CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	May 1, 2009
To:	Russell Katz, M.D. Director, Division of Neurology Products, HFD-120
Through:	Kristina C. Arnwine, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis, HFD-420
From:	Tselaine Jones Smith, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis, HFD-420
Subject:	Proprietary Name Review
Drug Name(s):	Sabril (Vigabatrin) Tablets 500 mg Sabril (Vigabatrin for Oral Solution) 500 mg per packet
Application Type/Number:	NDA 20-427 NDA 22-006
Applicant/applicant:	Ovation Pharmaceuticals, Inc.
OSE RCM #:	2008-73

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EXECUTIVE SUMMARY

DMEPA previously reviewed the proposed proprietary name; Sabril, without objection. Since that review, none of the product characteristics have been revised. However, during this re-review, we identified 22 new names for their similarity to Sabril. The results of the Proprietary Name Risk Assessment found that the proposed name, Sabril, is not vulnerable to name confusion that could lead to medication errors with any of these names. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Sabril, for this product.

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Neurology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Neurology Products (HFD-120) for a re-assessment of the proprietary name, Sabril, regarding potential name confusion with other proprietary or established drug names.

Additionally, labels and labeling for Sabril for Oral Solution were provided for evaluation to identify areas that could lead to medication errors. These, along with the labels and labeling for Sabril Tablets, will be reviewed in OSE #2008-73 (Label and Labeling Review).

On December 23, 2008, the Applicant submitted a Risk Evaluation and Mitigation Strategy (REMS). The Office of Surveillance and Epidemiology (OSE) will review the REMS and provide comments in a separate review.

1.2 REGULATORY HISTORY

DMEPA previously reviewed and had no objection to the proprietary name, Sabril, in OSE review #05-0250 and 05-0250-1 (NDA # 20-427) dated November 21, 2005.

Subsequently, the applicant submitted an additional NDA (22-006) for Sabril which included a new dosage form and indication of use (powder for oral solution for Infantile Spasms). Because of this revision, in OSE Consult # 2006-603 (NDA 20-427) and 2006-757 (NDA 22-006) dated November 9, 2006, DMEPA re-reviewed the proposed proprietary name, Sabril, to determine if the new dosage form, dosing, and indication of use pose any new safety concerns that were not considered at the time of initial review. Following consideration of the new product characteristics, we concluded the proposed name, Sabril, was acceptable for both dosage forms.

The Applicant has received two 'not approvable' letters from the Agency dated December 23, 2005 and February 15, 2006.

In a teleconference between DNP, DMEPA and the Applicant held on January 21, 2009, the Applicant confirmed that both dosage forms would be distributed through specialty pharmacies via controlled distribution and would not be distributed through regular pharmacy channels. In addition, the Applicant provided clear details of their distribution process.

1.3 PRODUCT INFORMATION

Sabril (vigabatrin) is available in two dosage forms (tablets and oral solution) for two different indications of use. Sabril tablets are indicated as adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral Field Vision Defect. The recommended dose for refractory complex partial seizures in adults is to initiate therapy of the 500 mg tablets twice daily with or without food. The total daily dose may be increased in 500 mg weekly intervals depending on the response. The usual effective dose of Sabril in adults is 3 grams/day (1.5 grams twice daily).

Sabril for Oral Solution is indicated as a monotherapy for pediatric patients (birth up to 2 years of age) with Infantile Spasms for whom the potential benefits outweigh the potential risk of developing the peripheral Field Vision Defect. The recommended dose for infantile spasms is 50 mg/kg/day (1 mL/kg/day) given in two divided doses and can be titrated by 25 mg/kg to 50 mg/kg increments every three days up to 150 mg/kg/day. The entire contents of the packet of powder should be emptied into a container and using a calibrated 10 mL syringe dissolved in 10 mL of liquid (water, milk or infant formula). The final concentration is 50 mg/mL.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Sabril, DMEPA searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). DMEPA normally conducts internal FDA prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, FDA prescription analysis studies were not conducted upon re-review of Sabril.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure 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

