CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-745

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 12, 2008
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia and Rheumatology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Melina Griffis, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Ryzolt (Tramadol Hydrochloride Extended-Release Tablets) 100 mg, 200 mg, 300 mg
Application Type/Number:	NDA 21-745
Applicant/sponsor:	Labopharm
OSE RCM #:	2008-1192

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EXECUTIVE SUMMARY

Our analysis found that the proposed name, Ryzolt, has some similarity to other proprietary names, but the findings of the Failure Mode and Effects Analysis (FMEA) indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name Ryzolt for this product. Revised labels and labeling based on recommendations in OSE review 2007-511 were not submitted for our evaluation, however, we recommend that they be provided for our evaluation prior to approval.

We consider this a final review, 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.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for re-assessment of the proprietary name, Ryzolt, regarding potential name confusion with other proprietary or established drug names.

1.2 REGULATORY HISTORY

This submission (dated July 2, 2008) is a complete response to the approvable letter dated May 30, 2007 issued by the Division of Anesthesia, Analgesia and Rheumatology Products.

In our previous OSE review 2006-178 (dated September 18, 2006), we had no objection to the proposed proprietary name, Ryzolt. We also provided recommendations for label and labeling revisions to minimize errors. Subsequently, we did a re-assessment of the proprietary name and review of revised labels in OSE review 2007-511 (dated March 15, 2007), and had no objections to the proprietary name, Ryzolt. We did, however, have recommendations for the proposed labels and labeling which were forwarded to the sponsor in a letter dated April 23, 2007. As of September 12, 2008, revised labels have not been submitted for our evaluation.

1.3 PRODUCT INFORMATION

Ryzolt contains tramadol as an extended-release tablet. Ryzolt is indicated for the management of moderate to moderately severe pain. The tablet is composed of a dual-matrix system where the outer compression coat releases tramadol immediately and the inner core that contains Contramid® to control the release of tramadol. Food does not significantly change the overall exposure to tramadol as the elevations of peak plasma concentration were not considered clinically significant. Breaking, crushing, chewing, or dissolving the product can result in the uncontrolled delivery of Ryzolt and poses a significant risk of overdose or death. The recommended initial dosage is 100 mg daily to be titrated up by 100 mg per day every two days until pain relief. The highest recommended dose is 300 mg daily, but therapy should be continued at the lowest effective dose.

2 METHODS AND MATERIALS

This section consists of methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis 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, Ryzolt, 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, Ryzolt, the medication error staff of the Division of Medication Error Prevention and Analysis 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). The Division also conducts 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. [1] 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. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the

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

Division of Medication Error Prevention and Analysis considers 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.[2]

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 'R' 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.[3,4]

To identify drug names that may look similar to Ryzolt, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (six letters), upstrokes (three, capital letter 'R', lower case 't,' and 'l'), downstrokes (lower case 'y'), cross-strokes ('t'), and dotted letters (none). Additionally, several letters in Ryzolt may be vulnerable to ambiguity when scripted, including the letter uppercase 'R' may appear as 'B'; lower case 'o' may appear as a lower case 'a' or 'e'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Ryzolt.

When searching to identify potential names that may sound similar to Ryzolt, the Medication Error Staff search for names with similar number of syllables (two), stresses (RI-zolt, RI-ZOLT, or Ree-Zolt), and placement of vowel and consonant sounds. Additionally, severally letters in Ryzolt may be vulnerable when spoken, including 'I' may sound like 'y' or a long 'e', and 'z' may sound like 's'. The 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 (Ryzolt), the established name (Tramadol Hydrochloride Extended-Release Tablets), proposed indication (treatment of moderate to moderately severe pain), strength (100 mg, 200 mg and 300 mg), dose (1 tablet), frequency of administration (once daily), route (oral) and dosage form of the product (tablet). 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 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

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

[3] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[4] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

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, Ryzolt, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis 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 Ryzolt 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 by the Division of Medication Error Prevention and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Ryzolt. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention Medication Errors Prevention and Analysis 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 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, 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.[5] When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention 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

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

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 Ryzolt 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 Ryzolt 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.

