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RESEARCH**

APPLICATION NUMBER:
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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: August 7, 2012

Reviewer(s): Walter Fava, RPh, MEd., Safety Evaluator
Division of Medication Error Prevention and
Analysis

Team Leader Zachary Oleszczuk, Pharm D., Team Leader
Division of Medication Error Prevention and
Analysis

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

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

Drug Name(s) and Strength(s): Minivelle (Estradiol) Transdermal System
(b) (4), 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg

Application Type/Number: NDA 203752

Applicant/Sponsor: Noven Pharmaceuticals

OSE RCM #: 2012-1147

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Minivelle, 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

The Applicant originally submitted the proposed name, (b) (4) which DMEPA denied and notified the Applicant in a letter dated, April 5, 2012.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 11, 2012 proprietary name submission.

- Active Ingredient: Estradiol
- Indication of Use: Moderate to severe vasomotor symptoms due to menopause
- Route of administration: Topical
- Dosage form: Transdermal Delivery System
- Strength: (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
- Dose: One patch applied twice a week
- How Supplied and Container/Closure System: Carton containing 8 individually pouch sealed transdermal systems
- Storage: Room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

2. RESULTS

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

2.1 PROMOTIONAL ASSESSMENT

OPDP determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Reproductive and Urologic Products concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

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

2.2.1 United States Adopted Names (USAN) SEARCH

On June 29, 2012 the United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a single word that contains the letter string, ‘Mini’ which makes reference to the size of the transdermal system relative to other similar transdermal systems in this therapeutic class which are currently marketed (i.e. Vivelle and Vivelle Dot). The name also contains the letter string, ‘velle’, which is used in proprietary names for similar products.

2.2.4 FDA Name Simulation Studies

Thirty-three practitioners participated in DMEPA’s prescription studies. The interpretations did or did not overlap with or appear or sound similar to any currently marketed products. Ten participants responded correctly. The majority misinterpretations stemmed from participants in the outpatient study responding with ‘Minirelle’ (n = 6). Other misinterpretations included ‘Minnelle’ (n = 5), ‘Minival’ (n = 4), ‘Mini-Val’ (n=1), and ‘Minivalle’ (n=1). DMEPA noted that the incorrect responses, ‘Minival’, ‘Mini-Val’, and ‘Minivalle’, are phonetically and orthographically similar to an over the counter product, (b) (4) and the prescription product, Menaval-20. However, both (b) (4) and Menaval-20 were already identified by DMEPA and despite the phonetic and orthographic similarity, were found to have differentiating product characteristics which will minimize the chance of confusion that could lead to medication errors. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, May 30, 2012 e-mail, the Division of Reproductive and Urologic Products (DRUP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 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, Minivelle. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Minivelle identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1: Collective List of Potentially Similar Names

Look Similar					
<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>	<i>Name</i>	<i>Source</i>
Minizide	FDA	Mircette	FDA	Bravelle	FDA
Lunelle	FDA	Vivelle Dot	FDA	Activella	FDA
Minipress	FDA	Minitran	FDA	Menactra	FDA
Nicorette	FDA	Nordette	FDA	Mimvey	FDA
Mimyx	FDA	Minoxidil	FDA	Mannitol	FDA
Natelle	FDA	Maxivate	FDA	Mini-Multi	FDA
Monistat	FDA	(b) (4)	FDA	Aranelle	FDA
Mini-pill	FDA				
Sound Similar					
Minute-Gel	FDA				
Look and Sound Similar					
(b) (4)	FDA	Menaval-20	FDA	Vivelle	FDA
(b) (4)	FDA	Menaval	FDA	Minodyl	FDA
(b) (4)	FDA				

Our analysis of the 30 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined the 30 names will not pose a risk for confusion as described in Appendix D through E.

2.2.7 Failure Mode and Effects Analysis of the prefix ‘Mini’

The proposed proprietary name contains the letter string, ‘Mini’. The prefix, ‘Mini’ is used in the proprietary names of other marketed drug products such as ‘Minipress’, ‘Minizide’, and ‘Minitran’. In this case, the prefix, ‘Mini’ of the proposed proprietary name, ‘Minivelle’, eludes to the comparative smaller size of the patch relative to the other transdermal systems currently marketed, Vivelle and Vivelle dot, as illustrated in Table 2 below.

