CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-159

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop Room 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 2006-859
November 17, 2006	May 16, 2007	
DATE OF DOCUMENT:	**PDUFA DATE:**	
November 1, 2006	February 9, 2008	

TO: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

THROUGH: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:
OraVerse
(Phentolamine Mesylate, Injection)
0.4 mg

NDA #: 22-159 (IND#: 65,095)

NDA SPONSOR: Novalar Pharmaceuticals, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, OraVerse. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/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, OraVerse, 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 Nancy Clark, project manager, at 301-796-1187.

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

PROPRIETARY NAME AND LABEL/LABELING REVIEW

DATE OF REVIEW: February 20, 2007

NDA#: 22-159 (**IND#**: 65,095)

NAME OF DRUG: OraVerse (Phentolamine Mesylate Injection) 0.4 mg

NDA HOLDER: Novalar Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170), for assessment of the proprietary name, OraVerse, regarding potential name confusion with other proprietary or established drug names. Container labels and package insert labeling were provided for review and comment.

PRODUCT INFORMATION

OraVerse is an alpha-adrenergic receptor antagonist indicated for the reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor. The usual dose of OraVerse is 0.2 mg to 0.8 mg dependent upon the amount of local anesthetic administered. OraVerse is supplied in 1.7 mL cartridges containing 0.4 mg of phentolamine mesylate.

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 OraVerse 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 conducted[5]. The Saegis[6] 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. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and

[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 98-07, 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.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

outpatient) and one verbal prescription 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 components, 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 drug 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 OraVerse. Potential concerns regarding drug marketing and promotion related to the proposed name(s) 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 OraVerse acceptable from a promotional perspective.

2. The Expert Panel identified 20 proprietary names that were thought to have the potential for confusion with [redacted] They are: Univasc, Norvasc, Oravir, Orinase, Orarinse, Orazinc, Ovarex, Aramine, Reversol, Oralone, Oracea, Orasone, Orencia, Oro-Cleanse, Alavert, Oracort, Oravue, Orapred, Orabase HCA, and Oravess. Additionally, the Expert Panel suggested an independent search of additional names beginning with the letters 'A', 'U', and 'Cr' for names that may have the potential to look and/or sound like OraVerse. That search did not yield any additional names. 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 OraVerse with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient drug requisitions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for OraVerse (see page 4). These requisitions 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
Requisition #1: 5 | 0704 | Oravrse	"Next item is for...OraVerse, five cartridges"
Requisition #2: 5 | 0704 | OraVerse cartridges	

2. Results:

None of the interpretations of the proposed name 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 ASSESSEMEMNT

DMETS evaluated the proposed name OraVerse from a safety perspective to determine if the name posed an increased risk of name confusion with currently marketed drug products. Additionally DMETS evaluated the risk of introducing new oral anesthetic reversing agents into the marketplace. We specifically looked to see if addition of an oral anesthetic reversing agent would create confusion with the currently marketed oral anesthetic agents which use a color coding system to identify each product.

1. Look-Alike and Sound-Alike Concerns

It was noted that the name is proposed using a capital letter 'O' at the beginning of the name, and a capital letter 'V' in the middle of the name (i.e. OraVerse). DMETS notes that postmarketing evidence demonstrates that despite the sponsor's intended presentation of the name practitioners often write the name without the capital letter in the middle of the name (i.e. Oraverse). Therefore the name will be evaluated without consideration of the capital letter 'V' in the middle of the name.

In reviewing the proprietary name OraVerse, 20 names were identified as either sounding similar or looking similar to OraVerse. These names are: Univasc, Norvasc, Oravir, Orinase, Orarinse, Orazinc, Ovarex, Aramine, Reversol, Oralone, Oracea, Orasone, Orencia, Oro-Cleanse, Alavert, Oracort, Oravue, Orapred, Orabase, and Oravess.

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, OraVerse. 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.

In the initial analysis of the 20 names DMETS determined the following 18 names, Norvasc, Univasc, Oravir, Orarinse, Orazinc, Ovarex, Aramine, Reversol, Oralone, Oracea, Orasone, Orencia, Oro-Cleanse, Alavert, Oracort, Oravue, and Orapred, and Oravess would not be considered further for the following reasons.

- Lack of orthographic and/or phonetic similarities with OraVerse
- Lack of overlapping product commonalities such as dosage form, route of administration, product strength, usual dose, indication of use, context of use and/or prescription only status.
- The name Oravir is a foreign product which lacks overlapping product commonalities such as dosage form, route of administration, product strength, and usual dose.
- The name Oravue only appears in Micromedex with limited drug information. The name does not appear in commonly used references such as Facts and Comparisons, Clinical Pharmacology, the Red Book, etc.
- The name Ovarex is an orphan drug that is being studied in clinical trials and is not yet available to the public.
- Oravess was [redacted]

b(4)

The remaining two proprietary names warranted further evaluation based on look-alike, sound-alike and product characteristics (see Table 1 on page 5).

