

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-152

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**

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Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): Stavzor (Valproic Acid Delayed-release Capsules)

Application Type/Number: NDA # 22-152

Applicant: Banner Pharmacaps Inc.

OSE RCM #: 2008-975

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Stavzor, has some similarity to other proprietary and established drug names, but the findings of the FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we do not object to the use of the proprietary name Stavzor for this product.

The results of the Label and Labeling Risk Assessment found areas of vulnerability which could lead to medication errors. A detailed discussion can be found in Section 4.2.

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. Additionally, if the product approval is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Neurology Products for re-assessment of the proprietary name and revised labeling of Stavzor. Additionally, revised container labels, carton and package insert labeling were submitted for review and comment.

1.2 REGULATORY HISTORY

In our previous OSE Review (2007-1690, dated September 17, 2007), we had no objection to the proposed proprietary name, Stavzor. We also provided recommendations for label and labeling revisions to minimize the potential for medication errors.

1.3 PRODUCT INFORMATION

Stavzor is an oral, delayed-release soft gelatin capsule formulation of valproic acid. Stavzor capsules are indicated for: 1) the treatment of the manic episodes associated with bipolar disorder, 2) as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures, and 3) for prophylaxis of migraine headaches. The recommended doses of Stavzor, based upon the indications as stated in the Full Prescribing Information, are listed in Table 1 on page 3.

Table 1. Recommended Doses of Stavzor

Indication	Recommended Dose of Stavzor
Mania associated with bipolar disorder	750 mg daily in divided doses
Seizures-Monotherapy	Initiate at 10-15 mg/kg/day. Dosage should be increased by 5-10 mg/kg/week to achieve optimal clinical response.
Seizures-Adjunctive therapy	Add to current regimen at dose of 10-15 mg/kg/day. Dose may be increased by 5-10 mg/kg/week to achieve optimal clinical response.
Simple and Complex Absence Seizures	Initiate at 15 mg/kg/day, increasing at one week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases.
Migraine headache prophylaxis	250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day.

If satisfactory clinical response is not achieved, plasma levels may be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). Some patients may be controlled with higher or lower serum concentrations.

Stavzor is available in bottles of 100 capsules in three strengths: 125 mg, 250 mg, and 500 mg. Each strength is described as an orange colored, oval shaped capsule with black print. Stavzor should be stored at controlled room temperature (25 degrees Celsius) with excursions permitted to 15-30 degrees Celsius.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error and Prevention's Medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division 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, Stavzor, and the proprietary and established names of drug products

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

existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, Stavzor, the medication error staff search 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). We normally conduct internal CDER prescription analysis studies. However, since this name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Stavzor.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.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. 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, we consider 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

The medication error prevention staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter ‘S’ when searching to identify potentially similar drug names, as 75% of the confused drug names

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

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

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 Stavzor, the 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 (seven letters), capital letters ('S'), up-strokes ('t'), down strokes ('z', depending on how it is scripted), cross-strokes ('t' or 'z', depending on how it is scripted) and dotted letters (none). Additionally, several letters in Stavzor may be vulnerable to ambiguity when scripted, including the capital letter 'S' may appear as capital letter 'G'; lower case 't' may appear as 'f' or 'l'; lower case 'a' may look like lower case 'o', 'e' or 'u'; lower case 'v' may look like lower case 'u' or 'r'; lower case z may appear as 'g', 'y' or 'p'; lower case 'o' may appear as 'a', 'e' or 'u'; and lower case letter 'r' may appear as lower case 'n', 'u' or 'v'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Stavzor.

When searching to identify potential names that may sound similar to Stavzor, the medication error staff search for names with similar number of syllables (2), stresses (STAV-zor; Stav-ZOR), and placement of vowel and consonant sounds. In addition, several letters in Stavzor may be subject to interpretation when spoken, including the letter 'a' which may be interpreted as 'e', 'v' may be interpreted as 'ph', 'f', 'b' or 't', and 'zor' may be interpreted as 'sor' or 'sore'. The Applicant'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 (Stavzor), the established name (Valproic Acid delayed release), proposed indications (treatment of manic episodes associated with bipolar disorder, monotherapy or adjunctive therapy in the treatment of complex partial seizures, and migraine headache prophylaxis), strength (125 mg, 250 mg and 500 mg), dose (10 mg/kg/day up to 60 mg/kg/day in divided doses, based on response), frequency of administration (two to three times a day), route (oral) and dosage form (capsule). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally takes into consideration.