Table 2: Estradiol Transdermal System Sizes by Product and Strength

Strength	0.025 mg/day	0.0375 mg/day	0.05 mg/day	0.075 mg/day	0.1 mg/day
Product	Size (cm²)				
Minivelle	(b) (4)	(b) (4)	3.3	4.95	6.6
Vivelle Dot	2.5	3.75	5	7.5	10
Vivelle	7.25	11	14.5	22	29

Thus, based on the information available to us today, we do not think that this particular name would cause errors or is misleading. However, if a smaller patch is developed in the future then this name may be misleading because the comparative size reference, ‘mini’ would no longer be accurate. Although this naming strategy is not cause for concern at this time, DMEPA discourages the practice of using comparative language in a proprietary name, as it may perpetuate the need to incorporate additional comparative size nomenclature in future names to differentiate products as the marketing landscape and pharmaceutical technology evolves over time. We previously communicated these concerns to the Applicant in a letter dated April 5, 2012, when we notified them of our denial of the name, ‘(b) (4)’ based on its orthographic similarity and overlapping product characteristics with (b) (4). The Applicant agreed with DMEPA’s comments and stated they were, ‘... comfortable with your guidance in that regard’.

2.2.8 Communication of DMEPA’s Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Reproductive and Urologic Products via e-mail on August 7, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Reproductive and Urologic Products on August 7, 2012, they stated no additional concerns with the proposed proprietary name, Minivelle.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective. The Applicant will be notified of this finding via letter.

The proposed proprietary name, Minivelle, must be re-reviewed upon submission of the NDA and 90 days before approval of the NDA.

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, Minivelle, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your May 11, 2012 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

4 REFERENCES

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. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. 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.

11. 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.

12. 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.

13. Red Book Pharmacy's Fundamental Reference

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

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

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

15. Medical Abbreviations Book

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

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

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

17. Walgreens (www.walgreens.com)

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

18. Rx List (www.rxlist.com)

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

19. 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.

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

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

proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. 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 product characteristics considered for this review appears in Appendix B1 of this review.

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 Division of Drug Marketing, Advertising, and Communications (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 Appendix B1 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

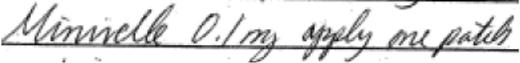
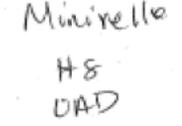
past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency’s credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors’ have changed a product’s proprietary name in the post-approval 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 with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Minivelle	Scripted May Appear as	Spoken May Be Interpreted as
Upper case ‘M’	‘IV’, ‘eu’, ‘N’, ‘Z’	‘N’, ‘mb’
Lower case ‘i’	‘e’, ‘l’	‘y’ or any vowel
Lower case ‘n’	‘m’, ‘u’, ‘r’, ‘x’, ‘h’, ‘s’	‘Dn’, ‘Gn’, ‘Kn’, ‘Mn’, ‘Pn’
Lower case ‘v’	‘r’, ‘u’, ‘w’	‘f’
Lower case ‘e’	‘a’, ‘i’, ‘l’, ‘o’, ‘u’, ‘p’	any vowel
Lower case ‘l’	‘b’, ‘e’, ‘s’, ‘A’, ‘P’, ‘i’	
Lower case ‘el’	‘d’, ‘cl’	‘al’, ‘il’, ‘ol’, ‘ul’, ‘yl’

Appendix C: Prescription Simulation Samples and Results

Figure 1. Minivelle Study (Conducted on May 25, 2012)

Handwritten Requisition Medication Order	Verbal Prescription
<p>Medication Order:</p> 	Minivelle Use as directed #8
<p>Outpatient Prescription:</p> 	

FDA Prescription Simulation Responses.