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

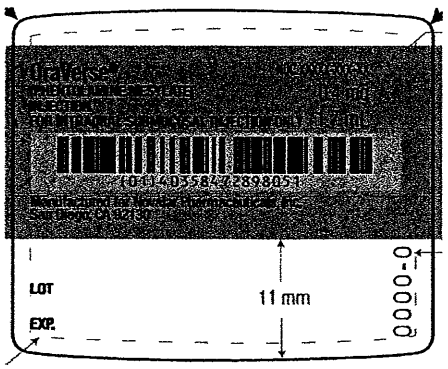
Product Name	Dosage form(s) Established name	Usual adult dose*	Other**	Differing Product Characteristics
OraVerse	Phentolamine Injection 0.4 mg	0.2 mg to 0.8 mg dependent upon the amount of local anesthetic previously administered	N/A	N/A
Orinase	Tolbutamide Tablet 500 mg	250 mg to 3000 mg per day in one to three divided doses	LA	No overlap • **Dosage Form** ➢ Injection vs. Tablet • **Product Strength** ➢ 0.4 mg vs. 500 mg • **Usual Dose** ➢ 0.2 mg to 0.8 mg vs. 250 mg to 3000 mg • **Context of Use** ➢ Dentist's office/operating room use only, not dispensed to patient vs. dispensed to patient • **Indication of Use** ➢ Oral anesthesia reversal vs. oral hypoglycemic • **Route of Administration** ➢ Intraoral injection vs. oral • **Storage Conditions** ➢ Operating room or dentist's office vs. pharmacy shelf • **Prescriber Population** ➢ Dentist or oral surgeon vs. Endcorinologists, general practitioners
Orabase	gelatin, pectin and sodium carboxymethylcellulose in Plastibase Paste	Apply a small amount of paste to affected area as needed.	SA	No Overlap • **Dosage Form** ➢ Injection vs. Paste • **Product Strength** ➢ 0.4 mg vs. 0.5% • **Usual Dose** ➢ 0.2 mg to 0.8 mg vs. Small amount • **Context of Use** ➢ Dentist's office/operating room use only, not dispensed to patient vs. dispensed to patient • **Indication of Use** ➢ Oral anesthesia reversal vs. oral anesthesia and skin protection • **Route of Administration** ➢ Intraoral injection vs. topical

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

After further evaluation of Orinase and Orabase both names were determined to not pose an increased risk for name confusion with OraVerse due to lack of overlapping product characteristics such as indication of use, product strength, usual dose, route of administration, dosage form, context of use, dosing frequency, storage location and/or prescriber population. See specifics above in "Differing Product Characteristics" column of table 1.

2. Introduction of Additional Oral Anesthetic Reversing Agents

The American Dental Association (ADA) currently utilizes a color-coding scheme for local anesthetic cartridges that is widely recognized by dental healthcare professionals (see Attachment B for the entire color code format). Each anesthetic agent has a "color bar" on the cartridge label that is associated with only that particular active ingredient (e.g. red bar for Lidocaine 2% with Epinephrine 1:100,000). However, at present the ADA has no plans to color code anesthetic reversal agents such as OraVerse. Since OraVerse is the first product in this category, DMETS is concerned that if/when another anesthetic reversing agent such as OraVerse is developed in the future, the new product will need to differentiate itself from oral anesthetics as well as OraVerse, but at the same time be readily recognizable as an anesthetic reversing agent. The sponsor has differentiated this product from oral anesthetics agents by differentiating the cartridge labeling by not using a color bar at all, but rather a solid colored cartridge label (see label graphic below). Additionally, the sponsor uses a [redacted] which is not used for any other dental anesthetic products in the U.S. Moreover, the sponsor plans on distinguishing the secondary packaging of the drug product. OraVerse will be packaged in a [redacted] blister tray, which differs from the clear, colorless PVC blister tray currently used for other dental cartridges. Thus, for this product, all these distinguishing features help to adequately distinguish OraVerse from oral anesthetic agents. Therefore, the proposed plan is acceptable. However, DMETS recommends that a systematic approach to differentiate the oral anesthetic reversing agents from the oral anesthetic products be undertaken by the Division, any further sponsors of reversing agents and the ADA. This will ensure that reversing agents approved in the future will not be confused with products currently marketed and ensure a consistent color coding scheme. b(4)



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of OraVerse, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which will minimize potential user error.

A. General Comments

The sponsor has differentiated this product from oral anesthetics agents by differentiating the cartridge labeling by not using a color bar at all, but rather a solid colored cartridge label (see label graphic below). Additionally, the sponsor uses a [redacted] " which is not used for any other dental anesthetic products in the U.S. Moreover, the sponsor plans on distinguishing the secondary packaging of the drug product. OraVerse will be packaged in a [redacted] blister tray, which differs from the clear, colorless PVC blister tray currently used for other dental b(4)

cartridges. Thus, for this product, all these distinguishing features help to adequately distinguish OraVerse from oral anesthetic agents. Therefore, the proposed plan is acceptable. However, DMETS recommends that a systematic approach to differentiate the oral anesthetic reversing agents from the oral anesthetic products be undertaken by the Division, any further sponsors of reversing agents and the ADA. This will ensure that reversing agents approved in the future will not be confused with products currently marketed and ensure a consistent color coding scheme.

B. Container Label

1. In order to be consistent with other injectable products, revise the product strength so that the total milligrams per total volume is immediately followed by the milligram per milliliter concentration (see below).

