

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, 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 Sponsor, 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 Sponsor'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 Sponsor 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 Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL, LABELING, AND PACKAGING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container 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 Medication Error Prevention staff analyze reported misuse of drugs, we 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 Applicant submitted on November 20, 2007 the following labels and labeling for our review (see Appendices I and J for images):

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

- Container Label
- Carton Labeling
- Insert Labeling (no image) – revised version submitted June 20, 2008
- Patient Instructions for Use (no image) – revised version submitted June 20, 2008

In order to evaluate the proposed packaging for ZolpiMist, we requested and received a working sample from the applicant (see Appendix K for photograph).

2.2.1 FDA Adverse Event Reporting System

In order to evaluate any medication errors with a packaging configuration similar to ZolpiMist (i.e. spray pump, no child-resistant container closure, no dose counter), DMEPA searched the FDA Adverse Event Reporting System (AERS) using the following products: Nitromist, Nitrolingual Pumpspray, and Evamist. On July 24, 2008, we conducted two separate searches of the AERS database to determine if any medication errors involving Nitromist, Nitrolingual, or Evamist have been reported.

The following criteria were used for the first search: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (nitroglycerin), trade name (Nitrolingual, Nitromist), and verbatim ('Nitro%') terms.

The following criteria were used for the second search: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (estradiol), trade name (Evamist), and verbatim ('Eva%') terms.

The cases were manually reviewed to exclude duplicate cases. Additionally, cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

We 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 ZolpiMist 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 names were identified as having some similarity to the name ZolpiMist.

Twelve of the names were thought to look like ZolpiMist (Nitromist, Evamist, Vitamist, Nolahist, Calahist, Zomig-ZMT, Zolimid, Topamax, Zolpinox, Zolpramex, Zolpi-Med, and Zolinza). Five names were thought to sound like ZolpiMist (Xopenex, Zoladex, Solaquin, Sulfatrim, and Soltamox). The remaining three names, Coldmist, Zolpidem, and Calomist, were thought to look and sound like ZolpiMist.

Additionally, the Division of Medication Error Prevention and Analysis did not identify any USAN stems in the name, ZolpiMist, as of December 20, 2007.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by Medication Error Prevention staff (see section 3.1.1. above) but did not identify any additional names with similarity to ZolpiMist. During the discussion the Expert Panel posed the following questions regarding the drug product:

Is this the same company that manufactures NitroMist?

Is there any feedback when taking the dose?

Is this package child-resistant?

Is the fill volume 10 mL or is it just packaged in a 10 mL bottle?

Is the product aerosolized?

In response, we note the following: the ZolpiMist applicant is NovaDel, which is the same company that manufactures NitroMist; there is no feedback mechanism or dose counter; the package is not child-resistant; the product is available in a — amber glass bottle, net fill is 7.7 mL (8.2 g) of product formulation; the product is not aerosolized.

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Additionally, the Expert Panel expressed concerns about the potential for diversion and misuse of this product (i.e. slip into a drink). The Expert Panel also indicated that the dosing units should be consistent across product labels and labeling.

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 Inquiry with the Consumer Product Safety Commission

Without identifying proprietary information, we informally discussed the product characteristics of ZolpiMist with Mr. John Boja of the Consumer Product Safety Commission via telephone on July 25, 2008. Mr. Boja indicated that based on the information that we provided, according to 16 CFR 1700.14(a)(4) and 1700.14(a)(10), this product requires a child resistant container closure because it is both a prescription drug for oral administration and a controlled drug for oral administration.

We also learned from a teleconference with the applicant, held on August 6, 2008, that the applicant has consulted with the CPSC and that they have committed to put in a child-resistant container closure prior to marketing the product.