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

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

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. DMEPA uses the clinical expertise of our 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 DMEPA 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, 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.[3]

2.1.1 Search Criteria

DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter '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.[4,5]

To identify drug names that may look similar to Sabril, the DMEPA staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (three, upper case letter 'S' and lower case letters 'b' and 'l') and dotted letters (one, lower case letter 'i'). Additionally, several letters in Sabril may be vulnerable to ambiguity when scripted, including the capital letter 'S' may appear as capital 'G', 'T', 'L', 'E', 'Z' or 'D'; lower case 'a' may look like lower case letters 'u', 'e' or 'o'; lower case 'b' may look like the letters 'h' or 'l'; lower case 'r' can resemble the letters 's' or 'v'; lower case letters 'br' may appear as the lower case letters 'hi' and lower case 'i' may look like lower case 'e" . As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Sabril.

When searching to identify potential names that may sound similar to Sabril, the DMEPA staff search for names with similar number of syllables (2), stresses (SA-bril or sa-BRIL), and placement of vowel and consonant sounds. Additionally, several letters in Sabril may be vulnerable to misinterpretation when pronounced including the letter 'S' may be misinterpreted as the letter 'X' or the letter 'Z', '-il' may be misinterpreted as 'el' and the letter 'b' may be misinterpreted as the letter 'v'. The Applicant's intended

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

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

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

pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The DMEPA 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, we were provided with the following information about the proposed product: the proposed proprietary name (Sabril), the established name (Vigabatrin), proposed indication of use (treatment of refractory complex partial seizures in adults and infantile spasms), strength (500 mg), dose (500 mg for complex partial seizures and 50 mg/kg/day for infantile spasms), frequency of administration (twice daily), route of administration (oral), and dosage forms (tablets and for oral solution). Appendix A provides a more detailed listing of the product characteristics the DMEPA staff generally takes into consideration.

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

2.1.1.1 Database and Information Sources

The proposed proprietary name, Sabril, was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Sabril using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, we 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 to gather CDER professional opinions on the safety of the product and the proprietary name, Sabril. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC) with backgrounds in pharmacy and nursing.

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

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, 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.[6] 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 Sabril 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 Sabril 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.

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)].

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

3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. DMEPA staff identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that we object 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 we 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 Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, Joint Commission, and ISMP, who have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe 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 we object 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. We are likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

For this review, 21 names were identified as having some similarity to the name Sabril: Tysabri, Zestril, Sectral, Gabitril, Teril, Enbrel, Detrol, Sabrilex, Sabrilan, Tobrex, Lybrel, Gelusil, Solaris, Isuprel, Supprelin, Tabrin, Santyl, Sabril, Sandril, Sobril and Sabadil.

Eleven of the 21 names (Enbrel, Detrol, Sabrilex, Sabrilan, Tobrex, Lybrel, Gelusil, Gabitril, Zestril, Teril and Solaris) were thought to look like Sabril. Four of the names (Isuprel, Supprelin, Tysabri and Santyl) were thought to sound similar to Sabril and six names (Sabril, Sandril, Tabrin, Sectral, Sobril and Sabadil) were thought to look and sound similar to Sabril.

The proposed name, Sabril does not contain a United States Adopted Name stem as of the last date search on March 31, 2009.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1.1. above) and noted no additional names.

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 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified the name, (b) (4), as a name thought to sound similar to Sabril. As such, a total of 22 names were analyzed to determine if the drug names could be confused with Sabril and if the drug name confusion would likely result in a medication error.

Four (Tysabri, Gabitril, Zestril and Teril) of the 22 names were previously evaluated in the two previous DMEPA reviews and since Sabril's product characteristics have not changed, these names were not re-evaluated. Two names lacked orthographic and/or phonetic similarity to Sabril and were not evaluated further (see Appendix B).