The Division of Medication Error Prevention and Analysis 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. The Division of Medication Error Prevention and Analysis identifies 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 the Division of Medication Error Prevention and Analysis objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, the Division 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 the Division will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the Division of Medication Error Prevention and Analysis will not object to the use of the proprietary name. If any of these conditions are met, then the Division 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 set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, 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, the Division of Medication Error Prevention and Analysis contends 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, the Division of Medication Error Prevention and Analysis believes 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 the Division of Medication Error Prevention and Analysis objects 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. The Division of Medication Error Prevention and Analysis is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for the Division of Medication Error Prevention and Analysis 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 the Division of Medication Error Prevention and Analysis may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1.1 Database and Information Sources

Our search of the internet, several standard published databases and information sources (see Section 7 References) identified 12 names as having some similarity to the name Ryzolt:

Ten of the 12 names were thought to look like Ryzolt (Eryzole, Bystolic, Rythmol, Riluzole, [redacted] Rizact, Zoloft, Ryzom, Ryzolin, an[redacted]nd two names (Ryzo and Rizalt) were thought to sound similar to Ryzolt. b(4)

A search of the United States Adopted Name (USAN) stem list on August 13, 2008 identified no USAN stems within the proposed name, Ryzolt.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), but did not identify any additional names with similarity to Ryzolt.

Additionally, a new concern was raised about the lack of the use of a modifier for this product (e.g. ER) and future product differentiation if an immediate release formulation was introduced into the marketplace.

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 identified no additional names. As such, a total of 12 names were analyzed to determine if the drug names could be confused with Ryzolt 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 Ryzolt, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Ryzolt, could potentially be confused with any of the 12 names and lead to medication error.

This analysis determined that the name similarity between Ryzolt and the identified names was unlikely to result in medication errors for all 12 product names for reasons outlined in Appendices B through G.

Although a concern regarding the absence of the use of a modifier in the proprietary name to express the extended release nature of this product was raised by our Expert Panel Discussion, we feel that the established name as proposed will alert prescribers to the extended-release characteristics of this product. The absence of a modifier would be more relevant in the event that an immediate release Ryzolt were to be marketed since it would be difficult to distinguish the two products if both were to be managed under the name Ryzolt. At this time, we understand the Applicant is not developing an immediate release product.

4 DISCUSSION

We evaluated 12 names for their similarity to the proposed name. Our FMEA indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors with the identified names.

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, the Division of Medication Error Prevention believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, 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. To help counterbalance this impact, the Division of Medication Error Prevention recommends that the proprietary name be re-submitted for review when the NDA is filed and 90 days prior to the goal date.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Ryzolt, is 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, Ryzolt, for this product. Since revised labels and labeling have not been submitted as of September 12, 2008, they should be requested from the sponsor for our final review prior to approval.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Errors Prevention and Analysis 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 sponsor with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0558.

1. The Division of Medication Error Prevention and Analysis has no objection to the use of the proprietary name, Ryzolt, for this product. We consider this a final review, 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. We note that as of September 12, 2008 revised labels have not been submitted for our evaluation.
2. Please request that the Applicant submit their final labels and labeling for our review prior to approval.

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

4. AMF Decision Support System [DSS]

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

5. Division of Medication Errors and 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.

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

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

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

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

8. WWW location http://www.uspto.gov.

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

17. Verispan Total Patient Tracker:

Verispan Vector One: Total Patient Tracker, Years 2002-2008 data extracted May 22, 2008.