0.4 mg/1.7 mL
(0.23 mg/mL)

2. Relocate the product strength so that it immediately follows the proprietary and established names. However, ensure the product strength is not presented in close proximity to the net quantity in order to prevent confusion.

3. DMETS notes that the cartridges are not marked with increments of measure. In light of the proposed dosing (0.2 mg to 0.8 mg), DMETS questions how one would accurately administer a dose which requires less than an entire cartridge (i.e. 0.2 mg)

B. Blister Backing Labeling

No comments at this time.

C. Carton Labeling (10 Cartridges and 50 Cartridges)

1. Per 21 CFR 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name.

2. 50 Cartridge Carton: Revise the "Contents" statement to read "Contents: 50 Cartridges, 0.4 mg per 1.7 mL each".

D. Package Insert Labeling

DOSAGE AND ADMINISTRATION Section

DMETS notes that the dosage and administration instructions only include doses up to two cartridges (0.8 mg). We question whether or not doses of greater than two cartridges may be used if more than two cartridges of local anesthetic have been administered. If not please include a statement discouraging the use of more than two cartridges of OraVerse (e.g. the use of more than two cartridges (0.8 mg) of OraVerse is not recommended).

Attachment A

Inpatient Written	Outpatient Written	Verbal
Oraversc	Ora Verse	Oraverse
Oraverse	Ora Verse	Oraverse
Oraverse	Orav Verse	Oraverse
Oraverse	Oraverse	Oraverse
Oraverse	Oraverse	Oraverse
Oraverse	oraverse	Oraverse
Oraverse	Oraverse	Oraverse
Oraverse	OraVerse	Oraverse
Oraverse	Oraverse	Oroverse
Oraverse	Oraverse	Oroverse
Oraverse	Oraverse	
Oraverse	OraVerse	
	Oraverse	
	Oraverse	
	Oraverse	
	Oraverse	
	Oraverse	
	Oraverse	
	Oraverse	
	Oraverse	

Attachment B

Color Code Format

Product	PMS Color Code*	
Lidocaine 2% with Epinephrine 1:100,000	Red: 185, 186, 199 or 200	 Red 185
Lidocaine 2% with Epinephrine 1:50,000	Green: 347, 348, 355 or 356	 Green 347
Lidocaine Plain	Light Blue: 279	 L. Blue 279
Mepivacaine 2% with Levonordefrin 1:20,000	Brown: 471, 477, 478, 498 or 499	 Brown 471
Mepivacaine 3%	Plain Tan: 466, 467 or 468	 Tan 466
Prilocaine 4% with Epinephrine 1:200,000	Yellow: 108, 109, 110, 115 or 116	 Yellow 108
Prilocaine 4%	Plain Black	 Black
Bupivacaine 0.5% with Epinephrine1:200,000	Blue: 300 or 301	 Blue 300
Articaine 4% with Epinephrine 1:100,00	Gold: 871, 872, 873, 874, or 875	 Gold 871

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/s/

Kristina Arnwine
8/3/2007 04:28:26 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/3/2007 04:30:28 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/3/2007 04:33:28 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/3/2007 04:44:52 PM
DRUG SAFETY OFFICE REVIEWER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: May 4, 2007

To: Geri Smith – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications

Subject: NDA 22-159
DDMAC labeling comments for OraVerse (phentolamine mesylate) Injection

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Per your e-mail consult request dated April 30, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the proposed product labeling (PI) and proposed carton and container labeling for OraVerse (phentolamine mesylate) Injection (OraVerse). We acknowledge this is a 505(b)(2) application, and thus may be commenting on sections of the Regitine and phentolamine mesylate (Bedford Laboratories, Inc.) PIs that are already approved. We offer the following comments.

Highlights

Warnings and Precautions

1. [redacted] b(4)

The above underlined terms are vague. Therefore, would it be possible to provide context (i.e., specify the incidence) for [redacted] and [redacted]? Also, would it be possible to provide context for [redacted] and to specify which cardiac arrhythmias occurred?

Use in Specific Populations

1. [redacted] b(4)

Is it appropriate to also list this as a limitation to the indication?

PI

Dosage and Administration

(Please see comments under Highlights – Use in Specific Populations).

Warnings and Precautions

(Please see comments under Highlights – Warnings and Precautions).

1. "
   (

   Would it be possible to provide context (i.e., incidence rates) for ——— ? If not, we recommend deletion as this term is promotional in tone and minimizes the risks of OraVerse therapy. b(4)

2. We recommend the discussion of pregnancy be moved to the "Use in Specific Populations" section of the proposed PI.

Adverse Reactions

1. —

   We recommend specifying the length of the study period for context. b(4)

2. ·

   (emphasis added).

   Would it be possible to provide context for ' —— "? As proposed, this term is promotional in tone and minimizes the risks of OraVerse therapy. b(4)

3. "**6.2 Adverse Reactions in Clinical Trials**" (original emphasis).

   Should this header be deleted as it is repetitive with the header "**6.1 Clinical Trials Experience**" (original emphasis)?