The remaining 16 names were determined to have some orthographic and phonetic similarity to Sabril, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Sabril, could potentially be confused with any of the 16 names and lead to medication error. This analysis determined that the name similarity between Sabril and the identified names was unlikely to result in medication errors for all 16 products for the reasons identified in Appendices C through H.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

This name was evaluated by DMEPA and found to be acceptable on two separate occasions. None of the product characteristics have been revised. Upon re-review of this name, 18 new names were evaluated for their similarity to Sabril. Two of the 18 names were not evaluated further because they lacked convincing orthographic and/or phonetic similarities to Sabril.

Our failure mode and effect analysis (FMEA) of the remaining 16 names determined that the name similarity between Sabril and these products was unlikely to result in medication errors for the reasons presented in Appendices C through H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Sabril, is not vulnerable to name confusion that could lead to medication errors. Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Sabril, for this product at this time. Additionally, DDMAC does not object to the proposed name, Sabril from a promotional perspective.

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 resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Additionally, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

DMEPA would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, project manager, at 301-796-0674.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Sabril, and have concluded that it is acceptable.

Sabril will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

6 REFERENCES

6.1 REVIEWS

OSE Review # 05-0250 and 05-0250-1 dated November 21, 2005

OSE Review # 2006-603 and 2006-757 dated November 9, 2006

6.2 DATABASES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

3. 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.

4. AMF Decision Support System [DSS]

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

5. Division of Medication Errors and Technical Support proprietary name consultation requests

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

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

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

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

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

8. United States Patent and Trademark Office http://www.uspto.gov.

Provides information regarding patent and trademarks.

9. 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.

10. 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.

11. 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.

12. 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.

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The DMEPA staff considers 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 proper 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 DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The DMEPA 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 (e.g., "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 DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, 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 Upstrokes Downstrokes Cross-stokes Dotted letters Ambiguity introduced	• Names may look similar when scripted, and lead to drug name confusion in written communication

		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: Proprietary names that lack convincing orthographic and/or phonetic similarities to the proposed name, Sabril.

Proprietary Name	Similarity to Sabril
Isuprel	Sound
Supprelin	Sound

Appendix C: Products marketed in other countries with the same active ingredient, dosage form (tablets) and indication of use as the proposed name Sabril.

Proprietary Name	Similarity to Sabril	Country	Sponsor
Sabrilex	Look	Denmark, Norway, Sweden Netherlands Finland, Spain	Aventis Euro Registratie Sanofi-Aventis
Sabrilan	Look	Israel	Agis
Sabril	Look and Sound	Mexico Belgium, Chile, France, Germany, Ireland, Italy, Netherlands, Singapore Poland	Sandoz Sanofi-Aventis Marion Merrell

Appendix D: Proprietary names used in foreign countries

Proprietary Name	Similarity to Sabril	Active Ingredient	Country
Sobril	Look and Sound	Oxazepam	Norway and Sweden
Soliris	Look	Eculizumab	United Kingdom
Tabrin	Look and Sound	Oxafloxacin	Greece

Appendix E: Product that is discontinued and no generic equivalent is available

Proprietary Name	Similarity to Sabril	Active Ingredient
Sandril	Look and Sound	Reserpine

Appendix F: Product with single strength but differentiating product characteristics

Product name with potential for confusion	Similarity to proposed proprietary name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics
Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**		**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**	
Santyl Collengenase Dosage form: ointment	Sound	250 units/gram	Apply a thin layer to the site once daily	Dose (75 mg to 1500 mg vs. thin layer) Frequency of administration (twice daily vs. once daily) Route of administration (oral vs. topical) Dosage form (powder for solution and tablets vs. ointment)
Gelusil Aluminum hydroxide, magnesium hydroxide and simethicone Dosage form: tablets	Look	200mg/200 mg/25 mg	Chew two to four tablets between meals and at bedtime	Frequency of administration (twice daily vs. four times a day) Prescription status (prescription vs. over-the-counter)
Sabadil (Allium Cepa 5C, Ambrosia Artemisiaefolia 5C, Euphrasia officinalis 5C, Histaminun Hydrochloricum 9C, Sabadilla 5 C, Solidago Virgaurea 5C) Dosage form: tablets	Look and Sound	Varies per ingredient	Take 2 tablets orally every 15 minutes for two hours, then 2 tablets 3 times a day	Frequency of administration (twice daily vs. eleven times a day) Prescription status (prescription vs. over-the-counter) Product type (seizure medication vs. nutritional supplement)

