CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-256

PROPRIETARY NAME REVIEW(S)

9/5/08

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

Date:	September 5, 2008
To:	Bob Rappaport, MD Director, Division of Anesthesia, Analgesia and Rheumatology Products
Thru:	Linda Y. Kim-Jung, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Denise V. Baugh, PharmD, BCPS, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Savella (Milnacipran HCL) Tablets 12.5 mg, 25 mg, 50 mg, and 100 mg
Application Type/Number:	NDA# 22-256 (IND# 63,736)
Sponsor:	Forest Laboratories, Inc.
OSE RCM #:	2007-1969

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

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EXECUTIVE SUMMARY

The Proprietary Name Risk Assessment findings indicate that the proposed name, Savella, is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Savella, for this product. Container label, carton and insert labeling are being reviewed under OSE# 2008-1255.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170), for assessment of the proposed proprietary name Savella, regarding potential name confusion with other proprietary or established drug names. Container label, carton and insert labeling are being reviewed under OSE# 2008-1255. Additionally, the sponsor submitted an independent name analysis by [ ] for review and comment. b(4)

1.2 PRODUCT INFORMATION

Savella (Milnacipran HCL) is indicated for the treatment of fibromyalgia syndrome. Savella will be available as 12.5 mg, 25 mg, 50 mg, and 100 mg oral tablets. Due to tolerability issues there will be an initial titration over [ ] weeks to a stable dose of 100 mg per day, administered in two divided doses with an option of increasing to 200 mg/day based on patient response. The proposed titration schedule is listed below. b(4)

Day 1: 12.5 mg
Days 2-3: 25 mg/day (12.5 mg twice a day)
Days 4-7: 50 mg/day (25 mg twice a day)
After Day 7: 100 mg/day (50 mg twice a day)
Target maintenance dose is 100 mg/day
May be increased to 200 mg/day based on individual patient response

We note that per e-mail from the Division dated December 10, 2007, due to tolerability issues the sponsor has investigated titration schedules ranging from [ ] weeks. b(4)

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) medication error staff to conduct a proprietary name risk assessment. The primary focus of this assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

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

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Savella, the medication error staff of the Division of Medication Error Prevention and Analysis (DMEPA) search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division of Medication Error Prevention and Analysis also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis 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. [3] We use the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the Division of Medication Error Prevention and Analysis considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[4]

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

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[4] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'S' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[5][6]

To identify drug names that may look similar to Savella, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (3, capital letter 'S'), downstokes (none), cross-strokes (none), and dotted letters (0). Additionally, several letters in Savella may be vulnerable to ambiguity when scripted, including the upper case letter 'S' may appear as 'G' or 'J'; lower case 'a' may appear as a lower case 'o' or 'c' or the combination letters '-ci', '-ce' or '-el'; and lower case 'v' may appear as a lower case 'r'; and lower case 'e' may appear as an 'l' or an undotted 'i' or vice versa. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Savella.

When searching to identify potential names that may sound similar to Savella, the Medication Error Staff search for names with similar number of syllables (3), stresses (Sa-VELL-a or SA-vell-a), and placement of vowel and consonant sounds. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Savella), the established name (Milnacipran HCL), proposed indication (treatment of fibromyalgia syndrome), strength (12.5 mg, 25 mg, 50 mg, 100 mg), dose (titrate up to 100 mg daily based on clinical response), frequency of administration (twice daily), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the Medication Error Staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Savella, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Savella using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication

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

[6] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the United States Adopted Names (USAN) stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

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

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 CDER Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Savella with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Savella in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Savella Prescription Analysis Study (conducted on October 29, 2007)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: Savella 12.5mg #120 Take 1 tab po bid	"Savella 12.5 mg # 120 Take one tablet by mouth BID"

Inpatient Medication Order :	
Savella 25 mg one tablet by mouth bid	

2.1.3 External Proprietary Name Risk Assessment

For this product, the Sponsor submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the DMEPA Medication Error Staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether DMEPA's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMEPA provides a detailed explanation of these differences.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[7] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Savella convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Savella to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

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

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. 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)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains a USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that 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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

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

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of

medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

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

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

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

Our search identified a total of fifteen names as having some similarity to the name Savella.

b(4)

Eleven of the fifteen names were thought to look like Savella, which include: Sabril, Activella, Salvia, Rubella, Bravelle, Lunelle, Jovola, Seville, Invella, Aranelle, and Sonata. Three names [ ] were thought to look and sound similar to Savella. One name, Sebulon, was thought to sound like Savella.