84 People Received Study

33 People Responded

Study Name: Minivelle

INPATIENT	VOICE	OUTPATIENT
MININELLE (1)	MINI-VAL (1)	MININELLE (1)
MINIVELLE (8)	MINIMOUTH (1)	MINIRELLE (6)
MINNELLE (5)	MINIVAL (4)	MINIVELLE (2)
MINNIVELLE (1)	MINIVALE (1)	
	MINIVALLE (1)	
	MINIVELL (1)	

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

Proprietary Name	Active Ingredient	Similarity to Minivelle	Failure preventions
Menactra	Meningococcal Diphtheria Toxoid Conjugate Vaccine	Look	This name pair has sufficient orthographic differences
Mimyx	Acetyethanolamine	Look	This name pair has sufficient orthographic differences
Mimvey	Norethindrone and Ethinyl Estradiol	Look	This name pair has sufficient orthographic differences
Mannitol	Mannitol	Look	This name pair has sufficient orthographic differences
Minipress	Prazosin	Look	This name pair has sufficient orthographic differences
Monistat	Miconazole	Look	This name pair has sufficient orthographic differences
Mini-pill	NA	Look and Sound	This is not a proprietary drug name, it is a term used to describe oral contraceptives that are progestin only tablets

(b) (4)		Look	This name pair has sufficient orthographic differences
(b) (4)	(b) (4)	Look and Sound	This was a proposed name submitted to the Agency however, the application was withdrawn and the name has not been resubmitted for review and does not represent the name of a marketed drug product and therefore would not be confused with Minivelle.
Menaval	NA	Look and Sound	No proprietary drug marketed under this name. The correct name is Menaval-20 which is included in Appendix E.

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.

Proposed name: Minivelle (Estradiol)	Strength(s): (b) (4) mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg	Usual dose: Apply one transdermal system to skin twice a week or use as directed.
Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion	Causes (could be multiple)	Prevention of Failure Mode
Minizide (Prazosin and Polythiazide) 1 mg/0.5 mg; 2 mg/0.5 mg; 5 mg/0.5 mg Capsules <u>Usual dose:</u> One capsule by mouth two to three times a day	<i>Orthographic similarities: Both names begin with the letter string, 'Mini' and end in the letter, 'e'. They are also similar in length when scripted (9 vs. 8 letters)</i>	Orthographic differences: The letter, 'z' in Minizide may be scripted as a downstroke which will help differentiate the name pair on written orders. In addition, there are three upstroke letters in Minivelle, 'M', 'l', 'l', compared to only two upstroke letters, 'M' and 'd' in Minizide. Strength: Both products are available in multiple strengths which would require a practitioner to indicate a strength on orders for either product. Since there are no identical overlapping strengths, this will help prevent errors between this name pair. Frequency of Administration: Apply twice a week or use as directed vs. two to three times a day.

<p>Bravelle (Urofollitropin) 75 IU for Injection 0.9% Injection <u>Usual dose:</u> Inject 150 IU subcutaneously or intramuscularly daily for the first 5 days of treatment.</p>	<p><i>Orthographic similarities: Both names contain the ending letter string, 'velle'.</i></p>	<p>Orthographic differences: The beginning portion, 'Mini' in Minivelle looks different from the beginning portion, 'Bra' in Bravelle. Frequency of Administration: Twice a week or use as directed vs. daily for 5 days</p>
<p>Mircette (Desogestrel and Ethinyl Estradiol) 0.125 mg/0.025 mg; 0.15 mg/0.025 mg; 0.1 mg/0.025mg Tablets 0.15 mg/0.02 mg; 0.15 mg/0.01 mg Tablets 0.15 mg/0.03mg Tablets <u>Usual dose:</u> One tablet by mouth daily</p>	<p><i>Orthographic similarities: Both names begin with the letters, 'Mi' and are similar in length when scripted (9 vs. 8 letters). Both names also contain two upstroke letters preceded and proceeded by the letter, 'e' ('elle' vs. ette'), giving them a similar shape when scripted.</i></p> <p><u>Product characteristics:</u> Frequency of administration: Use as directed</p>	<p>Orthographic differences: The letter, 'c' as well as the two cross stroke letters, 'tt' in Mircette, help to distinguish the names when scripted. Strength: Multiple (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg) vs. Single (different strength tablets are contained in a sequentially arranged blister pack and the product is not ordered with a strength)</p>
<p>(b) (4) (b) (4)</p>	<p>(b) (4)</p>	<p>Orthographic differences: (b) (4)</p>