APPENDICES

Appendix A:

The medication error staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention 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 examine 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 (i.e. "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 compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, the Division of Medication Error Prevention also considers 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 Upstokes 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: Names previously reviewed by DMEPA and found not to be vulnerable to name confusion

Proprietary Name	Similarity to Ryzolt
Zoloft (OSE review 2006-178)	Look Alike
——— (OSE review 2007-511	Sound Alike
Rizalt (OSE review 2006-178)	Sound Alike
Eryzole (OSE review 2006-178)	Look Alike
——— (OSE review 2007-511)	Look Alike
——— OSE review 2006-178	Look Alike

b(4)

b(4)

Appendix C: Names of products not considered to be pharmaceutical products

Proprietary Name	Product Type
Ryzom	Computer software; paper goods; educational and entertainment service
Ryzolin	Cosmetic and cleaning preparation

Appendix D: Unapproved Proposed Proprietary name

Proposed Proprietary Name	Status
[redacted] not reviewed by DMEPA)	Product approved under name Zyflo (NDA 22-052)

b(4)

Appendix E: Proprietary names Safety Evaluator unable to identify in any pharmaceutical databases

Proprietary Name	Similarity to Ryzolt	Status of product name
[redacted]	Look alike	Listed in Saegis as a pharmaceutical preparation, however, unable to locate in any other drug database

b(4)

Appendix F: Proprietary names used only in Foreign Countries

Product name with potential for confusion	Similarity to Ryzolt	Country
Rizact (rizatriptan benzoate)	Look alike	India (marketed in the US under the proprietary name Maxalt available in 5 mg and 10 mg tablets)

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Appendix G: Potential confusing name with numerical overlap in strength

Ryzolt Tramadol Hydrochloride Extended-Release Tablets)	100 mg, 200 mg, 300 mg	100 mg to 300 mg once daily
Failure Mode: Name confusion	**Causes (could be multiple)**	**Effects**
Bystolic (nebivolol HCL) Tablets 2.5 mg, 5 mg and 10 mg	Orthographic similarity ('By' when scripted looks similar to 'Ry" and both contain 'ol' in similar positions) Numerical overlap in strength (10 mg versus 100 mg)	Orthographic and phonetic differences as well as product characteristics in names minimize the likelihood of medication error in the usual practice setting. Rationale: Medication errors unlikely to occur given that there are orthographic and phonetic differences between theses names. Specifically, Bystolic contains 3 syllables instead of 2 and lacks a cross-stroke 't' at the end of the name which is present in Ryzolt. Additionally, Bystolic appears longer when written since it contains 2 additional letters. Further, the recommended adult dose for Bystolic (5 mg up to 40 mg once daily) and is indicated for anti-hypertension treatment whereas Ryzolt's recommended adult dose is 100 mg to 300 mg and is indicated for the treatment of moderate to severe pain.

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/s/

Kellie Taylor
9/25/2008 05:36:35 PM
DRUG SAFETY OFFICE REVIEWER
signing on behalf of M. Griffis

Denise Toyer
9/26/2008 02:21:55 PM
DRUG SAFETY OFFICE REVIEWER

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

To: Bob A. Rappaport, MD
Director, Division of Anesthesia, Analgesia and Rheumatology Products, HFD-550

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

From: Judy Park, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: March 15, 2007

Subject: DMETS Proprietary Name, Label, and Labeling Review
Ryzolt (Tramadol Hydrochloride Extended-release) Tablets, 100 mg, 200 mg, and 300 mg
NDA#: 21-745

Project #: 2007-511

This memorandum was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products for a re-assessment of the proprietary name, Ryzolt, and a review of the revised labels and labeling submitted on February 28, 2007. DDMAC initially found the name, Ryzolt, unacceptable from a promotional perspective (OSE consult #06-0050-2 dated July 14, 2006) but withdrew its objection on August 31, 2006 after the sponsor submitted a rebuttal. Subsequently, DMETS evaluated the proprietary name, Ryzolt in OSE consult #2006-178 dated September 22, 2006 and found the name acceptable at that time. DMETS also reviewed the labels and labeling in OSE consults #06-0050-3 and 2006-178.