Appendix G: Potential confusing names with numeric similarity in dose and/or strength

Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**	**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**
Failure Mode: Name confusion	**Causes** **(could be multiple)**	**Effects**
Enbrel Etanercept <u>Strength and dosage form:</u> 25 mg powder for injection 25 mg/0.5 mL and 50 mg/mL solution for injection <u>Adult Subcutaneous Dose:</u> 50 mg once weekly Twice weekly dose: two 25 mg doses given three to four days apart <u>Pediatric Subcutaneous Dose:</u> 0.8 mg/kg for once weekly for patients < 31 kg or ≥ 63 kg (maximum dose: 50 mg) 0.4 mg/kg for patients 31 kg to 62 kg twice weekly dose as two 25 mg doses given three to four days apart (maximum dose: 25 mg)	Both names contain similar beginnings ‘Sa-’ vs. ‘En-’ which look alike when scripted Both names contain similar endings ‘-bril’ vs. ‘-brel’ which look alike when scripted Potential for numerical overlap in strength and dose (50 mg vs. 50 mg Sabril for oral solution and 500 mg Sabril tablets)	Product characteristic differences minimize the likelihood of medication error in the usual practice setting. *Rationale:* The frequency for administration for both dosage forms of Sabril is twice daily vs. once weekly or twice weekly for Enbrel. The route of administration for both dosage forms of Sabril is oral vs. subcutaneous for Enbrel. *vs. Sabril Tablets* Although there is numeric overlap in dose (500 mg vs. 50 mg) with Sabril Tablets and Enbrel, the dose of Enbrel would have to be written with a trailing zero. Usual practice would not typically involve the inclusion of trailing zeros, though medication errors have been linked to this dangerous habit. Numerous campaigns (JCAHO, ISMP, FDA) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error. Even if Enbrel is written with trailing zero, its route of administration would help distinguish it from Sabril. *vs. Sabril for Oral Solution* Although there is numeric overlap in dose (50 mg) with Sabril for Oral Solution and Enbrel, a 50 mg dose for Sabril would be for an infant weighing 1 kg and a 50 mg dose of Enbrel would be for a 63 kg child. In addition, Enbrel’s oral route of administration would help distinguish it from Sabril. .

Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**	**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**
Failure Mode: Name confusion	**Causes** **(could be multiple)**	**Effects**
Sectral Acebutolol hydrochloride <u>Strength and dosage form:</u> 200 mg and 400 mg capsules <u>Oral dose:</u> 200 mg to 1200 mg daily in one to two divided doses	Both names contain similar beginnings ‘Sa-’ vs. ‘Se-’ which look and sound alike Both names contain similar endings ‘-tral’ vs. ‘-bril’ which look and sound alike Similar length of names (six letters vs. seven letters) Overlapping number of syllables in the names (two) Overlapping dosage form (tablet/capsules) Overlapping route of administration (oral) Potential for numerical overlap in dose of Sabril for Oral Solution and Sectral Potential for numerical overlap in dose of Sabril tablets and Sectral (1000 mg) Potential for similar frequency of administration (twice daily)	Phonetic and product characteristic differences minimize the likelihood of medication error in the usual practice setting. *Rationale:* The hard sound of the letter ‘c’ in Sectral differentiates the two names when spoken. <u>Oral solution:</u> Sectral is not available as an oral solution. While doses in the range from 200 mg to 1200 mg are achievable with Sabril for Oral solution, it is indicated for infantile spasms in pediatric patients from birth to 2 years of age vs. Sectral is indicated for the treatment of hypertension and premature ventricular contractions in adults. In addition, the safety and efficacy of Sectral has not been established in children. <u>Tablets/Capsules:</u> While it is possible that doses for Sectral and Sabril can be written without a strength (i.e. ‘2 tablets’ or ‘3 tablets’); Sectral is available in multiple strengths and the strength would need to be clarified in prescriptions. Sabril tablets do not have doses less than 500 mg. Although the two products can overlap in their total daily dose (1000 mg), the maximum dose for Sectral is 1200 mg daily. Even if a prescription for Sectral was misinterpreted as 1000 mg, the dispenser would have to contact the specialty pharmacy for distribution of Sabril. Alternately, prescriptions for Sabril would generally not be presented through the normal retail distribution process.

Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**	**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Lybrel Ethinyl Estradiol and Levonorgestrol <u>Strength and dosage form:</u> 200 mcg/90 mcg tablets <u>Oral dose</u>: One tablet daily	Same length of name (six letters) Similar endings (‘-bril’ vs. ‘-brel’) Overlapping dosage form (tablets) Overlapping route of administration (oral) Overlapping dose (one tablet) Overlapping strength (single)	Orthographic and product characteristic differences minimize the likelihood of medication error in the usual practice setting. *Rationale:* The down stroke of the letter ‘y’ in Lybrel differentiates the two names when scripted. Sabril is available in two dosage forms. Thus, the dosage form will most likely be written on prescriptions. Sabril has a twice daily frequency of administration vs. Lybrel’s once daily frequency of administration.
Tobrex Tobramycin <u>Strength:</u> 0.3% <u>Dosage form:</u> Ophthalmic ointment Ophthalmic solution <u>Topical dose ointment:</u> Apply a thin strip to the conjunctiva every 8 to 12 hours (two to three times daily) <u>Topical dose solution:</u> One to two drops in affected eye(s) every 4 hours (6 times a day)	‘Sabri-’ can look similar to ‘Tobre-’ when scripted Overlapping strength (single strength) Potential for overlap in dose (two) Potential for overlap in frequency of administration (twice daily)	Orthographic and product characteristic differences minimize the likelihood of medication error in the usual practice setting. *Rationale:* The upstroke of the letter ‘l’ in Sabril and the cross stroke of the letter ‘x’ in Tobrex help to differentiate the names when scripted. Dosage forms for Sabril (tablet and oral solution) vs. Tobrex (ointment and ophthalmic solution) differ. In addition, prescriptions for both products will most likely specify the preferred dosage form. Sabril’s route of administration is oral vs. Tobrex has a topical route of administration.

Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**	**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**
Failure Mode: Name confusion	**Causes** **(could be multiple)**	**Effects**
Detrol Tolteridine tartrate <u>Strength:</u> 1 mg and 2 mg <u>Dosage form:</u> Tablet <u>Usual Dose:</u> 2 mg orally twice daily (one tablet or two tablets twice daily)	Same length of name (six letters) Upstrokes in the same positions (position numbers one, three and six) Names looks similar when scripted (‘Sabril’ vs. ‘Detrol’) Overlapping dose (one tablet or two tablets) Overlapping frequency of administration (twice daily) Overlapping dosage form (tablets) Overlapping route of administration (oral)	Medication errors between the two names are minimized by orthographic and product characteristic differences in the usual practice settings. *Rationale:* The beginning letter ‘S’ of Sabril and the beginning letter ‘D’ of Detrol, along with the cross stroke of the letter ‘t’ in Detrol help to differentiate the two names when written. <u>vs. Sabril Tablets:</u> Doses for Sabril and Detrol can be written as the number of tablets (e.g. ‘2 tablets’). However, Detrol is available in multiple strengths, thus the strength would need to be clarified prior to dispensing.