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

2.1.1.1 Database and information sources

The proposed proprietary name, Stavzor, was provided to the medication error staff to conduct a search of the internet, several standard published drug product reference texts, and FDA

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)

databases to identify existing and proposed drug names that may sound-alike or look-alike to Stavzor 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 uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication error staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

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

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name. As part of the Expert Panel Discussion, the group also provides handwriting samples of the proposed proprietary name along with other look-alike names identified by the panel and the Reviewing Safety Officer.

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 Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the Division seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not 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.

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

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 Stavzor 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 Stavzor to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

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

We will object to the use of proposed proprietary name when 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. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication error 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, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, World Health Organization, Joint Commission on the Accreditation of Healthcare Organizations and the Institute for Safe Medication Practices, 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, we contend 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 us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error

Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁷

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

For this product, the review division forwarded the following revised label and labeling for our review on June 23, 2008 (See Appendix E):

- Container Labels: 125 mg, 250 mg, 500 mg
- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The search retrieved twenty names which sound-alike or look-alike to Stavzor to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice setting.

The twenty names identified as having some similarity to the name Stavzor are: Stevia, Tazorac, Staveran, Advicor, Starlix, Stalevo, Stadol, Azor, Gemzar, Glukor, Stavudine, Storax, Serzone, Stanozide, Starnoc, Stieprox, Simcor, Estazor, Stanza and Stanzar.

Six (Advicor, Starlix, Stalevo, Stadol, Azor, Stavudine) of the twenty names were previously reviewed in OSE review # 2007-1690 and were deemed unlikely to result in medication errors, therefore they will not undergo further analysis in this review. Of the fourteen names not previously reviewed, 10 names (Stevia, Tazorac, Staveran, Gemzar, Glukor, Storax, Serzone, Stanozide, Starnoc and Stieprox) were thought to look like Stavzor. Simcor was thought to sound like Stavzor and the remaining names, Estazor, Stanza, and Stanzar were thought to look and sound similar to Stavzor.

Additionally, the Division of Medication Error Prevention did not identify any United States Adopted Names (USAN) stems in the name Stavzor as of June 24, 2008.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the staff (see section 3.1.1. above) but did not identify any additional names with similarity to Stavzor. The Expert Panel indicated that the proposed name Stavzor has been previously reviewed and found acceptable.

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

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

3.1.3 Safety evaluator risk assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look and/or sound similar to Stavzor and represent a potential source of drug name confusion. As such, a total of fourteen names were analyzed to determine if the drug names could be confused with Stavzor 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 Stavzor, and thus determined to present some risk of confusion. Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name Stavzor could potentially be confused with any of the fourteen names and lead to medication error. This analysis determined that the name similarity between Stavzor and the identified names was unlikely to result in medication errors for the fourteen product names

Six of the fourteen names (Stanza, Stanzar, Staveran, Estazor, Starnoc, and Stieprox) were not considered further because they are only available in foreign markets (See Appendix B).

_____ received a non-approvable action in 1975 by the FDA and is not currently marketed (Appendix C).

b(4)

Five of the names, Stevia, Tazorac, Gemzar, Storax and Stanozide were determined by FMEA that medication errors were unlikely to occur because they do not overlap in strength, dose, or indication with Stavzor. (See Appendix D).

The remaining two names, Simcor and Serzone had some numerical overlap with Stavzor in dosage and strength. Our analysis of the failure modes determined that the effects of these similarities to result in medication errors in the usual practice setting were not likely (See Appendix E).

3.2 LABEL AND LABELING RISK ASSESSMENT

We note that the revised labels and labeling address most of our recommendations from our previous review (OSE Review 2007-1690). However, review of the container labels have found an additional area of vulnerability that could lead to medication error.

3.2.1 Label

The graphic logo presented in front of the proprietary name resembles a 'V' on the primary panel.

3.2.4 Package Insert Labeling

No comments at this time.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Stavzor, has some similarity to other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

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, we believe that these limitations are sufficiently minimized by the use of an Expert Panel 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.