<p>Vivelle (Estradiol) 0.025 mg/24 hrs; 0.0375 mg/24 hrs; 0.05 mg/24 hrs; 0.075 mg/24 hrs; 0.1 mg/24 hrs Transdermal System</p> <p><u>Usual dose:</u> Apply one system topically twice a week.</p>	<p><i>Orthographic similarities: Both names contain the ending letter string, 'ivelle'.</i></p> <p><u>Product characteristics:</u></p> <p>Dosage Form: Transdermal system</p> <p>Strength: (b) (4) overlapp</p> <p>Frequency of Administration: Twice a week</p> <p>Route of Administration: Topical</p>	<p>Orthographic differences: The beginning portion, 'Mini' of Minivelle looks longer than the beginning portion, 'Vi' of Vivelle when scripted.</p>
<p>Vivelle Dot (Estradiol) 0.025 mg/24 hrs; 0.0375 mg/24 hrs; 0.05 mg/24 hrs; 0.075 mg/24 hrs; 0.1 mg/24 hrs Transdermal System</p> <p><u>Usual dose:</u> Apply one system topically twice a week</p>	<p><i>Orthographic similarities: Both names contain the ending letter string, 'ivelle'.</i></p> <p><u>Product characteristics:</u></p> <p>Dosage Form: Transdermal system</p> <p>Strength: (b) (4) overlapp</p> <p>Frequency of Administration: Twice a week</p> <p>Route of Administration: Topical</p>	<p>Orthographic differences: The beginning portion, 'Mini' of Minivelle looks longer than the beginning portion, 'Vi' of Vivelle when scripted. In addition, Vivelle Dot contains the suffix modifier, 'Dot' which makes it appear longer than Minivelle when scripted.</p>

<p>Activella (Norethindrone and Ethinyl Estradiol)</p> <p>0.5 mg/0.1 mg; 1 mg/0.5 mg Tablets</p> <p><u>Usual dose:</u></p> <p>One tablet by mouth once a day.</p>	<p><i>Orthographic similarities: Both names contain 9 letters and are similar in length when scripted. In addition, both names contain the letter string, 'ivell'.</i></p> <p><u>Product characteristics:</u></p> <p>Numerical overlapping strengths: 0.05 mg vs. 0.5 mg and 0.1 mg vs. 0.1 mg</p> <p>Frequency of administration: Use as directed</p>	<p>Orthographic differences: The beginning letters, 'Min' in Minivelle look different than the beginning letters, 'Act' in Activella. In addition, Minivelle contains three upstroke letters, 'M', 'I', 'I', compared to four upstroke letters, 'A', 't', 'I', and 'I' in Activella, giving it a different shape when scripted.</p>
<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>	<p><i>Orthographic similarities:</i> (b) (4)</p> <p>(b) (4)</p> <p><i>Phonetic similarities:</i> (b) (4)</p> <p>(b) (4)</p>	<p>Orthographic differences: (b) (4)</p> <p>(b) (4)</p> <p>Strength: (b) (4)</p> <p>(b) (4)</p> <p>Frequency of Administration: (b) (4)</p> <p>(b) (4)</p>
<p>Minitran (Nitroglycerin)</p> <p>0.1 mg/hr; 0.2 mg/hr; 0.4 mg/hr; 0.6 mg/hr Transdermal System</p> <p><u>Usual dose:</u></p> <p>Apply one system to skin every 24 hours.</p>	<p><i>Orthographic similarities: Both names begin with the letter string, 'Mini'.</i></p> <p><u>Product characteristics:</u></p> <p>Strength: 0.1 mg</p> <p>Dosage Form: Transdermal System</p> <p>Route of Administration: Topical</p>	<p>Orthographic differences: Minivelle contains three upstroke letters, 'M', 'I', and 'I' and has a different shape when scripted compared to the two upstroke letters, 'M' and 't' in Minitran. In addition, the ending letters, 'elle' in Minivelle look different than the ending letters, 'tran' in Minitran when scripted.</p> <p>Frequency of Administration: Twice a week or use as directed vs. once a day</p>