4. ⌐

b(4)

Would it be possible to provide context for ' [redacted] ," and [redacted] ? As proposed these terms are promotional in tone and minimize the risks of OraVerse therapy. In addition, we recommend specifying the length of the study period for context. b(4)

5. [redacted]

Would it be possible to provide context for [redacted] ' and specify which cardiac arrhythmias occurred? b(4)

Drug Interactions

1. We recommend adding "(PK)" after the first mention of "pharmacokinetic" since the "PK" abbreviation is used later in this section.

2. [redacted] b(4)

This statement is promotional in tone; we recommend revision if this statement is essential for safe and effective use of the drug. If not, we recommend deletion.

Use in Specific Populations

1. [redacted] b(4)

Were these studies indeed [redacted] ;" to be included in labeling and to serve as substantial evidence for promotional claims? If not, we recommend deletion. b(4)

Overdosage

1. Is it appropriate to include the following additional information that appears in the Overdosage section of the Regitine and phentolamine mesylate (Bedford Laboratories, Inc.) PIs in this section of the proposed PI:

"The patient's legs should be kept raised and a plasma expander should be administered. If necessary, intravenous infusion or norepinephrine, titrated to maintain blood pressure at the normotensive level, and all available supportive measures should be included. Epinephrine should

not be used, since it may cause a paradoxical reduction in blood pressure."

Clinical Pharmacology

1. [redacted]

[redacted] is promotional in tone and overstates the efficacy of OraVerse therapy; therefore, we recommend revision to a term such as "causes." b(4)

2. [redacted]

Would it be possible to provide context for "[redacted]"

3. [redacted]

[redacted] is promotional in tone and overstates the efficacy of OraVerse therapy; therefore, we recommend providing context or deleting.

4. "[redacted]" b(4)

We recommend deletion of this claim as context (i.e., 100% absolute bioavailability and peak concentration 10-20 minutes after injection) is provided in the next sentence.

Clinical Studies

1. [redacted]

Since the Clinical Studies section should discuss efficacy, not safety, findings, we recommend deletion of the word "[redacted]" from the above statement.

2. ". [redacted]

While we acknowledge that what follows is a discussion of the three studies used to support the efficacy of OraVerse therapy, [redacted] is promotional in tone. Therefore, we recommend revising to a statement such as "...were studied in the following three clinical studies." b(4)

3. [redacted]

b(4)

Are STAR and FAB validated instruments in this patient population to serve as substantial evidence to support these secondary endpoints in labeling (specifically, the Indications and Usage and Clinical Studies sections of the proposed PI)? We recommend consulting the SEALD team.

5. [redacted]

b(4)

Is this an appropriate method for using a control/placebo? Or, should the statement read, "The control was a sham injection, which was performed with making an actual injection"?

6. [redacted]

This information is repetitive with that presented in Table 2; therefore, we recommend deletion.

b(4)

7. [redacted]

[redacted] s promotional in tone, particularly since labeling does not distinguish between [redacted] and simply presents p-values instead. Therefore, we recommend deletion.

b(4)

8. [redacted]

[redacted] is promotional in tone; therefore, we recommend deletion. b(4)

Carton and Container Labeling

We have reviewed the proposed carton and container labeling and have no comments at this time.

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/s/

Michelle Safarik
5/4/2007 01:13:33 PM
DDMAC REVIEWER

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 7, 2008
To:	Bob Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Rheumatology Products
Through:	Linda Kim-Jung, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention, HFD-420
From:	Cathy A. Miller, M..P.H., Division of Medication Error Prevention, HFD-420
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name(s):	OraVerse (Phentolamine Mesylate Injection) 0.4 mg/1.7 mL
Application Type/Number:	NDA # 22-159
Applicant:	Novalar Pharmaceuticals, Inc.
OSE RCM #:	2008-651

CONTENTS

EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, OraVerse, 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 OraVerse for this product.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed cartridge labels and carton labeling appear to be vulnerable to confusion that could lead to medication errors. As identified in our previous review of OraVerse, we continue to have concerns about the lack of increments of measure on the cartridge label, which would clearly identify the 0.2 mg (1/2 cartridge) dose. Additional areas of concern include the presentation of the proposed proprietary name, product strength and manufacturer logo which impact readability and clarity of important product information. (See Section 3.2).

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 Analgesics, Anesthetics and Rheumatology Products for re-assessment of the proprietary name and revised labeling of OraVerse. Additionally, revised cartridge label, carton and package insert labeling were submitted for review and comment.

1.2 REGULATORY HISTORY

In our previous OSE Review 2006-651 (dated November 1, 2006), we had no objection to the proposed proprietary name, OraVerse. We also provided recommendations for label and labeling revisions to minimize errors. Subsequently, we did a re-assessment of the proprietary name in OSE Review 2007-2087 (dated December 19, 2007) and had no objections to the proprietary name, OraVerse.