3.1.4 CDER Prescription analysis studies

A total of 34 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. Only one participant interpreted the name correctly as "Zolpimist". The remainder of the participants misinterpreted the drug name. In the written outpatient study, the majority of misinterpretations involved the transcription of the letter "a" for the letter "o" and transcription of the letters "o", "u", "ri", or "ro" for the letter "i" in the beginning of the name. In the written inpatient study, the majority of misinterpretations involved the transcription of the ending of the name as "dent", "dint", or "dlint" instead of "mist". In the verbal study, half of the responses involved the transcription of the letter "a" for the letter "i" (i.e., Zolpamist). See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.5 Safety evaluator risk assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar to ZolpiMist and represent a potential source of drug name confusion. As such, a total of twenty names were analyzed to determine if the drug names could be confused with ZolpiMist 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 ZolpiMist, and thus determined to present some risk for confusion. Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, ZolpiMist, could potentially be confused with any of the twenty names and lead to medication error.

This analysis determined that the name similarity between ZolpiMist and the identified names was unlikely to result in medication errors for all twenty products. See Appendices C through H for our evaluation of the twenty products identified.

3.2 LABEL, LABELING, AND PACKAGING RISK ASSESSMENT

Review of the proposed product packaging identified several areas of concern regarding the potential for accidental exposure to or improper dosing of the drug. Review of the container labels and carton and insert labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to the prominence and presentation of important product information, as well as the clarity and completeness of the patient instructions for use.

3.2.1 Product Packaging

There is no child-resistant closure container.

There is no feedback mechanism or dose counter.

The packaging configuration resembles commercially available breath or throat sprays.

3.2.2 General Comments

The proprietary name is presented with a capital letter 'M' in the sixth letter position of the name (i.e. ZolpiMist).

The presentation of the proprietary and established names and product strength lacks prominence.

The product strength and net quantity are listed inconsistently across product labeling.

The "Keep out of reach of children" statement is missing.

3.2.3 Container Label

The net fill or total volume statement is missing.

3.2.4 Carton Labeling

The product strength is separated from the proprietary and established names by a blue line.

3.2.5 Insert Labeling

In the Dosage and Administration Section, the recommended dose is only presented in terms of mg strength.

3.2.6 Patient Information

The dosing instructions lack specific information regarding timing (i.e. how long the patient should let the medication rest in the mouth and how long the patient should wait before administering a second spray for the 10 mg dose).

The precautions against swallowing a dose are unclear.

The term "expectorate" may be confusing to patients.

There are no instructions for handling a product malfunction.

There are no maintenance, storage, or disposal instructions.

3.2.7 FDA Adverse Event Reporting System

For the first search, no medication error reports were identified for NitroMist. However, two relevant cases were identified for Nitrolingual Pumpspray where practitioners expressed concern about the potential for harm to children due to the appearance of the bottle (i.e. looks like breath spray), the fruity flavoring of the product, and the lack of a child-proof cap.

For the second search regarding Evamist, no medication error reports were identified.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, ZolpiMist, has some similarity to twenty 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 the Prescription Studies that involved 123 FDA 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. To help counterbalance this impact, we recommend that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

4.2 LABEL, LABELING, AND PACKAGING RISK ASSESSMENT

The results of the Label, Labeling and Packaging Risk Assessment found that the product packaging design and the presentation of information on the proposed carton labeling and container label appear to be vulnerable to confusion that could lead to medication errors.

4.2.1 Product Packaging Issues

In review of the proposed product packaging, we identified several areas of concern due to the design of the pump bottle (i.e. lacks a child-resistant container closure and dose counter) that may lead to potential accidental exposure or improper dosing of this product.

This product is covered by a plastic cap which is not child resistant. A child could easily open the cap and access the medication inside, which could lead to accidental exposure to zolpidem and potentially serious outcomes. We have preliminary information from the Consumer Product Safety Commission that a child-resistant container closure may be required for this product according to 16 CFR 1700.14(a)(4) and 1700.14(a)(10). Subsequent to obtaining this information, the applicant informed the review division that they are committed to developing a child-resistant container closure which is compliant with the CPSC prior to marketing this product.

Additionally, we are concerned about the risk of improper dosing with this packaging configuration due to lack of a feedback mechanism or dose counter. Without feedback from the device, the patient may be

unsure that he received a dose and may continue to spray the product, which could lead to overdose of zolpidem. However, we note that in meetings with the review division we learned that the product has a cherry flavor and is likely to be detected by the patient when a dose is received. Additionally, when we evaluated other products with a similar packaging configuration we found no cases of improper dosing because of the lack of a feedback mechanism or dose counter.