<p>Menaval-20 (Estradiol Valerate) 20 mg/mL Injection</p> <p><u>Usual dose:</u></p> <p>Inject 10 mg to 20 mg intramuscularly once a month</p>	<p><i>Orthographic similarities: Both names begin with the letter, 'M' and have the letters, 'n', 'v', and 'l' in the same positions.</i></p> <p><i>Phonetic similarities: Both names have three syllables and the vowels in each name may sound similar when spoken.</i></p>	<p>Orthographic differences: Minivelle contains three upstroke letters, 'M', 'l', and 'l', and has a different shape when scripted compared to the two upstroke letters, 'M' and 'l' in Menaval-20. The ending modifier, '20' also helps differentiate the names.</p> <p>Strength: Multiple (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg vs. Single (20 mg/mL)</p> <p>Frequency of Administration: Twice a week or use as directed vs. once a month</p>
<p>Nicorette (Nicotine Polacrilex) 2 mg and 4 mg Gum and Lozenge</p> <p><u>Usual dose:</u></p> <p>One piece of gum or lozenge every 2 to 3 hours initially, titrating to one every 6 to 8 hours as needed.</p>	<p><i>Orthographic similarities: Both names share the letters, 'i', 'e' and 'e' in similar positions and both names contain three upstroke letters, ('M', 'l', 'l' vs. 'N', 't', 't'), giving them a similar shape when scripted.</i></p>	<p>Orthographic differences: The letters, 'co' in Nicorette, help to differentiate it from Minivelle when scripted.</p> <p>Strength: Multiple (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg vs. 2 mg and 4 mg)</p>
<p>Nordette (Levonorgestrel and Ethinyl Estradiol) 0.15 mg/0.03 mg Tablets</p> <p><u>Usual dose:</u></p> <p>One tablet by mouth once a day</p>	<p><i>Orthographic similarities: Both names are similar in length when scripted (9 vs. 8 letters) and the beginning letter, 'N' in Nordette may look similar to the beginning letter, 'M' in Minivelle when scripted.</i></p>	<p>Orthographic differences: Minivelle contains three upstroke letters, 'M', 'l', and 'l', giving it a different shape when scripted compared to the four upstroke letters, 'N', 'd', 't', and 't', in Nordette. In addition, the letter, 'o' in Nordette helps to differentiate it from Minivelle when scripted.</p>
<p>Minoxidil 2.5 mg and 10 mg Tablets</p> <p><u>Usual dose:</u></p> <p>10 mg to 40 mg by mouth in single or divided doses</p>	<p><i>Orthographic similarities: Both names begin with the letter string, 'Min' and are similar in length when scripted (9 letters).</i></p>	<p>Orthographic differences: The letters 'o', 'x' and 'd' in Minoxidil help to differentiate it from Minivelle when scripted.</p> <p>Strength: Multiple (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg vs. (2.5 mg and 10 mg). Prescribers would need to include a strength on orders for either drug and there is no overlapping strength between this name pair.</p> <p>(b) (4)</p>

<p>Maxivate (Betamethasone) 0.05% and 0.10% Cream</p> <p><u>Usual dose:</u> Apply once or twice a day</p>	<p><i>Orthographic similarities: Both names begin with the letter, 'M' and share the letters 'i', 'v', and 'e'. In addition, both names are similar in length when scripted (9 vs. 8 letters)</i></p> <p><u>Product characteristics:</u></p> <p>Numerical overlapping strength: 0.05 mg vs. 0.05%</p>	<p>Orthographic differences: Minivelle contains three upstroke letters, 'M', 'l', and 'l' and has a different shape when scripted compared to the two upstroke letters, 'M' and 't' in Maxivate.</p> <p>Frequency of administration: Twice a week or use as directed vs. once or twice a day</p>
<p>Mini-Multi (Vitamin and Mineral Supplement)</p> <p><u>Usual dose:</u></p> <p>Take one tablet by mouth one to three times a day with meals</p>	<p><i>Orthographic similarities: Both names begin with the letter string, 'Mini' and are similar in length when scripted (9 letters)</i></p>	<p>Frequency of administration: Twice a week or use as directed vs. one to three times a day</p>
<p>Minute-Gel (Acidulated Phosphate Fluoride) Dental Gel</p> <p>0.44%, 0.31%, 1.2%, 1.23%, 1.24%, 1.64%</p> <p><u>Usual dose:</u></p> <p>Apply a thin ribbon to teeth using toothbrush once a day for at least one minute.</p>	<p><i>Phonetic similarities: Both names contain three syllables and have identical sounding first syllables (Min). The ending syllables also sound similar when spoken ('elle' vs. 'gel')</i></p>	<p>Phonetic differences: The hard sounding letter, 't' in Minute-Gel helps to differentiate the names when spoken. In addition, the letter, 'v', in Minivelle helps to distinguish this name pair.</p> <p>Strength: Multiple (b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg vs. 0.44%, 0.31%, 1.2%, 1.23%, 1.24%, 1.64%</p> <p>Frequency of administration: Twice a week or use as directed vs. once a day</p>
<p>Lunelle (Estradiol Cypionate and Medroxyprogesterone) 5 mg/25 mg/0.5 mL Injection</p> <p><u>Usual dose:</u></p> <p>Inject 0.5 mL intramuscularly once a month</p>	<p><i>Orthographic similarities: Both names end in the letter string, 'elle' and share the letter, 'n' in the same position.</i></p>	<p>Orthographic differences: The beginning letter, 'L' in Lunelle looks different from the beginning letter, 'M' in Minivelle when scripted. In addition, Minivelle appears longer when scripted compared to Lunelle (9 vs. 7 letters).</p> <p>Frequency of administration: Twice a week or use as directed vs. once a month</p>