1.3 PRODUCT INFORMATION

OraVerse is a non-specific alpha-adrenergic blocker indicated for the reversal of soft-tissue anesthesia , i.e., anesthesia of the lip and tongue, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor. OraVerse is not recommended for use in children less than six years of age or less than 15 kg (33 lbs). OraVerse should be administered following the dental procedure using the same location (2) and technique(s) (infiltration or block injection) employed for the administration of the local anesthetic. OraVerse is available in 0.4 mg/1.7 mL solution per cartridge containing 0.4 mg of phentolamine mesylate. The recommended dose is based on the number of cartridges of local anesthetic with vasoconstrictor administered:

Amount of Local Anesthetic Administered	Dose of OraVerse [mg]	Dose of OraVerse [Cartridge(s)]
1/2 Cartridge	0.2	1/2
1 Cartridge	0.4	1
2 Cartridges	0.8	2

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, OraVerse, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, and ANDA products currently under review by the Agency.

For the proprietary name, OraVerse, 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 OraVerse.

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

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

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

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 'O' 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 OraVerse, 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 (eight letters), capital letters ('O' and 'V')., downstrokes (none), cross-strokes (none) and dotted letters (none). We assessed the applicant's capitalization of the letter 'V' in the fourth letter position of the proposed proprietary name, considering the two probably orthographic presentations of the word, with a capital 'V', : OraVerse and with a lower case 'v' Oraverse. This consideration draws on the probability that the name will not always be scripted as 'OraVerse' but rather 'Oraverse', by healthcare practitioners.

Additionally, several letters in OraVerse may be vulnerable to ambiguity when scripted, including the capital letter 'O' may appear as capital letter 'A' ; lower case 'r' may appear as 'n', 'v' or 'u'; 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 letter 'e' may appear as lower case 'i', 'c', 'a', or 'u'; and lower case 's' may appear as 'r or 'e'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to OraVerse.

When searching to identify potential names that may sound similar to OraVerse, the medication error staff search for names with similar number of syllables (3), stresses (OR-a-verse; or-a-VERSE), and placement of vowel and consonant sounds. Phonetic consideration was also given to the pronunciations that include 'Oro' rather than 'Ora' and 'bers' rather than 'verse'. In addition, several letters in OraVerse may be subject to interpretation when spoken, including the letter 's' may be interpreted as the letters 'sh'. 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

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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)

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 (OraVerse), the established name (phentolamine mesylate), proposed indication (reversal of soft tissue anesthesia and the associated functional deficits resulting from an intraoral injection of a local anesthetic containing a vasoconstrictor), strength (0.4 mg/1.7 mL), dose (0.2 mg to 0.8 mg), frequency of administration (one dose administered following dental procedure), route (administered using the same location and technique [infiltration or block injection] and dosage form (solution for injection). 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, OraVerse, was provided to the medication error 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 OraVerse 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, OraVerse. 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 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 OraVerse 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 OraVerse 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.

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

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

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 cartridge labels 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 April 24, 2008 (See Appendix E, F and G images):

- Cartridge Label: 0.4 mg/1.7 mL
- Blister Backing Labeling: 10 Cartridges and 50 Cartridges
- Carton Labeling: 10 Cartridges and 50 Cartridges
- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The Division of Medication Error Prevention conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to OraVerse to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, twenty-two names were identified as having some similarity to the name OraVerse.

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

The twenty-two names identified as having some similarity to the name OraVerse are: Acupress, Alvesco, Arava, Aranelle, Aranesp, Alavert, Avonex, Corvert, Orabase, Oracea, Oralone, Orapred, Orasone, Oravue, Oravess, Oravescent, Orinase, Orudis, Oruvail, Ovace, Phentolamine Mesylate and Versed.

The thirteen names not previously reviewed are: Acupress, Aranelle, Aranesp, Alvesco, Arava, Avonex, Corvert, Oravescent, Ovace, Orudis, Oruvail, Phentolamine Mesylate and Versed. Twelve of the thirteen names were thought to look like OraVerse: Acupress, Aranelle, Aranesp, Orudis, Oruvail, Alvesco, Arava, Avonex, Oravescent, Ovace, Phentolamine Mesylate (generic for Regitine) and Versed. The remaining name, Corvert, was thought to look and sound similar to OraVerse.

Additionally, the Division of Medication Error Prevention did not identify any United States Adopted Names (USAN) stems in the name OraVerse as of April 23, 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 OraVerse. The Expert Panel indicated that the proposed name OraVerse has been previously reviewed on two occasions 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.

3.1.3 Safety evaluator risk assessment

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

Four of the names (Acupress, Aranelle, Aranesp and Orudis) were not considered further because they were assessed by the primary safety evaluator to lack convincing orthographic and/or phonetic similarities with OraVerse (See Appendix B).

Oravescent was a proposed drug name in 2005 for a pending new drug application. Since that time, the product was approved under a different name.

Six of the names , Alvesco, Avonex, Ovace, Oruvail, Corvert and Versed (which is discontinued but is widely available as generic Midazolam) were determined by FMEA that medication errors were unlikely to occur because they do not overlap in strength, dose, or indication with OraVerse. (See Appendix C).

The remaining two names, Arava and Phentolamine Mesylate (generic for discontinued Regitine) had some numerical overlap with OraVerse 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 D).

3.2 LABEL AND LABELING RISK ASSESSMENT

We note that the revised label/labeling addresses most of our recommendations from our previous review (OSE Review 2006-859). However, review of the cartridge labels and carton labeling identified additional areas of vulnerability that could lead to medication error, specifically with respect to the proper use of the product, clear communication of the established name, product strength and presentation of product information on the label.

