

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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Subject: Proprietary Name, Label, and Labeling Review

Drug Name(s): ZolpiMist (Zolpidem Tartrate) Oral Spray
5 mg (100 microliters) per spray

Application Type/Number: NDA # 22-196

Applicant: NovaDel Pharma, Inc.

OSE RCM #: 2007-2495

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, ZolpiMist, 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. The Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name ZolpiMist for this product at this time.

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

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling are vulnerable to confusion that could lead to medication errors. We note needed improvements with respect to the prominence and presentation of important product information, as well as the clarity and completeness of the administration and maintenance instructions. The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Neurology Products (HFD-120) for assessment of the proprietary name, ZolpiMist, regarding potential name confusion with other proprietary or established drug names. Additionally, the container label, carton and insert labeling, and patient instructions for use, were provided for review and comment.

We note that the patient instructions for use will be addressed under separate cover by the Patient Labeling and Education Team of the Division of Risk Management.

1.2 REGULATORY HISTORY

ZolpiMist is a 505(b)(2) application. The reference listed drug is Ambien (zolpidem tartrate) tablets (NDA 19-908), which was approved on December 16, 1992. Ambien is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The usual recommended dose is 10 mg once daily immediately before bedtime. The product is available as 5 mg and 10 mg tablets.

At the labeling meetings for ZolpiMist, held on July 23 and 31, 2008, DMEPA discussed our preliminary concerns with the proposed product packaging. Specifically, our concerns dealt with the potential for accidental exposure due to lack of a child-resistant closure, as well as improper dosing due to lack of a feedback mechanism or dose counter.

1.3 PRODUCT INFORMATION

ZolpiMist (zolpidem tartrate) Oral Spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The product is designed to be sprayed directly into the mouth over the tongue. Each metered actuation delivers 5 mg of zolpidem in 100 microliters. The recommended dose for adults is 10 mg (2 sprays) immediately before bedtime. The product is available in a amber glass bottle with a metered-dose pump assembly and clear over cap. Each bottle contains 8.2 g of product formulation. There are 60 metered actuations per bottle after 5 initial priming actuations. However, the total number of available doses is dependent on the number of actuations per

b(4)

dose (1 or 2 actuations) and the frequency of priming. The applicant proposes that ZolpiMist be classified as Schedule IV consistent with all currently approved zolpidem drug products and the related class of benzodiazepine drug products.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by 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 Container Label, Carton and Insert 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. We define 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, ZolpiMist, 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, ZolpiMist, 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 also conduct internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

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

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

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

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

For this review, particular consideration was given to drug names beginning with the letter 'Z' 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 ZolpiMist, 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 (nine letters), upstrokes (four: upper case letters 'Z' and 'M' and lower case letters 'l' and 't'), downstrokes (one: lower case letter 'p'), cross-strokes (one, lower case letter 't') and dotted letters (two: lower case letters 'i'). Additionally, several letters in ZolpiMist may be vulnerable to ambiguity when scripted, including the upper case letter 'Z' may appear as upper case 'L', 'T', or 'F'; lower case letter 'o' may appear as lower case 'e' or 'a'; lower case 'l' may appear as lower case 'b' or 'e'; lower case 'i' may appear as lower case 'e'; capital or lower case 'M' or 'm' may appear as capital or lower case 'N' or 'n'; and lower case 't' may appear as lower case 'r'. As such, the staff also consider these alternate appearances when identifying drug names that may look similar to ZolpiMist.

When searching to identify potential names that may sound similar to ZolpiMist, the medication error staff search for names with similar number of syllables (3), stresses (ZOL-pi-mist or zol-pi-MIST), and placement of vowel and consonant sounds. In addition, several letters in ZolpiMist may be subject to interpretation when spoken, including the letter 'Z' may be interpreted as 'S', 'X', or 'C'; the letters 'ol' may be interpreted as 'all'; or the letter 'i' may be interpreted as 'a' or 'y'. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the medication error staff were provided with the following information about the proposed product: the proposed proprietary name (ZolpiMist), the established name (zolpidem tartrate), proposed indication (short-term treatment of insomnia characterized by difficulties with sleep initiation), strength (5 mg per spray), dose (10 mg or 2 sprays), frequency of administration (immediately before bedtime), route (over the tongue), and dosage form (oral spray). Appendix A provides a more detailed listing of the product characteristics the medication error staff generally take into consideration.

Lastly, the medication error staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has

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 Doer, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error staff provide additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and information sources

The proposed proprietary name, ZolpiMist, 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 ZolpiMist using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the medication error staff use a computerized method of identifying phonetic and orthographic similarity between medication 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 to gather CDER professional opinions on the safety of the product and the proprietary name, ZolpiMist. 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.

2.1.2 Inquiry with the Consumer Product Safety Commission

In an effort to determine if a child-resistant container closure is required for ZolpiMist, we researched the regulations for child-resistant packaging. In the process we identified conflicting information. We contacted a representative from the Consumer Product Safety Commission (CPSC) for clarification of the requirements for this product.

2.1.3 CDER Prescription analysis studies

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

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

their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. ZolpiMist Study (conducted on January 3, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Outpatient Prescription:</u></p> <p>Zolpimist #1 1 or 2 spray po QHS</p>	<p>"ZolpiMist Dispense #1 Take 1 to 2 sprays by mouth QHS"</p>
<p><u>Inpatient Medication Order:</u></p> <p>Zolpidist 1 or 2 spray by mouth qh</p>	

2.1.4 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, we seek to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name ZolpiMist 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 ZolpiMist to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

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

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. 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 identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that 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 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 Sponsor; however, the safety concerns