4.2 LABEL AND LABELING RISK ASSESSMENT

Although the applicant has addressed most of our label/labeling recommendations from our previous review, the results of the Label and Labeling Risk Assessment found that the presentation may lend itself to vulnerability that could lead to medication errors.

4.2.1 Container Label

Our analysis notes that the container labels can be improved to optimize readability. The graphic logo, which is presented on the top left corner of the container label, is directly in front of the proprietary name, Stavzor. The position of the graphic logo and the shape of the logo (the shape of a U or V) may lend itself to misinterpretation of the name. As it is presented, the name could be interpreted as U-Stavzor or V-Stavzor.

5 CONCLUSIONS

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

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels introduces vulnerability to confusion that could lead to medication errors. We believe the risks identified can be addressed and mitigated prior to drug approval, and provide recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

6.1.1 Proprietary name:

The Division of Medication Error Prevention has no objections to the use of the proprietary name Stavzor for this product.

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.

If the product approval is delayed beyond 90 days from the signature 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 clarifications, please contact Dan Brounstein, project manager, at 301-796-0674.

6.1.2 Container Label and Insert Labeling:

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention has identified areas of needed improvement. We have provided recommendations in section 6.2 and request this information be forwarded to the Applicant.

6.2 COMMENTS TO THE APPLICANT

A. The Division of Medication Error Prevention has no objections to the use of the proprietary name Stavzor for this product. 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 evaluation

B. Labels and Labeling

1. Container Label

Delete or relocate the graphic circular 'V' logo from immediately in front of the proprietary name. The placement of the logo may lend itself to misinterpretation of the proprietary name (i.e. UStavzor or VStavzor).

2. Package Insert Labeling

No comments at this time.

7 REFERENCES

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 The Division of Medication Error Prevention, 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 Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division 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.

Appears This Way
On Original

APPENDICES

Appendix A:

The Medication error staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We 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 examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The Medication error 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 Medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we 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, we also consider 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	Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes 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	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Foreign Drugs Identified As Look-Alike and/or Sound-Alike

Drug Name	Similarity to Stavzor	Country
Stanza	Look-Alike and Sound-Alike	Indonesia
Stanzar	Look-Alike and Sound-Alike	Pakistan
Staveran	Look-Alike	Poland
Estazor	Look-Alike and Sound-Alike	Indonesia
Starnoc	Look-Alike	Canada
Stieprox	Look-Alike	Canada

Appendix C: Drugs that received non-approvable from FDA or no longer marketed

Product Name	Application # and Sponsor	Status
_____	NDA _____	Non-approvable, not currently marketed

b(4)

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

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Stavzor (Valproic Acid Delayed Release Capsules)		125 mg, 250 mg, 500 mg oral delayed release capsules	5 mg/kg/day – 60 mg/kg/day in divided doses, titrated based on therapeutic response
Stevia (Stevia rebaudiana)	Look-Alike	Stevia leaf	As needed for sweetening foods
Tazorac (Tazarotene)	Look-Alike	Topical Cream; 0.05%, 0.1% 15 gm and 30 gm tubes Topical Gel; 0.05%, 0.1% 30 gm and 100 gm tubes	Apply cream or gel once daily to affected area
Gemzar (Gemcitabine Hydrochloride)	Look-Alike	200 mg lyophilized powder; 10 mL single vial 1 g lyophilized powder; 50 mL single use vial	Pancreatic Cancer: 1000 mg/m ² once weekly Non-Small Cell Lung Cancer: 1000 mg/m ² days 1, 8, 15 of each 28-day cycle Breast Cancer: 1250 mg/m ² days 1 and 8 of each 21 day cycle Ovarian Cancer: 1000 mg/m ² on days 1 and 8 of each 21 day cycle
Storax (Liquidambar orientalis)	Look-Alike	Resin from the leaf oil	As a stimulant and expectorant a dose of 1 g has been used
Stanozide (Isoniazid)	Look-alike	100 mg oral tablets 100 and 1000 bottles 300 mg oral tablets 30, 100 and 1000 bottles	Adults: 5 mg/kg daily up to 300 mg daily in a single dose or 15 mg/kg up to 900 mg/day, two-three times/week Children: 10-15 mg/kg up to 300 mg daily in a single dose, or 20-40 mg/kg up to 900 mg/day, two or three times a week