3.2.1 Cartridge Label

The cartridges are not marked with increments of measure. Given the proposed dosing of 0.2 mg to 0.8 mg, there are no increments of measurement for doses less than an entire cartridge.

The proposed proprietary name contains a capital letter 'V' in the fourth letter position of the name OraVerse, which gives more prominence to one portion of the name

3.2.2 Blister Labeling

Although the strength of the product appears on the blister label in the total content statement, it does not appear directly following the proprietary and established name. Additionally, the strength is too small and lacks prominence.

The proposed proprietary name contains a capital letter 'V' in the fourth letter position of the name OraVerse, which gives more prominence to one portion of the name.

3.2.3 Carton Labeling (10 Cartridge Package and 50 Cartridge Package)

The proposed proprietary name (OraVerse) appears in colored green and black font.

The proposed proprietary name contains a capital letter 'V' in the fourth letter position of the name OraVerse, which gives more prominence to one portion of the name.

The size of the applicant's logo (Novalar) is large and has more prominence than the product strength.

The product strength does not appear directly following the proprietary name and lacks prominence on the carton labeling.

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, OraVerse, 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 of information and design of the proposed cartridge labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, we note problems with the prominence, presentation, and clarity of information on the cartridge label and carton labeling.

4.2.1 Cartridge Label and Carton Labeling

Our analysis notes that the cartridge labels and carton labeling can be improved to optimize readability. Currently, green and black fonts are used in addition to a circular graphic of an arrow in the capital letter 'O' of Oraverse. These features diminish the readability of the name on both the cartridge and carton labeling. Changing the font color to one consistent color will enhance clarity and alleviate any ambiguity in the readability of the name. Additionally, the capital letter "V" separates the second part of the name from the first. This gives more prominence to one portion of the name. Revising the letter to a lower case 'v' may provide consistency and clarity to the appearance of the drug name. Furthermore, the circular mixed color graphic arrow in the capital letter 'O' distracts from the readability of the drug name.

The applicant's logo (Novalar) which is presented on the bottom right corner of the carton labeling is larger than the product strength which is currently located on the top left corner of the carton labeling. Increasing the size of the product strength and relocating it to the center of the principal display panel, immediately following the established name, will enhance the prominence of this information.

4.2.2 Design of Cartridge

We continue to be concerned that the dosing for OraVerse starts at 1/2 cartridge, but there are no increments of measurement on either the cartridge or cartridge label indicating this measurement. Without measurements, the practitioner will have to estimate a 0.2 mg (1/2 of the cartridge) dose which could lead to over or under dosing. However, on a May 1, 2008 conversation with the medical officer, the Division agreed with our recommendations but explained that it is currently standard practice among dental practitioners to use the same method of measure (1/2 cartridge or full cartridge) when administering the dental anesthesia therefore, administration of OraVerse would also fall within this standard practice. Despite this practice standard, we emphasized that this does not represent good labeling practice. The Division acknowledged and indicated that should the applicant seek to extend the use of OraVerse to the pediatric population, this recommendation would be considered.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding

of medication error causality would benefit from underreporting medication errors; and that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, OraVerse, 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, OraVerse, for this product.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed cartridge labels and carton labeling 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 OraVerse 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 Darrell Jenkins, project manager, at 301-796-0558.

6.1.2 Label and 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 OraVerse 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. Cartridge Label

a. Revise the font lettering in the proposed proprietary name OraVerse so that the fourth letter 'V' appears in lower case lettering, which may provide consistency and clarity to the appearance of the drug name.

b. Add an increment of measure at the 1/2 cartridge mark, to designate the 0.2 mg (1/2 cartridge) dose.

2. Blister Labeling

a. The product strength is currently located on the same line as the net quantity statement on the blister labeling. Relocate the product strength (0.4 mg/1.7 mL) directly under the established name and relocate the net quantity towards the bottom of the label. Additionally, ensure that trade name, established name and product strength are presented in similar size.

b. Revise the font lettering in the proposed proprietary name OraVerse so that the fourth letter 'V' appears in lower case lettering, which may provide consistency and clarity to the appearance of the drug name.

3. Carton Labeling

a. Increase the size of the product strength (0.4 mg/1.7 mL) and relocate it to the center of the principal display panel, in order to enhance the prominence of this information.

b. Revise the font lettering in the proposed proprietary name OraVerse so that the fourth letter 'V' appears in lower case lettering, which may provide consistency and clarity to the appearance of the drug name.

c. Change the font coloring in the proposed proprietary name OraVerse on the carton labeling to one solid color.

d. Remove the arrow graphic in the capital letter 'O' of OraVerse on the carton labeling

e. Decrease the size of the manufacturer's logo 'Novalar' which appears on the bottom right corner of the carton labels.

4. Package Insert Labeling

No comments at this time.