Sabril **(Vigabatrin)** **(Vigabatrin for oral solution)**	**500 mg tablet** **500 mg per packet**	**Usual Dose:** **500 mg (1 tablet) to 1500 mg (3 tablets) orally twice daily** **50 mg/kg/day (75 mg to 1500 mg orally twice daily)**
Failure Mode: **Name confusion**	**Causes** **(could be multiple)**	**Effects**

(b) (4)

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/s/

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MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; White Oak BLDG 22, Room 4447 Center for Drug Evaluation and Research

To: Russell Katz, M.D.
Director, Division of Neurology Products, HFD-120

Through: Nora Roselle, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Judy Park, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: November 9, 2006

Subject: DMETS Proprietary Name, Label, and Labeling Review
NDA#: 20-427 Sabril (Vigabatrin) Tablets, 500 mg
NDA#: 22-006 Sabril (Vigabatrin) for Oral Solution, 500 mg

Project #s: 2006-603 & 2006-757

This memorandum was written in response to a request from the Division of Neurology Products (HFD-120), for a re-assessment of the proprietary name, Sabril and a review of the revised labels and labeling. DMETS comments on the Risk Minimization Action Plan (RiskMAP) for Sabril will be included in the OSE RiskMAP review. DMETS first evaluated the name, Sabril, for the indication of use of Refractory Complex Partial Seizures in OSE Consults #'s 05-0250 and 05-0250-1, dated July 6, 2006, and found the proposed proprietary name acceptable at that time.

I. NAME REVIEW

Since our original review, the Sponsor has submitted an additional NDA for Sabril which includes a new dosage form and indication of use (oral solution for Infantile Spasms). Because of this revision, DMETS re-reviewed the names from our previous consult to determine if the new dosage form, dosing, and indication of use pose any new safety concerns that were not considered at the time of initial review. Following consideration of the new product characteristics, we have concluded that the new dosage form, dosing and indication of use do not pose any concerns with the names previously reviewed.

However, DMETS has identified one additional proprietary name, Teril, with potential for confusion with Sabril which was not captured in the previous review. Teril is a proprietary name for the generic drug carbamazepine. Both names end with the same three letters (-ril). However, the beginning letters of each name (Te- vs. Sab-), the additional letter in Sabril (five letters vs. six letters), as well as the upstroke letter of "b" in Sabril noticeably differentiate the names when scripted (see sample on page 2).

Teril

Sabril

Both products have an overlapping indication of use (seizures), route of administration (oral), frequency of administration (twice daily), and dosage form (oral tablet and oral solution/suspension). Both drugs are dosed in mg/kg/day then converted to an mL equivalent for the total dose. Sabril and Teril are both available in a single product strength (200 mg tablets vs. 500 mg tablets, 100 mg/5 ml oral suspension vs. 500 mg oral solution) which therefore does not need to be indicated on a prescription order. Additionally, Teril is available in a bottle of liquid oral suspension and Sabril is available as powder which requires reconstitution prior to oral administration. Since Teril is a brand name of a generic product, it may be more likely that a prescription will be ordered by the brand name (e.g. Tegretol) or the established name (e.g. carbamazepine). In addition, while the name is listed in Drugs@FDA, Orange Book, NDC Directory, and Micromedex, Teril is not found in Facts & Comparison, Clinical Pharmacology, The 2006 Redbook, or DSS. Similarly, the name Teril was identified in Saegis as being available in several foreign countries, but is not listed in the United States. Thus, despite the overlapping product characteristics, DMETS believes the orthographic differences and the limited use of the name will help to decrease the risk of confusion and error between Teril and Sabril.

II. LABEL AND LABELING REVIEW

The Sponsor has submitted revised labels and labeling in response to DMETS comments dated July 10, 2006. We note that the Sponsor has addressed most of the concerns noted in our original review. However, DMETS has the following additional recommendations for revisions to minimize medication errors.