Appendix E: Potential confusing names due to numerical overlap in dose and/or strength

Stavzor (Valproic Acid Delayed Release Capsules)	125 mg, 250 mg, 500 mg capsules oral capsule	5 mg/kg/day – 60 mg/kg/day in divided doses, titrated based on therapeutic response
Potential Confusion	Causes (could be multiple)	Effects
<p>Simcor Tablets (Niacin XR/ Simvastatin) 500 mg/20 mg, 750 mg/20 mg, 1000 mg/20mg oral tablets</p>	<p>Numerical overlap in dose and achievable dose (Stavzor 250 mg and 500 mg vs. Simcor 500 mg, 750 mg, 1000 mg)</p> <p>Share similar prescriber population once patient is stabilized.</p> <p>Share similar patient population</p>	<p>Medication errors are unlikely due to the prominent phonetic differences between Stavzor and Simcor.</p> <p>Phonetically there are many differences between Simcor and Stavzor. They begin with ‘S’ and are two syllables, however the presence of ‘t’ in the first syllable and ‘a’ sound in Stavzor are very distinct from ‘Sim-‘. Additionally in Stavzor the second syllable begins with a ‘z’ rather than a ‘c’ as in Simcor, and in the case of Simcor, it is definitively a ‘hard c’, which phonetically is very distinct from a ‘z’.</p> <p>Stavzor is given in divided doses throughout the day. Simcor is given once daily at bedtime.</p> <p>Stavzor contains one ingredient, Valproic Acid. Simcor contains two products, Niacin XR and Simvastatin. Simcor may have both the Simvastatin and Niacin dose on the prescription.</p> <p><i>There was not thought to be any orthographic similarities as determined by reviewer and EPD.</i></p>
<p>Serzone (Nefazodone hydrochloride) 50 mg, 100 mg, 150 mg, 200 mg, 250 mg oral tablets</p>	<p>Numerical overlap in dose and achievable dose (Stavzor 250 mg, 500mg vs. Serzone 50 mg, 100 mg, 150 mg, 200 mg, 250 mg)</p> <p>Similar prescribing population.</p> <p>Similar patient population.</p>	<p>Orthographic and phonetic differences minimize the likelihood of medication errors in the usual practice setting.</p> <p>Orthographic distinction between Stavzor and Serzone include: upstroke provided by the presence of the ‘t’ in the first syllable of Stavzor, this increases the amount of space utilized when scripted in the first part of the word by spacing the ‘S’ and ‘a’ and also provides a cross-stroke which aids in differentiation. The name Stavzor ends with ‘r’ while Serzone has ‘e’ on the end, which when written extends the name by one letter and bulks up the length of</p>

	<p>Share possible twice daily dosing regimen</p>	<p>the name Serzone.</p> <p>Phonetically both Serzone and Stavzor have 2 syllables and begin with 'S', however Stavzor contains a 't' present in the first syllable. The first syllable in Stavzor ends in 'v', rather than 'r'. When the whole first syllable is considered, the sound of 'Stav' compared to 'Ser' is very distinct. The vowel sounds are distinct because of the presence of the 't'. In addition the ending 'one' found in Serzone, versus 'or' in Stavzor further differentiates the names.</p> <p>Serzone is given twice daily and is usually initiated at 200 mg per day in divided doses. Doses should not be above 600 mg.</p> <p>Stavzor may be given twice or three times daily, dosed by mg/kg, typically daily doses exceed 600 mg.</p> <p>Serzone was removed from the US market in May of 2004. It is unlikely that practitioners will prescribe under the name, Serzone. Practitioners will more than likely refer to it as Nefazodone, the established name, which is still marketed. However, if the proper name is utilized during prescribing, the aforementioned orthographic differences would help distinguish the two medications.</p>
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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Anne Crandall
7/21/2008 03:49:26 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
7/22/2008 12:17:26 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/22/2008 02:57:54 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; HFD-420)**

DATE RECEIVED: August 3, 2007	DESIRED COMPLETION DATE: October 3, 2007	OSE CONSULT #: 2007-1690
DATE OF DOCUMENT: July 19, 2007	PDUFA DATE: October 22, 2007	

