeNU) Capsules 10 mg, 40 mg, 100 mg</p> <p>Usual Dose: The recommended dose in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m² as a single oral dose over 6 weeks. In patients with compromised bone marrow function, dose should be reduced to 100 mg/m² every 6 weeks.</p>	<p>Orthographic: If the modifier 'Fe' is omitted from Lo Minastrin fe, both names begin with 'Lo' followed by similar scripted letter strings '-min-' vs. '-mu-', and similar scripted ending letter strings '-strin' vs. '-stine'.</p> <p>Route of Administration: Oral</p> <p>Dosage form: Solid oral</p>	<p>Usual Dose and strength: One tablet vs. dosing calculated based on the body surface area (100 mg/m² or 130 mg/m²) with no overlap in the strength or dosing.</p>

Appendix F: Names identified in the previous reviews, not re-evaluated in this review

Collective List of Potentially Similar Names (DMEPA and EPD)					
Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Loestrin 24 Fe	EPD	Lo Loestrin Fe	EPD	Menotropins	EPD
Westrim	PR	Mirena	EPD	Minocin	EPD
Mircette	EPD	Vivelle	PR	Mestinon	EPD
Vaseretic	EPD	Neurontin	EPD	Bacentra	EPD
Metastron	PR	Micatin	EPD	Norlestrin Fe	EPD
Maxivate	PR	Miacalcin	EPD	Microgestin Fe	EPD
Monistat	EPD	Momentum	EPD	Menostar	EPD
Menactra	EPD	Micaderm	EPD	Novantrone	EPD
Namenda	EPD	Mesantoin	EPD	Memantine	EPD
Vincristine	EPD	Nerventra***	PR	(b) (4)	PR
Vasocidin	EPD	(b) (4)	PR	Menest	EPD
Look and Sound Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Minastrin 24 Fe	EPD	Miestrin	EPD	Minirin	EPD
Miniprin	EPD	Minitran	EPD		

Appendix G: List of Cases Retrieved From the July 2, 2013 FAERS Search

Case #	Vrsn	FDA Initial Recd Date	MFR Ctrl #
3266816	1	4/29/1999	001-0376-980130
3457779	1	4/14/2000	
3642999	1	4/17/2001	
3789868	1	4/30/2002	
3848731	1	10/3/2002	
4005061	1	9/16/2003	
4005917	1	9/16/2003	
4005931	1	9/16/2003	
4009934	1	9/23/2003	
4055204	1	9/20/2002	
4107478	1	3/12/2004	
5710151	1	1/3/2005	
6121029	2	8/22/2006	06-000814
6267641	1	3/9/2007	07-000418
6333249	1	6/1/2007	07-001138
6449221	1	10/16/2007	07-002004
6615744	2	4/3/2008	08-000480
6750367	3	8/26/2008	08-001341
6755612	1	9/2/2008	08-001363
6964699	1	3/30/2009	
6970096	1	4/8/2009	09-000482
6983673	1	4/22/2009	09-000579
7257704	3	1/14/2010	09-002021
7295238	1	2/4/2010	10-000121
7368317	1	4/14/2010	09-000102
7384273	1	4/19/2010	09-001375
7393727	1	5/14/2010	
7407983	1	5/27/2010	10-000449
7511262	1	7/16/2010	10-001018
7602300	1	9/10/2010	09-001033
7761852	1	12/17/2010	10-001700
7837830	1	1/10/2011	10-001437
7913363	1	4/1/2011	11-000299
7919902	2	4/6/2011	11-000320
8054570	1	7/19/2011	
8362429	1	1/24/2012	
8382122	1	1/25/2012	
8655084	1	6/27/2012	
8668651	1	7/9/2012	
8749865	1	10/21/2011	

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MANIZHEH SIAHPOUSHAN
07/09/2013

JAMES H SCHLICK
07/10/2013

CAROL A HOLQUIST
07/10/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name Review

Date: June 11, 2013

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Acting Team Leader: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: (b) (4)
(Norethindrone Acetate and Ethinyl Estradiol Chewable
Tablets, Ethinyl Estradiol Tablets, and Ferrous Fumarate
Tablets)
1 mg/10 mcg and 10 mcg and 75 mg

Application Type/Number: NDA 204654

Applicant/Sponsor: Warner Chilcott

OSE RCM #: 2013-860

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