A. GENERAL COMMENTS

1. "Sachet" is not a recognized proper dosage form listed in the USP. DMETS consulted Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee for the proper designation of the established name and dosage form. He advised that the proper designation of the established name should be "(Vigabatrin) for Oral Solution." If you have further questions regarding the proper established name and dosage form, please contact Guirag Pooichikian for further discussion. In addition, "sachet" is not an easily recognizable packaging unit. Please replace all references of "sachet" with the proper dosage form or recognizable packaging unit (e.g. packet) in all the labels and labeling.

B. CONTAINER LABELS (Tablets and Sachets)

1. If space permits, per 21 CFR 201.55, please include a usual dose statement (e.g. Usual dosage: See package insert for full prescribing information).

2. As per 21 CFR 208.24, the authorized dispenser is to "provide" a Medication Guide to each patient and a statement of how the Medication Guide will be provided must be included. Please

change the reminder statement for the pharmacists, "Review Medication Guide with Patient" to reflect this regulation. In addition, the regulation states that "these statements shall appear on the label in a prominent and conspicuous manner." We recommend increasing the font size of this statement as it is not prominent and maybe easily overlooked.

C. CARTON LABELING (Tablets and Sachets)

1. See comments B1-B3.

2. For the tablet carton labeling, please revise the net quantity statement to read [redacted] (b) (4)

D. INSERT LABELING

1. Highlights of Prescribing Information – *Indications and Usage*

   a. Please include "in Adults" after the first bullet "Refractory Complex Partial Seizures" to be consistent with the full prescribing information.

   b. Please define the age range for the indication of infantile spasms so that the prescriber has a clear understanding of the patient's age limit.

2. Full Prescribing Information

   a. Section 1 - *Indications and Usage*

      i. Under Section 1.2, please insert the age range for the indication of infantile spasms so that the prescriber has a clear understanding of the patient's age limit.

   b. Section 2 - *Dosage and Administration*

      i. Under Section 2.1, the dosage and administration instructions for Refractory Complex Partial Seizures in Adults are to give the doses in "two divided doses." Please clarify if the two divided doses should be 12 hours apart or some other specified time frame.

      ii. Under Section 2.2, the dosage and administration instructions for Infantile Spasms are confusing. The first sentence "Sabril 500 mg sachets should be given as twice daily oral administration with or without food" implies that 500 mg should be given twice daily (e.g. 1000 mg/day). But the later instructions indicate that infants should be dosed based on weight (mg/kg/day). Because of these dosing instructions, it is conceivable that doses lower than 500 mg will be required. Thus, there should be clear instructions on how to administer only the required amount of drug in volume measurement. A final solution concentration should also be included (500 mg/10 mL = 50 mg/mL). DMETS is concerned that there will be cases of underdosing or overdosing with incorrect calculation of the doses especially with a complex titration schedule as listed.

iii. Under Section 2.2, please include instructions on what to do with the leftover solution (e.g. discard unused portion, use immediately after mixing) as noted on the labels and labeling.

iv. For Section 2.2, please be consistent in the instructions in other labeling (e.g. Medication Guide, carton labeling). In the Medication Guide (question #4) and carton labeling, instruction is given to "dissolve" the drug in liquid but in the full prescribing information, instruction is given to "mix."

v. Under Section 2.3, *Patients with Renal Impairment*, patients with renal impairments are categorized by their creatinine clearance. However, the recommended dose adjustment is based on patient's creatinine concentration and not clearance. Please be consistent. Revise accordingly.

vi. Under Section 2.4, *General Dosing Considerations*, it is recommended when discontinuing Sabril, "the dose should be gradually reduced." However, there are no instructions on how to "gradually reduce" the dose (e.g. reduce in increments of 500 mg per day?). Revise accordingly.

c. Section 8 - *Use in Specific Populations*

i. Under Section 8.3 *Pediatric Use*, please define the age range for the indication of infantile spasms.

In summary, DMETS has no objections to the use of the proprietary name, Sabril. DMETS also recommends implementation of the label and labeling recommendations outlined above. Additionally, DDMAC finds the proprietary name acceptable from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/

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