7 REFERENCES

1. Adverse Events Reporting System (AERS)

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

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

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

5. AMF Decision Support System [DSS]

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

6. Division of Medication 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.

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

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

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication error staff 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 lead to medication errors. The Medication error staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (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	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	• Names may look similar when scripted, and lead to drug name confusion in written communication

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

Appendix B: Drug names without convincing orthographic and/or phonetic similarities to OraVerse

Proprietary Name	Similarity to OraVerse
Acupress	Look-Alike
Aranelle	Look-Alike
Aranesp	Look-Alike
Orudis	Look-Alike

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

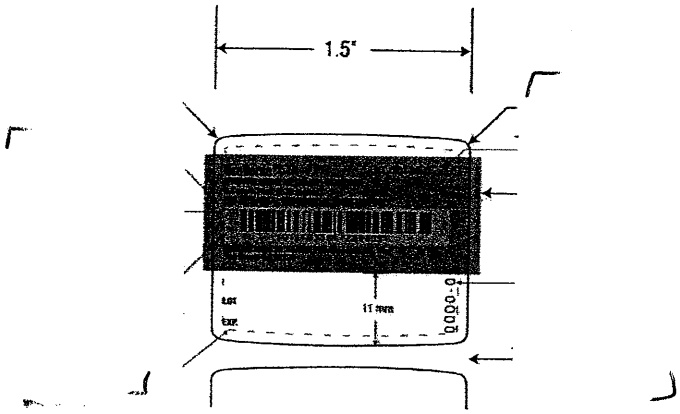
Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
OraVerse (Phentolamine Mesylate Injection)		**0.4 mg/1.7 mL solution per cartridge**	**0.2 mg to 0.8 mg (1/2 cartridge to 2 cartridges) based on the number of cartridges of local anesthetic given**
Alvesco (Ciclesonide)	Look-Alike	80 mcg, 0.08 mg/inhaler 0.16 mg/inhaler Aerosol Metered Inhalation	80 mcg to 160 mcg twice daily bronchodilators alone; 80 mcg-320 mcg for patients who receive inhaled corticosteroids; 320 twice daily for patients who receive oral corticosteroids
Avonex (Interferon Beta 1A)	Look-Alike	30 mcg Powder for reconstitution; 30 mcg/5 mL prefilled syringe	30 mcg injected intramuscularly once weekly
Corvert (Ibutilide Fumarate)	Look- and Sound-Alike	0.1 mg/mL injectable solution	For 60 kg or more patient: 1 mg (one vial) intravenous infusion For less than 60 kg patient: 0.1 mL/kg (0.01 mg/kg) intravenous infusion Administered undiluted or diluted in 50 mL of diluent
Oruvail (Ketoprofen)	Look-Alike	50 mg, 75 mg, 200 mg oral capsule and extended release capsule	75 mg three times daily or 50 mg four times daily. Smaller doses should be utilized initially in small individuals or in debilitated or elderly patients.
Ovace (Sulfacetamide Sodium)	Look-Alike	10% Lotion; 10% Topical Liquid Face Wash	Apply thin layer to affected area twice daily for 8-10 days or as directed by physician
Versed (Midazolam Hydrochloride) 1 mg and 5 mg injection Brand name Versed has been discontinued but is widely available generically as Midazolam	Look-Alike	1 mg and 5 mg solution for injection	For adult patients below the age of 60 years old, approximately 5 mg IM administered one hour before surgery. When used for sedation/amnesia for a procedure, individualize dosage and titrate intravenously; recommened 1 mg/mL over two minutes with no more than 2.5 mg over a period of two minutes

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

Failure Mode: (Name confusion)	Causes (could be multiple)	Effects
OraVerse (Phentolamine Mesylate Injection)	**0.4 mg/1.7 mL solution per cartridge**	**0.2 mg – 0.8 mg (1/2 cartridge to 2 cartridges) based on the number of cartridges of local anesthetic given**
Arava (Leflunomide) 10 mg, 20 mg and 100 mg oral tablets	Numerical overlap in dose (OraVerse 0.2 mg and Arava 20 mg daily).	The likelihood of medication error is minimized due to variations in dose form, indication and practice setting/patient population for the two products vary: *Rationale:* OraVerse is available in 0.4 mg/1.7 mL solution for injection only with a recommended dose of 0.2 mg to 0.8 mg given directly into the dental anesthesia site . Arava is available in multiple strength oral tablet form in strengths of 10 mg, 20 mg, 75 mg and 100 mg with a recommended dose of 20 mg daily. Arava is indicated for the treatment of active rheumatoid arthritis while OraVerse is used during dental procedures for reversal of soft-tissue anesthesia and would be used exclusively by dental practitioners within a dental setting. OraVerse use is limited to dental settings involving oral/dental procedures by dental practitioners (dentists, orthodontists, endodontists, exodontists, periodontists, or oral surgeons). Arava would likely be prescribed and administered in an outpatient setting by general or rheumatology practitioners. The variation in the dose form, indication of use and practice setting minimizes the risk of medication error occurring in the typical practice setting.
Phentolamine Mesylate The trade name, Regitine, is discontinued but the product is available generically in 5 mg injectable solution for intravenous infusion	Same established name available generically in 5 mg/vial strength for intravenous injection. Both drug products are available in only one strength.	The likelihood of medication error is minimized due variations in product characteristics, practitioners utilizing drug, patient population and practice setting: *Rationale:* OraVerse and phentolamine mesylate do not overlap in dose or strength. The risk of medication error is reduced by the fact that the two drug products vary in multiple product characteristics: *Rationale:* OraVerse is indicated for reversal of soft-tissue anesthesia during dental procedures. OraVerse is available in a 0.4 mg/1.7 mL cartridge for injection and the recommended