The proposed proprietary name does not contain a USAN stem which is contradictory to the USAN Council's definition as of the last date searched, September 2, 2008.

3.1.2 CDER Expert panel discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1.1. above), and noted an additional name, Renvela, thought to have phonetic similarity to Savella and have the potential for confusion. The Expert Panel also noted that despite orthographic similarity of the letter 'S' with the letter 'G' in some handwriting samples, no names beginning with those letters were included in the pool. The Expert Panel recommended that independent searches consider the potential for confusion with drug names beginning with this letter.

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

3.1.3 FDA Prescription Analysis Studies

A total of thirty-two (32) practitioners responded, but none of the responses overlapped with any existing or proposed drug names. Over half of the participants (n=21) interpreted the name correctly as "Savella," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the phonetic prescription study, with the vowel 'a' reported as an 'e' or the first letter 'S' was misinterpreted as a 'Z' or a 'C' or the double 'l' was thought to be a single 'l'. See Appendix A for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Name Studies

In the proposed name risk assessment submitted by the Applicant, [ ] identified and evaluated a total of twenty-seven (27) drug names thought to have some potential for confusion with the name Savella. b(4)

Twenty-five (25) of the twenty-seven (27) names were not previously identified in DMEPA Staff searches, the Expert Panel Discussion, or FDA prescription studies. Four names (Mellaril, sevelamer, Vivelle, and Zavesca) were thought by practitioners to have similar sound and/or appearance to Savella. The remaining twenty-one (21) names were identified by [ ] Expert Panel or their Computerized Orthographic and Phonetic Analysis (COPA) as having some similarity (phonetic or orthographic) to Savella: Barbella, Paverolan, Sanfed A, Selora, [ ] Velban, Velsar, Isagel, Maravilla, Avail, Avelox, Natelle, Saleto, Stevia, Saliva (substitute), Camellia, Salac, Salex, Surelac and Syllact. b(4)

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified no additional names thought to look similar to Savella and represent a potential source of drug name confusion. Careful evaluation was afforded to drug names beginning with the letters 'G' in accordance with the Expert Panel's recommendations, but no drug names beginning with these letters were thought to have the potential for confusion with Savella. As such, a total of forty-one (41) names were analyzed to determine if the drug names could be confused with Savella and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Savella, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Savella, could potentially be confused with any of the forty-one (41) names and lead to medication error.

This analysis determined that the name similarity between Savella and the identified names was unlikely to result in a medication error with any of the forty-one (41) products identified for the reasons presented in Appendices C through I.

4 DISCUSSION

We analyzed forty-one (41) product names for their similarity to Savella. The findings of the FMEA indicate that the proposed name is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which

confusion could arise. However, DMEPA believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Sponsor from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, DMEPA recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

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

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Savella, is not vulnerable to name confusion that could lead to medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant. As such, DMEPA does not object to the use of the proprietary name, Savella, for this product.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis has no objections to the use of the proposed proprietary name, Savella for this product.

However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be submitted for review. If the product approval is delayed beyond 90 days form the date of this review, the proposed name must be resubmitted for evaluation.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarification, please contact Chris Wheeler, OSE Project manager, at (301) 796-0151.

5.2 COMMENTS TO THE APPLICANT

The Division of Medication Error Prevention and Analysis has no objections to the use of the proprietary name, Savella, for this product at this time. However, if **any** of the proposed product characteristics as stated in our review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. This name will also be re-evaluated 90 days prior to approval.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

5. AMF Decision Support System [DSS]

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

6. Division of Medication Error Prevention and Analysis proprietary name consultation requests

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

7. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

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

8. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. U. S. Patent and Trademark Office website http://www.uspto.gov.