TO: Russell Katz, M.D., Director
Division of Neurology Products

THROUGH: Kellie Taylor, Pharm.D., M.P.H., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Stavzor Valproic Acid Delayed-release Capsules 125 mg, 250 mg, and 500 mg	NDA SPONSOR: JDS Pharmaceuticals, LLC
NDA #: 22-152	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Stavzor. This is considered a final decision. However, if approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Stavzor, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion if needed. Please copy DMETS on any communications forwarded to the Sponsor regarding this review. If you have further questions or need clarifications, please contact Daniel Brounstein, Project Manager, at 301-796-0674.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; WO 22; Mail Stop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: September 17, 2007

NDA #: 22-152

NAME OF DRUG: Stavzor
Valproic Acid
Delayed-release Capsules
125 mg, 250 mg, and 500 mg

NDA HOLDER: JDS Pharmaceuticals LLC

I. INTRODUCTION:

This review was written in response to a request from the Division of Neurology Products, for assessment of the proprietary name, Stavzor, regarding potential name confusion with other proprietary or established drug names. Container labels, insert labeling, and a Drug Safety Institute, Inc. 'Proprietary Name Safety Assessment' for Stavzor were provided for review. A secondary proposed proprietary name _____, was provided for review should DMETS find Stavzor not acceptable.

b(4)

PRODUCT INFORMATION

Stavzor is an oral delayed-release soft gelatin capsule formulation of valproic acid. Stavzor capsules are indicated for: 1) the treatment of the manic episodes associated with bipolar disorder, 2) as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures, and 3) for prophylaxis of migraine headaches. The recommended doses of Stavzor, based upon the indications as stated in the Full Prescribing Information, are listed in Table 1 on page 3.

Table 1. Recommended Doses of Stavzor

Indication	Recommended Dose of Stavzor
Mania associated with bipolar disorder	750 mg daily in divided doses
Seizures-Monotherapy	Initiate at 10-15 mg/kg/day. Dosage should be increased by 5-10 mg/kg/week to achieve optimal clinical response.
Seizures-Adjunctive therapy	Add to current regimen at dose of 10-15 mg/kg/day. Dose may be increased by 5-10 mg/kg/week to achieve optimal clinical response.
Simple and Complex Absence Seizures	Initiate at 15 mg/kg/day, increasing at one week intervals by 5-10 mg/kg/day until seizures are controlled or side effects preclude further increases.
Migraine headache prophylaxis	250 mg twice daily. Some patients may benefit from doses up to 1000 mg/day.

If satisfactory clinical response is not achieved, plasma levels may be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 mcg/mL). Some patients may be controlled with higher or lower serum concentrations.

Stavzor is available in bottles of 100 capsules in three strengths: 125 mg, 250 mg, and 500 mg. Each strength is described as an orange colored, oval shaped capsule with black print. Stavzor should be stored at controlled room temperature (25 degrees Celsius) with excursions permitted to 15-30 degrees Celsius.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Stavzor to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Stavzor. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of

¹ MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

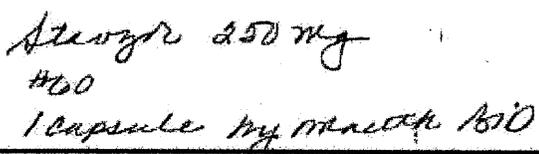
1. DDMAC finds the proprietary name, Stavzor, acceptable from a promotional perspective.
2. The Expert Panel identified the following 12 proprietary names that were thought to have the potential for confusion with Stavzor: Advicor, Atragen***, Stavudine, Stalevo, Stadol, Starlix, Atarax, Atacand — — *, Ativan, Azor***, and Javlor***.

b(4)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Stavzor with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten requisition forms or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a request for Stavzor (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were 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 sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient Order:</u></p> 	<p>“Stavzor 250 mg, Number 60, Take 1 capsule by mouth bid...”</p>
<p><u>Inpatient Order:</u></p> 	

2. Results:

None of the interpretations of the proposed name, Stavzor, overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, twelve names were identified as having the potential to look and sound similar to Stavzor: Advicor, Atragen***, Stavudine, Stalevo, Stadol, Starlix, Atarax, Atacand _____, Ativan, Azor***, and Javlor***. b(4)