I. NAME REVIEW

Since the previous reviews, DMETS has identified eight additional names with potential for confusion with Ryzolt. They are Ryzen (Canada), Pytest, Zylet, Rythmol, Lozol, Trysul, Ryzo (Indonesia) and Nytol. However, upon further analysis of these names, it was determined that DMETS will not review the names due to the lack of significant look-alike and/or sound-alike similarities to Ryzolt in addition to differentiating product characteristics such as indication for use, product strength, usual dosage, route of administration, frequency of administration, dosage form, prescriber population, patient population, storage conditions, product unavailability, and/or area of marketing. Thus, DMETS believes the potential for confusion with the aforementioned names is minimal.

b(4)

II. LABELS AND LABELING REVIEW

The Sponsor has submitted revised labels and labeling in response to DMETS comments in OSE consults # 06-0050-3 and 2006-178. We note that the Sponsor has addressed most of the concerns noted in our original review. However, DMETS has the following additional recommendations to minimize medication errors.

A. GENERAL COMMENTS

Please submit the container labels for [redacted] in addition to carton labeling for all package sizes for review. b(4)

B. CONTAINER LABELS

1. Please include a warning statement as such, "The tablets should be swallowed whole with liquid and not split, chewed, dissolved or crushed." on the principal display panel.

2. For the unit-of-use bottles (30 and 90 tablets), please ensure they comply with The Poison Prevention Packaging Act, which denotes the necessity for child-resistant closure.

C. INSERT LABELING

The established name and dosage form are currently presented as "(tramadol hydrochloride) tablet, extended release." Revise to read "Tramadol Hydrochloride Extended-release tablets."

In summary, DMETS has no objections to the use of the proprietary name, Ryzolt. DMETS also recommends implementation of the label and labeling recommendations outlined above. Additionally, DDMAC had no objections to the proprietary name, Ryzolt, from a promotional perspective.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. Please copy DMETS on any correspondence to the sponsor on this issue. If you have any questions or need clarification, please contact Nancy Clark, OSE Project Manager, at 301-796-1187.

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/s/

Judy Park
4/13/2007 02:51:56 PM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
4/13/2007 02:56:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/13/2007 03:19:14 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/13/2007 03:38:38 PM
DRUG SAFETY OFFICE REVIEWER

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CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 2006-178
September 5, 2006	September 18, 2006	
DATE OF DOCUMENT:	**PDUFA DATE:**	
June 12, 2006	September 28, 2006	

TO: Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-530

THROUGH: Alina Mahmud, R.Ph., M.S., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:	**SPONSOR:** LaboPharma Canada, Inc.
Ryzolt (Tramadol Hydrochloride Extended-release Tablets) 100 mg, 200 mg, 300 mg **NDA#: 21-745**	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Ryzolt from a safety perspective. This is considered a final decision. However, if the approval of this NDA is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary names Ryzolt unacceptable from a promotional perspective. This information was presented to the Division in previous reviews (see 06-0050-1, 06-0050-2). DDMAC's objection is repeated in this review on page 3 and 4.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: September 13, 2006

NDA #: 21-745

NAME OF DRUG: **Ryzolt**
(Tramadol Hydrochloride Extended-release Tablets)
100 mg, 200 mg, and 300 mg

NDA SPONSOR: LaboPharma Canada, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-530) for assessment of the proprietary name "Ryzolt", regarding potential name confusion with other proprietary or established drug names. Insert labeling and containers labels (30 count bottles) were provided for review and comment. In addition, the sponsor submitted a proprietary name research report from _____ b(4)

DMETS has previously reviewed one proprietary name for this NDA. The memorandum dated May 30, 2006 (06-0050) described why "Tramadol Contramid OAD" was not an appropriate proprietary name. In addition, the memo dated July 10, 2006 (06-0050-1, 06-0050-2) shares DDMAC's objection statement for the proprietary name "Ryzolt." The last review dated July 14, 2006 (06-0050-3) details recommendations for the submitted labels and labeling.