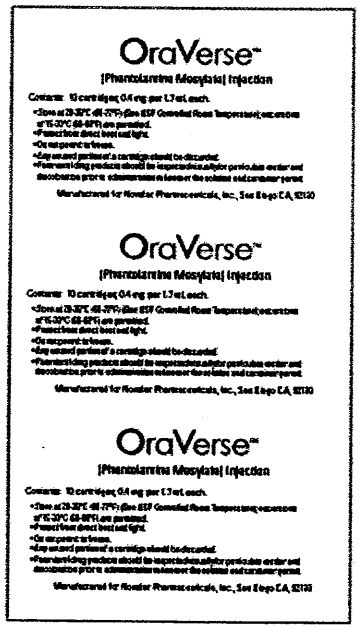
		dose is 0.2 mg to 0.8 mg injection given directly into the same site of the dental procedure anesthetic. Phentolamine mesylate is indicated for prevention/control of hypertensive episodes in patients with pheochromocytoma as well as prevention of dermal necrosis and sloughing following intravenous extravasation of norepinephrine. Phentolamine mesylate is available in 5 mg/2 mL vial with recommended dosing of 5 mg injected intravenously for control of hypertensive episodes and 5-10 mg for dermal necrosis. The two drug products vary considerably not only in their indication of use, but also route of administration (dental anesthesia site versus intravenous use) which minimizes the likelihood of medication error for these products. Practice setting and Prescribing Practitioner: OraVerse use is limited to settings involving oral dental procedures by dental practitioners (dentists, orthodontists, endodontists, exodontists, periodontists, or oral surgeons. Phentolamine Mesylate would be used in an inpatient hospital setting most likely to be an intensive care or progressive care setting by internists or general practitioners.

Appendix E: Cartridge Label (note: images are not to scale)



b(4)

Appendix F: Blister Backing Labeling (note: images are not to scale)



Appendix G: **Carton Labeling (10 Cartridge and 50 Cartridge)**
(note: images are not to scale)

b(4)

10 Cartridge Package - Draft

b(4)

50 Cartridge Package - Draft

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/s/

Cathy A Miller
5/7/2008 01:25:14 PM
DRUG SAFETY OFFICE REVIEWER

Cathy A Miller
5/7/2008 02:52:30 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
5/7/2008 02:56:06 PM
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Denise Toyer
5/9/2008 08:59:51 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/9/2008 12:43:09 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Bob Rappaport, MD
Director, Division of Analgesics, Anesthetics and Rheumatology Products
HFD-170

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: December 19, 2007

OSE Review # 2007-2087 OraVerse (Phentolamine Mesylate Injection) 0.4 mg
NDA# 22-159

This memorandum was written in response to a request from the Division of Analgesics, Anesthetics and Rheumatology Products (HFD-170), for a reassessment of the proprietary name, OraVerse, regarding potential name confusion with other proprietary or established drug names. OraVerse was found acceptable by DMETS in OSE review 2006-859 dated August 3, 2007. Revised container labels and insert labeling were not provided for review and comment.

Since our last review, DMETS has identified the following ten proprietary names that were thought to have the potential for confusion with OraVerse. They are: Orapred ODT, Aranelle, Claravis, Ioversol, Arava, Versed, Oravesin, Uronkinase, Activase, and Oravera.

In the initial analysis of the ten names DMETS determined none of the aforementioned names pose an increased risk for name confusion with OraVerse due to the following reasons.

- In addition to lacking orthographic and or phonetic similarities with OraVerse: Orapred ODT, Aranelle, Claravis, Ioversol, Arava, Versed, Urokinase, and Activase do not share product commonalities such as dosage form, route of administration, product strength, usual dose, dosing frequency, and/or indication of use.
- Oravesin is a chemical name, not an active ingredient in a drug product. No additional information was found in commonly used drug references such as the Orange Book, Clinical Pharmacology, Facts and Comparisons, and the Red Book.
- Oravera is a trademarked name found in the USPTO database. The name is intended for medicated oral analgesics. However, the owner of the trademark is an individual, rather than a pharmaceutical company. Additionally, the name could not be found in other commonly used drug references such as the Orange Book, Clinical Pharmacology, Micromedex, Facts and Comparisons, and the Red Book.

In summary, DMETS has no objections to the use of the proposed proprietary name, OraVerse. DDMAC has no objections to the use of the proposed proprietary name, OraVerse, from a promotional perspective. Please submit revised container labels, carton labeling, and package insert labeling for review and comment. This is considered a final decision. If the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have questions or need clarification, please contact Nancy Clark, OSE Project Manager, at 301-796-1187.

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/s/

Linda Kim-Jung
12/19/2007 10:40:46 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Kristina Arnwine 12/19/07.

Denise Toyer
12/20/2007 02:30:20 PM
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12/20/2007 04:17:03 PM
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