<p>Natelle One Capsules</p> <p>(Folate 1 mg; Calcium 102 mg; Iron 28 mg; Vitamin E 30 Units; Vitamin B6 25 mg; Vitamin C 30 mg; DHA 250 mg; EPA 0.625 mg)</p> <p><u>Usual dose:</u></p> <p>Take one capsule by mouth once a day</p>	<p><i>Orthographic similarities: Both names contain the ending letter string, 'elle' and the beginning letter, 'M' in Minivelle may look similar to the beginning letter, 'N' in Natelle</i></p>	<p>Orthographic differences: Minivelle contains three upstroke letters, 'M', 'l', 'l' and has a different shape when scripted compared to the four upstroke letters, 'N', 't', 'l', 'l' in Natelle. In addition, there is a modifier 'One' in Natelle One, which makes the name longer when scripted compared to Minivelle.</p> <p>Frequency of administration: Twice a week or use as directed vs. once a day.</p>
<p>Aranelle (Norethindrone and Ethinyl Estradiol)</p> <p>0.5mg/0.035 mg (7 tablets); 1 mg/0.035 mg (9 tablets); 0.5 mg/0.035 mg (5 tablets)</p> <p><u>Usual dose:</u></p> <p>One tablet by mouth daily</p>	<p><i>Orthographic similarities: Both names contain the ending letter string, 'elle'. In addition, both names are similar in length and shape when scripted (9 letters vs. 8 letters and both have three upstroke letters in the same positions)</i></p> <p><u>Product characteristics:</u></p> <p>Frequency of administration: Use as directed</p>	<p>Orthographic differences: The beginning letters, 'Mi' in Minivelle look different from the beginning letters, 'Ar' in Aranelle.</p>
<p>Minodyl (Minoxidil) 2.5 mg and 10 mg Tablets</p> <p><u>Usual dose:</u></p> <p>Take 10 mg to 40 mg by mouth daily in one dose or divided doses</p>	<p><i>Orthographic similarities: Both names begin with the letter string, 'Min' and share the letter, 'l'.</i></p>	<p>Orthographic differences: Minivelle contains 9 letters and appears longer when scripted compared to the 7 letters in Minodyl. In addition, the names have different shapes when scripted due to the position of the three upstroke letters, 'M', 'l', 'l' in Minivelled compared to the position of the three upstroke letters, 'M', 'd', and 'l' and the downstroke letter, 'y' in Minodyl.</p> <p>Strength: Multiple strengths ((b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg vs. 2.5 mg and 10 mg.</p>

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/s/

WALTER L FAVA
08/07/2012

KELLIE A TAYLOR
08/07/2012

CAROL A HOLQUIST
08/07/2012

**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: April 04, 2012

Reviewer(s): Walter Fava, RPh, MSED, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

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

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

Drug Name(s) and Strength(s): (b) (4) (Estradiol) Transdermal System
(b) (4) 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg

Application Type/Number: NDA 203752

Applicant/Sponsor: Noven Pharmaceuticals

OSE RCM #: 2012-132

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/s/

WALTER L FAVA
04/04/2012

ZACHARY A OLESZCZUK
04/04/2012

KELLIE A TAYLOR
04/04/2012

CAROL A HOLQUIST
04/04/2012