PRODUCT INFORMATION

Ryzolt contains tramadol as an extended-release tablet. Ryzolt is indicated for the management of moderate to moderately severe pain. The tablet is composed of a dual-matrix system where the outer compression coat releases tramadol immediately and the inner core that contains Contramid® to control the release of tramadol. Food does not significantly change the overall exposure to tramadol as the elevations of peak plasma concentration were not considered clinically significant. There was no increase in the release rate of tramadol in the presence of ethanol. Ryzolt was not studied in patients with severe renal dysfunction (creatinine clearance less than 30 mL/min) and severe hepatic impairment; thus, dosing in these patient populations is not recommended. Alterations in plasma concentrations and elimination half-life were found in geriatric patients; thus, the recommendation is to start at the low end of dosing. Breaking, crushing, chewing, or dissolving the product can result in the uncontrolled delivery of Ryzolt and poses a significant risk of overdose or death. The recommended initial dosage is 100 mg

daily to be titrated up by 100 mg per day every two days until pain relief. The highest recommended dose is 300 mg daily, but therapy should be continued at the lowest effective dose. The bioavailability of a 200 mg Ryzolt is compared to 50 mg immediate release tablet every six hours. Ryzolt is available as 100 mg, 200mg, and 300 mg tablets.

Strength	Package Configurations
100 mg	Bottles: 30 tablets, 90 tablets
200 mg	Bottles: 30 tablets, 90 tablets
300 mg	Bottles: 30 tablets, 90 tablets,

b(4)

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of 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 Ryzolt 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 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.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Ryzolt. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with 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 names Ryzolt unacceptable from a promotional perspective as stated in a previous review (06-0050-1 and 06-0050-2). See comment below and page 4:

> "DDMAC objects to the proposed trade name Ryzolt because it overstates the effectiveness of the drug product. Depending on the pronunciation, Ryzolt sounds like "result." Result is

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[1] MICROMEDEX Integrated Index, 2006, 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, Missouri.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, 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

defined as "something that happens or exists because of something else (www.dictionary.cambridge.org accessed 06/19/06) or "an outcome; a favorable or concrete outcome or effect" (www.bartleby.com (American Heritage) accessed 06/19/06). The proposed trade name Ryzolt suggests a guaranteed favorable or concrete outcome (pain relief) for the typical patient taking tramadol, thus creating an unrealistic expectation for patients and healthcare providers. In absence of substantial evidence to support such a treatment response, the proposed trade name is misleading.

Please note that 21 CFR 201.10(c)(3) states that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(6)(i)]."

2. The Expert Panel identified five proprietary names (Result, Xyzal, Rizalt, Eryzole, and Riluzole) as having the potential for confusion with Ryzolt. Independent investigation identified an additional eighteen proprietary names (Maxalt, Prialt, Razadyne, Rezulin, Bryrel, Nizoral, Nysert, Nystex, Nystop, Reyataz, Lyger [redacted], Drysol, Tycolet, Xysall, Zylol, Kefzol, and Kytril) as having the potential for confusion with Ryzolt. These products along with the available dosage forms and usual dosage are listed in Table 1 (see below and pages 5 and 6). In addition, the expert panel discussion participants noted that the name sounds like "results." b(4)