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case there was no confirmation that the proposed name could be confused with any of the aforementioned names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Stavzor. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Upon initial analysis of the aforementioned twelve names, it was determined the twelve names Advicor, Atragen***, Stavudine, Stalevo, Stadol, Starlix, Atarax, Atacand _____, Ativan, Azor***, and Javlor*** lacked convincing look-alike and sound-alike similarities with Stavzor. In addition, the products had numerous differentiating product characteristics as noted below, including product strength, indication for use, route of administration, frequency of administration, prescription status, patient population and/or dosage formulation. In some cases, there was no additional product information available for a drug or the drug was no longer marketed. b(4)

When compared to Stavzor Capsules:

- Advicor lacks product commonalities such as product strength, frequency of administration, and indication for use.
- Atragen*** lacks product commonalities such as route of administration and dosage formulation. Current information is incomplete for Atragen*** as it is an investigational drug that lacks FDA approval.
- Stavudine is the established name for Zerit. The name Stavudine lacks product commonalities such as dose, product strength, and indication for use.
- Stalevo lacks product commonalities such as dose, product strength, and indication for use.
- Stadol lacks product commonalities such as dosage formulation, route of administration, product strength, dose, indication for use, duration of therapy, and area of use.
- Starlix lacks product commonalities such as product strength, dose, and indication for use.
- Atarax is a brand of hydroxyzine that is no longer marketed although generics remain available. Atarax lacks product commonalities such as product strength, dose, and indication for use.
- Atacand lacks product commonalities such as product strength, dose, and indication for use.
- _____* was a proposed proprietary name for a brand of Fosamprenavir Calcium Tablets. This product was eventually approved under the name Lexiva (NDA 21-548), thus the name _____ is no longer active. b(4)
- Ativan lacks product commonalities such as product strength, dose, and indication for use.
- Azor*** is a proposed name pending for Amlodipine Besylate and Olmesartan Medoxomil Tablets (NDA 22-100). Azor*** lacks product commonalities such as product strength, dose, frequency of administration, and indication for use.
- Javlor*** is a proposed name pending for Vinflunine Injection (IND 69,972). Javlor*** lacks product commonalities such as dosage formulation, route of administration, length of therapy, indication for use, and area of use.

D. INDEPENDENT TRADENAME ANALYSIS (Drug Safety Institute, Inc.)

The sponsor submitted a Drug Safety Institute (DSI) proprietary name evaluation in support of the proposed name Stavzor. Drug Safety Institute identified eight names that looked similar or sounded similar to Stavzor: Stadol, Stalevo, Stanazolol, Statrol, Stavudine, Stelazine, Tazorac, and Zocor.

Similar to DSI, DMETS also identified the three names Stadol, Stalevo and Stavudine. DMETS did not identify the following five names that DSI identified as looking and/or sounding similar to Stavzor: Stanazolol, Statrol, Stelazine, Tazorac, and Zocor.

DMETS considers the additional names identified by DSI to have low potential for confusion with Stavzor due to a lack of convincing look-alike and/or sound-alike similarities in addition to numerous differentiating product characteristics, such as dose, strength, route of administration, dosage form, or frequency of use, and/or the lack of availability of the drug. Following independent review of the names identified by DSI, DMETS concurs with the overall findings of DSI.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS reviewed the labels and labeling from a medication errors perspective, applying principles of human factors and post-market medication experiences. DMETS has identified the following areas of improvement, to minimize user error and maximize patient safety.

A. GENERAL COMMENTS

DMETS notes that all three capsule strengths are described as orange colored, oval shaped capsules with black print. The imprints are also similar. These visual similarities may increase the chance for confusion among strengths. It would be beneficial if the capsules could be a different color or the actual strength were printed on each capsule to assist in visual differentiation between the strengths.

B. CONTAINER LABELS (125 mg, 250 mg, and 500 mg: 100 count)

1. DMETS notes that the container labels for the three strengths feature the same layout, formatting, and colors. Thus they all look very similar to one another. DMETS recommends that the label for each strength feature a different color or some other method to increase the prominence of the strength to help differentiate between the three strengths. For example, the white block with purple border that contains the product strength could each be color-blocked with different colors to help differentiate among the three strengths.
2. The established name should not include 'soft gelatin' to be consistent with the NDA filed which refers to 'Valproic Acid Delayed Release Capsules'.
3. The established name should be featured completely in the same font (e.g., Valproic Acid Delayed-release Capsules) and color.

