

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-181

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

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

DATE RECEIVED: October 18, 2007	DESIRED COMPLETION DATE: November 19, 2007	OSE CONSULT #: 2007-1801 and 2007-2193
DATE OF DOCUMENT: May 25, 2007	PDUFA DATE: November 25, 2007	

TO: Daniel Shames, MD
Acting Director, Division of Gastroenterology Products, HFD-180

THROUGH: Linda Y. Kim-Jung, Pharm D, Team Leader
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Division of Medication Errors and Technical Support, HFD-420

FROM: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: Kuvan (Sapropterin Dihydrochloride) Tablets 100 mg	NDA SPONSOR: BioMarin Pharmaceutical, Inc.
NDA#: 22-181	

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, Kuvan. 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.
2. DMETS recommends the implementation of the 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, Kuvan, acceptable from a promotional perspective.
4. DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence forwarded to the sponsor pertaining to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

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

PROPRIETARY NAME, LABELS AND LABELING REVIEW

DATE OF REVIEW: October 25, 2007

NDA#: 22-181

NAME OF DRUG: Kuvan
(Sapropterin Dihydrochloride) Tablets
100 mg

NDA HOLDER: BioMarin Pharmaceutical, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastroenterology Products (HFD-180), for a re-assessment of the proprietary name, "Kuvan" regarding potential name confusion with other proprietary and/or established drug names. Previously, DMETS had no objection to the use of the proprietary name, Kuvan, in OSE review# 2007-172 dated July 25, 2007. Container labels, carton and insert labeling were submitted for review and comment via the electronic document room (dated August 17, 2007).

PRODUCT INFORMATION

Kuvan (Sapropterin Dihydrochloride) is an enzyme cofactor to be used for the treatment of hyperphenylalaninemia associated with phenylketonuria (PKU). The usual dose is based upon patient weight and will be dosed at 10 mg/kg/day. Kuvan will be available in 100 mg tablets and is to be administered once daily

II. SAFETY EVALUATOR 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 Kuvan 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-

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 97-07, 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>.

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. In addition, DMETS conducted three prescription analysis studies consisting of two written inpatient requisition studies and one verbal requisition study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial steps, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Kuvan. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of 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, Kuvan, acceptable from a promotional perspective.
2. Since the previous review, the Expert Panel identified five (5) proprietary or established names that were thought to have the potential for confusion with Kuvan. These names included Kavain, Ku-Zyme, Ativan, and Trovan.

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

B. SAFETY EVALUATOR RISK ASSESSMENT

In re-reviewing the proprietary name Kuvan, five (5) names were thought to have the potential to sound like or appear similar to Kuvan. These names included [REDACTED], Kavain, Ku-Zyme, Ativan, and Trovan.

Upon review of the five (5) aforementioned names, [REDACTED] Ku-Zyme, Ativan, and Trovan were not considered further because they lack significant look-alike and/or sound-alike similarities with Kuvan, in addition to having differentiating product characteristics that may include: the product strength, indication for use, frequency of administration, route of administration, dosage formulation, therapeutic class, storage conditions, patient population, prescriber population, product unavailability and/or type of marketing or distribution.

The remaining name, Kavain, is listed in Table 1 (see below) along with the dosage form available and usual dosage. The analysis of Kavain is discussed in detail following Table 1.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Kuvan	Sapropterin Dihydrochloride Tablets 100 mg	10 mg/kg once daily [REDACTED]	
Kavain	Kava Scientific name: Piper methysticum Family: Piperaceae Root Powder	Anxiety disorders: 100 mg (70 mg kava-lactones) three times daily <u>Prevention of benzodiazepine withdrawal:</u> 50 mg to 300 mg per day over one week while the benzodiazepine is tapered over 2 weeks	LA/SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

1. Kavain was identified as a name that looks similar to Kuvan. Kavain is also known as Kava which is an herbal product. The applicable parts of kava are the rhizome, root, and stem. Current literature attributes much of the pharmacological effect to kavalactones found in the lipid-soluble portion of the root. The kavalactone content of the kava root varies considerably which is why commercial preparations are preferred. Kava root powder can be added to teas and steeped in a tea ball to make tinctures to use as drops either directly on the tongue or mixed in with beverages, or packed into capsules. A common indication for its use is anxiety disorders and the dose is 100 mg orally three times daily.

Kavain resembles Kuvan when scripted because they share three letters in the same position, 'K', 'v', and 'n' (K A V A I N vs. K U V A N). Additionally, they can appear similar in length although Kavain has one more letter than Kuvan (see sample below).

Both drugs can be given orally and the 100 mg strength for Kuvan overlaps with the dose for Kavain. However, the frequency of administration for Kuvan and Kavain is different (once daily vs. three times a day) and in contrast to Kavain, Kuvan will require several tablets to be administered because the dose is weight based. Additionally these two products would be encountered in different healthcare settings. Kavain would be found in an alternative treatment setting because it is an herbal product and does not require a prescription whereas Kuvan would be prescribed in a traditional medical environment that involves a physician or other healthcare prescriber. Thus, it is unlikely that a nurse or pharmacist in an acute care or ambulatory setting would encounter a prescription written for Kavain.

Kavain
Kuvan

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Kuvan, DMETS has conducted a failure modes and effects analysis and applied the principles of human factors to the evaluation of these labels and labeling. Our analysis identified several areas of possible improvement which might minimize potential user error.

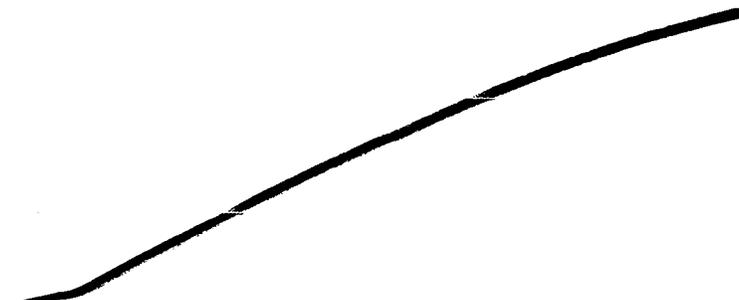
A. GENERAL COMMENTS

1. DMETS is concerned that this product will only be available as a 100 mg un-scored tablet. This limited availability raises several concerns with respect to proper use and dosing of the product. When dosed based upon weight (5 mg/kg to 20 mg/kg), most patients will need to take multiple tablets. For example, a 70 kg person would need to take three (3) to fourteen (14) tablets. The availability of this drug in this sole strength (100 mg) may lead to adherence problems or improper dosing. As patient weight and phenylalanine levels fluctuate, dose titration may be a problem as well. Guidance to practitioners regarding dose titration and adjustments may decrease the potential for medication errors related to over- or under-dosing as a result of the availability of this sole strength. Please consider providing this information to assist with proper dosing and to support acceptable clinical outcomes.

2.

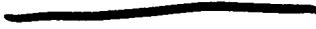
3.

4.



1

DMETS recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (The Project Manager Assigned to the LNC) and the assigned ONDQA Chemist regarding the proper designation of the established name.

5. 

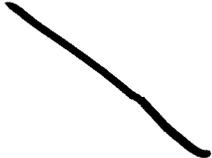
6. 

B. CONTAINER LABEL

See Comments A1 through A6 under General Comments.

C. CARTON LABELING

See Comments A1 through A6 under General Comments.



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 correspondence forwarded to the sponsor pertaining to this review. If you have further questions or need clarifications, please contact Cherye Milburn, OSE project manager, at 301-796-2084.

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/s/

Linda Kim-Jung
11/14/2007 08:30:00 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Denise Baugh 11/14/07.

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