Provides information regarding patent and trademarks.

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

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

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

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

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

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

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

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. USAN Stems (http://www.ama-assn.org/ama/pub/category/4782.html)

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

16. Lexi-Comp (www.pharmacist.com)

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 Upstokes Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Outpatient Written	Inpatient Written	Voice
Savella	Savilla	Zavella
Savella	Savella	Sevela
Savella	Savella	Savella
Savella	Savilla	Sevela
Savella	Savella	Savela
Savella	Savilla	Sevela
Savella	Savella	Savella
Savella	Savella	Civella
Savella	Savella	Sevella
Savella	Savella	Savella
Savella		Sevella

Appendix C. Drug names lacking convincing look or sound-alike similarities to Savella.

Proprietary Name	Similarity to Savella
Sabril	Look- and Sound-Alike
[ ]	Look- and Sound-Alike
[ ]	Look- and Sound-Alike
Sebulon	Sound-Alike
Zavesca	Look- and Sound-Alike
Paverolan	COPA
Sanfed A	COPA
[ ]	COPA
[ ]	COPA
Velban	COPA
Velsar	COPA
Isagel	COPA
Maravilla	COPA
Avail	COPA
Avelox	COPA
Stevia	COPA
Salac	COPA
Salex	COPA
Surelac	COPA
Syllact	COPA

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Appendix D. Identified names which are not drug names.

Proprietary Name	Similarity to Savella
Barbella	Sound

Appendix E: Drug products which are not approved.

Proprietary Name	Similarity to Savella	Explanation
[ ]	Look- and Sound-Alike	Incomplete application submitted to FDA
Invella	Look	Abandoned trade mark per the USPTO website

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Appendix F. Drug names no longer marketed in the U.S. and no generic is available.

Proprietary Name	Status	Date
Lunelle	Discontinued – no generic available	Withdrawn by Commissioner June 4, 2004

Appendix G. Drug names with little or no information in commonly used databases.

Proprietary Name	Similarity to Savella
Selora	Look or Sound (COPA)

Appendix H: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose
Savella (Milnacipran HCL)		**12.5 mg, 25 mg, 50 mg, 100 mg**	**Usual dose: Initial titration — period to a stable dose of 100 mg per day administered in two divided doses**
Activella	Look	Estradiol 1 mg/norethindrone 0.5 mg	One tablet daily
Salvia (herbal product)	Look	Not stated (leaves)	No typical dosage stated
Jovola	Look	174 mg, 348 mg, 522 mg	174 mg to 522 mg once daily
Aranelle	Look	0.035 mg ethinyl estradiol/0.5 mg norethindrone and 0.035 mg ethinyl estradiol/1 mg norethindrone	One tablet daily
Vivelle	Look or Sound (COPA)	0.025 mg/24 hour, 0.0375 mg/24 hour, 0.075 mg/24 hour	One patch twice weekly
Natelle	Look or Sound (COPA)	Multiple vitamins	One tablet daily

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Saleto	Look or Sound (COPA)	Acetaminophen 115 mg, aspiring 210 mg, salicylamide 65 mg, caffeine 16 mg	One to two capsules every 2 to 6 hours
Saliva (substitute)	Look or Sound (COPA)	0.3 mg oral lozenge	Use as necessary for dry mouth or throat
Camellia (black tea)	Look or Sound (COPA)	Not stated	Several cups per day