4. Ensure that the established name is at least ½ the size of the proposed proprietary name, Stavzor.
5. DMETS recommends that the net quantity (100 Capsules) and the product strength (e.g., 125 mg) not be presented in close proximity to one another in order to decrease the potential for confusion. The current presentation features the product strength and net quantity adjacent to each other in the center of the label. Thus, DMETS recommends relocating the net quantity to the top or bottom of the label away from the product strength and established name.

C. HIGHLIGHTS OF PRESCRIBING INFORMATION LABELING

DMETS notes that in the HIGHLIGHTS OF PRESCRIBING INFORMATION, the indications for Stavzor have been abbreviated and as a result, broaden the approved indications for Stavzor.

HIGHLIGHTS OF PRESCRIBING INFORMATION	FULL PRESCRIBING INFORMATION
'Mania'	'treatment of the manic episodes associated with bipolar disorder'
'Epilepsy'	'monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures'
'Migraine'	'for prophylaxis of migraine headaches'

The full indications for Stavzor, including any limitations to the indications, should be communicated completely and accurately in this section.

D. FULL PRESCRIBING INFORMATION LABELING

1. DOSAGE AND ADMINISTRATION section 2

In section 2.1, which describes the dosing for mania, the recommended initial dose is 750 mg daily in divided doses. DMETS requests that the Sponsor clarify this recommendation and be more specific. For example, instead of 'divided doses' it could be stated 'in 2 to 3 doses' to provide more helpful recommendations to the health care providers who are prescribing and dispensing this drug. Section 2.2 also uses the 'divided doses' recommendations in several places and clarification should also be provided in those sections as appropriate.

2. DMETS did not see any recommendations to 'swallow whole' or similar recommendations against dividing/opening the capsules. DMETS wonders if opening the capsule compromises the delayed release mechanism of the drug? If so, recommendations against compromising the capsule should be included in all labels and labeling. This is particularly concerning with use of the term 'divided doses' as some patients and prescribers may be creative and literally divide their doses through tampering with the capsules, thus compromising the delayed release dosing mechanism.

3. PATIENT COUNSELING INFORMATION section 17

DMETS notes that hepatotoxicity is not mentioned in this section despite the fact that Stavzor features a boxed warning about hepatotoxicity and fatalities have occurred in patients who have taken valproic acid. The mention of 'Hyperammonemia' and 'hyperammonemic encephalopathy' may not be sufficient to convey this important risk both to healthcare professionals and patients. DMETS recommends that Hepatotoxicity be included in this section with appropriate discussion.

4. FDA APPROVED PATIENT LABELING section 17.6

This section appears to be incomplete as it primarily targets women who could become pregnant and are at risk of having a child with birth defects. This is very problematic because it only discusses issues with teratogenicity. DMETS believes that any approved patient labeling should be complete with regards to the risks of the medication so that patients are informed. DMETS notes that not even the boxed warnings for hepatotoxicity and pancreatitis are currently included, and neither are many of the adverse events reported in the clinical trials. These risks and adverse events should be communicated in patient friendly language. Additional important information is also lacking in this section, including dosing and monitoring recommendations that patients need to know. Thus, DMETS recommends that this section be rewritten to convey a more complete picture of Stavzor as appropriate for patients. Furthermore, DMETS recommends that the patient labeling be reviewed by the Division of Surveillance, Research, and Communication Support for patient friendly wording.

Appendix A-Stavzor

Outpatient	Inpatient	Voice
Stavzor	Stavzor	Stazor
Stavzr (?)	Stavzir	Staphsore
Stavzor	Starzor	Stafzor
Stavzor	Stavzor	Stasor
Stavzor	Stavzar	Stafzor
Stavzor	Stavzor	Stabsor
Stozor	Stavzor	Staphzor
Stavzor	Stavzor	Staphzor
Staozor	Stavzor	Statzor
Stavzor		Stazor
Stavzor		Stassore

**This is a representation of an electronic record that was signed electronically and
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Laura Pincock
10/18/2007 01:35:56 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/18/2007 01:57:04 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her
absence