4.2.2 Proposed Container Label, Carton and Insert Labeling

We note that the applicant's intended presentation of the proprietary name includes a capital letter 'M' in the sixth letter position of the name (i.e. ZolpiMist). The capital letter "M" separates the second part of the name from the first. When presented in this manner, the name may be misinterpreted as 'Zolpi' followed by 'Mist' where 'Mist' may be misinterpreted as the dosage form and increase the potential for the two separate parts to be misinterpreted as different names.

We also found that important information is presented in a manner that lacks prominence. On the container label and carton labeling, the proprietary and established names and product strength are presented in small, light weight font, which blends with the other product information. Since the name(s) and strength are vital to the proper identification and use of the product, this information should be readily visible when looking at the product labels/labeling. Similarly, on the carton labeling, a blue line separates the product strength from the proprietary and established names. Per 21 CFR 201.10(a), there should be no interfering matter between the drug name and strength. Additionally, in promoting the safe use of the product, the statement "Keep out of the reach of children" should be displayed on all product labels and labeling.

Our analysis revealed information presented in an inconsistent or otherwise confusing manner. The product strength and net quantity are described in terms of "spray" and "metered spray" on the container label and carton labeling, while in the insert labeling the terms used are "actuation" and "metered actuation. In the Dosage and Administration Section of the insert labeling, the recommended dose is only stated in terms of mg strength. This inconsistent terminology could be confusing to patients. For consistency, the dose should also be stated in terms of number of metered sprays or actuations, depending upon the term used.

The patient instructions for use are written in an unclear manner and need some specificity. There are no instructions regarding what a patient should do after dosing (i.e. should the patient let the liquid rest in the mouth or on the tongue and if so, how long; how much time should the patient wait before taking the second spray for a 10 mg dose?). The precautions against swallowing a dose are unclear (i.e. Will the patient experience any adverse effects? How long does the patient have to wait before taking another dose?) The word "expectorate" may not be easily understood by patients. Additionally, there are no instructions regarding what to do if the spray mechanism malfunctions or any storage, maintenance, or disposal instructions. Because this product is a controlled substance prescribed for outpatient use, patients need this information readily available in order to safely use, maintain, and dispose of the product.

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 unreported 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, ZolpiMist, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, 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.

The Packaging Risk Assessment findings indicate that there are several areas of concern regarding the potential for accidental exposure or improper dosing of this product. However, in light of the applicant's commitment to develop a child-resistant container closure, and upon evaluation of other products with a similar packaging configuration, our concerns are minimized at this time.

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container label and carton and insert labeling introduces vulnerability to confusion that could lead to medication errors.

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.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

6.1.1 *Proprietary Name*

1. 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.
2. If the product approval is delayed beyond 90 days from the 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 Daniel Brounstein, project manager, at 301-796-0674.

6.2 COMMENTS TO THE APPLICANT

6.2.1 *Proprietary Name*

1. 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.
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. This name will be re-evaluated 90 days prior to approval.

6.2.2 Labels, Labeling, and Packaging

6.2.2.1 Packaging

Consult the Consumer Product Safety Commission regarding the requirements for a child resistant container closure.

6.2.2.2 General Comments

Revise the font lettering in the proprietary name so that the letter 'm' appears in lower case (i.e. Zolpimist) to avoid the misleading appearance and misinterpretation of the name as two separate words (i.e. Zolpi Mist) where the product name is Zolpi and dosage form is Mist.

Increase the prominence of the proprietary and established names and product strength.

Use consistent terminology for the strength and net quantity (i.e. spray or metered spray vs. actuation or metered actuation) across all product labeling to decrease the risk of confusion.

Add the "Keep out of reach of children" statement.

6.2.2.3 Container Label

If space permits, add the net fill or total volume statement.

6.2.2.4 Carton Labeling

Relocate the product strength so that it appears directly below the established name. Remove the blue line in accordance with CFR 201.10(a).

6.2.2.5 Insert Labeling

In the Dosage and Administration Section, present the recommended dose in terms of mg strength as well as number of metered sprays or actuations, for consistency.

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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 manufacturers 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 Technical Support proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention 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 biologics, 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.

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