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

Savella (Milnacipran HCL)	**12.5 mg, 25 mg, 50 mg, 100 mg**	**Usual dose: Initial titration over a — period to a stable dose of 100 mg per day administered in two divided doses**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Rubella	Orthographic and phonetic similarity stems from sharing the same suffix ('-ella'). Additionally, lower case 'b' may look like a 'v' in some handwriting samples. Numerical overlap in strength (100 mg versus 1000 units) exacerbated if the units of measurement were to be omitted	Medication error unlikely to occur in the usual practice setting. *Rationale*: Confusion leading to medication errors are unlikely to occur due to different product characteristics such as route (oral versus parenteral), and frequency (twice daily versus one time). Additionally, rubella vaccine would likely be given as a single injection in a clinic setting or physician's office and not self administered chronically as you would expect for Savella.
Mellaril	Orthogarphic and phonetic similarity stems from sharing the letters '-ella-'in their name. Attainable strengths (25 mg, 50 mg and 100 mg) Overlapping product characteristics such as dosage form (tablet), route of administration (oral) and frequency of	Orthographic differences in the names minimize the likelihood of medication error in the usual practice setting. *Rationale:* Mellaril is no longer available in the marketplace but generic drug products are available and therefore, a prescriber could write for Mellaril. The risk for medication error is minimized by the orthographic differences in these names. The first letter 'M' (in Mellaril) has two 'humps' versus one 'hump' for 'S' (in Savella). Additionally, Mellaril ends in an upstroke represented by a lower case 'l' which is absent in the trade name, Savella.

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	administration (three times a day).	
Bravelle	Orthographic similarity stems from the shared letters '-avell-' (Bravelle versus Savella). Attainable strengths include 75 (international units) and 25 (milligrams).	Medication error unlikely to occur in the usual practice setting. *Rationale:* Product characteristics differ such as units of measurement (international units versus milligrams), route of administration (subcutaneously versus oral), frequency (daily versus twice daily) and duration of treatment (5 days versus indefinite).
Seville (herbal product also known as bitter orange)	Orthographic similarity stems from shared consonants, 's', 'v' and two 'l's, (Seville versus Savella). Additionally, first two vowels in both names are soft ('e' versus 'a' and 'i' versus 'e') and indistinguishable when spoken. Attainable strengths include 150 mg (for Seville) versus 25 mg, 50 mg, and 100 mg (for Savella)	Medication error unlikely to occur in the usual practice setting. *Rationale:* Seville is taken once daily versus Savella which is taken twice daily. Patient populations and markets are different. Seville is an herbal product available without a prescription in the self-care, alternative products marketplace. Savella is a prescription item only available through a physician and/or pharmacist.
Renvela	Phonetic similarity stems from same suffix ('vela' and 'vella'). Attainable strengths include 800 mg (Renvela) and 100 mg (Savella).	Medication error unlikely to occur in the usual practice setting. *Rationale:* Confusion leading to medication errors is unlikely to occur due to phonetic differences with their prefix ('Ren-'versus 'Sa-'. Additionally, the 800 mg dose for Renvela would require the dispensing/administration of 8 tablets of Savella (100 mg) for each dose which would cause the nurse/pharmacist to inquire about the proper dose due to the number of tablets. Furthermore, Renvela is taken three times daily with meals whereas Savella is administered twice daily.
Sevelamer	Orthographic and phonetic similarity include shared letters – '-vela-' (in sevelamer) and '-vella' (in	Medication error unlikely to occur in the usual practice setting. *Rationale:* Phonetically this name pair does not sound alike because

	Savella) Attainable strengths include 400 mg and 800 mg (sevelamer) and 50 mg and 100 mg (Savella) Shared product characteristics include route of administration (oral) and dosage form (tablet).	sevelamer has four syllables versus three for Savella. Additionally, sevelamer is longer in length than savella when scripted due to the 'double hump' (created by the lower case 'm' and the letters 'e' and 'r'). Sevelamer is administered three times daily with meals whereas Savella should be given twice daily.
Sonata	Orthographic similarity is related to the shared first and last letters ('s' and 'a') as well as the same location for the upstrokes ('t' in Sonata and 'll' for Savella). Additionally both names have the same shape when scripted. Attainable strengths include 5 mg and 10 mg (for Sonata) and 25 mg and 50 mg (for Savella) Shared product characteristics include route of administration (oral)	Medication error unlikely to occur in the usual practice setting. *Rationale:* Confusion is unlikely to occur because Sonata is given once daily at bedtime and Savella is given twice daily. Additionally, in order to provide the lowest Savella dose, five capsules of Sonata would have to be given which may alert the nurse or pharmacist to the potential for an inappropriate dose.

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