Table 1: Potential Look-Alike and Sound-Alike Names Identified for Ryzolt

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Ryzolt	Tramadol Hydrochloride Extended-release Tablets 100 mg, 200 mg, and 300 mg	One tablet daily.	
Result (Canada, South Korea)	Acid Pump Inhibitor in South Korea Pregnancy and Ovulation Test in Canada	Unable to find information	LA/SA
Xyzal*** (05-0312-name approved in other countries)	Levocetirizine Dihydrochloride Tablets, 5 mg	2.5 mg to 5 mg daily	LA/SA
Rizalt (Isreal, Maxalt in the US)	Rizatriptan Tablets 5 mg and 10 mg	5 mg to 10 mg as a single dose	LA/SA
Maxalt	Rizatriptan Tablets 5 mg and 10 mg	5 mg to 10 mg as a single dose	SA
Prialt	Ziconotide Intrathecal Infusion, 25 mcg/mL in 20 mL vial 100 mcg/mL in 1 mL, 2 mL, or 5 mL vials (store refrigerated- to be used with Infusion Pump)	Initiate at 2.4 mcg per day with dosing up to 19.2 mcg/day	SA
Razadyne	Galantamine Hydrobromide Tablets-4 mg, 8 mg, and 12 mg Oral Solution- 4 mg/mL	8 to 16 mg twice daily. (Starting dose 4 mg twice daily for 4 weeks, then titrate up).	LA
Eryzole	Erythromycin Ethylsuccinate and Sulfisoxazole Powder for Oral Suspension, 200 mg/600 mg in 5 mL Bottles of 100 mL, 150 mL, and 200 mL	2.5 mL to 10 mL four times per day for 10 days. (50 mg/kg/day of Erythromycin and 150 mg/kg/day of Sulfisoxazole)	LA/SA
Riluzole (Rilutek)	Riluzole Tablets, 50 mg Bottles of 60	50 mg every 12 hours	SA

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Ryzolt	Tramadol Hydrochloride Extended-release Tablets 100 mg, 200 mg, and 300 mg	One tablet daily.	
Rezulin (withdrawn from market)	Troglitazone Tablets, 200 mg, 300 mg and 400 mg	200 mg daily with sulfonylurea, up to 600 mg 400 mg daily with metformin 200 mg to 600 mg daily with insulin	LA
Bryrel (Discontinued, no generic available)	Piperazine Citrate Syrup, 500 mg/5 mL	Adults: 3.5 grams daily for 2 days. Children: 75 mg/kg daily for 2 days. (Ascariasis) 65 mg/kg daily for 7 days (enterobiasis).	LA
Nizoral	Ketoconazole Tablets, 200 mg Suspension, 100 mg/5 mL (discontinued, no generic available) Cream, 2% (discontinued- 15, 30, and 60 grams) Shampoo, 2% (118 mL)	200 mg daily (oral), up to 400 mg daily. 3.3 mg to 6.6 mg/kg in children (oral) Apply cream daily to twice daily for 2 to 4 weeks. Shampoo twice weekly for 4 weeks.	LA
Nysert (discontinued)	Nystatin Vaginal Suppository 100,000 Units (no generic suppository, but vaginal tabs available)	One daily for 2 weeks.	LA
Nystex (discontinued)	Nystatin Oral Suspension 100,000 units/mL Cream, Ointment All discontinued May 2003	200,000 to 600,000 units four times daily. Apply twice daily.	LA
Nystop	Nystatin Topical Powder 100,000 units per gram, 15 and 30 gram	Apply to lesion two to three times per day until healed	LA
Reyataz	Atazanavir Sulfate Capsules 100 mg, 150 mg, 200 mg	Therapy-naïve: 400 mg daily with food. Therapy-experienced: 300 mg daily with ritonavir 100 mg	LA
Lygen (discontinued)	Chlordiazepoxide Hydrochloride Capsules, 5 mg, 10 mg, 25 mg	5 to 25 mg three to four times daily. For acute alcohol withdrawal- 50 to 100 mg. Children- 5 mg two to four times daily.	LA
[redacted]			LA
Drysol	Aluminum Chloride 20% in 90 % SD alcohol Solution, 37.5 mL 35 mL or 60 mL bottle with applicator	Apply daily at bedtime	LA
Tycolet (discontinued)	Acetaminophen/Hydrocodone Bitartrate Tablets, 500 mg/5 mg	1 to 2 every four to six hours.	LA
Xyzall (Austria, Belgium, France)	Levocetirizine Dihydrochloride Tablets, 5 mg	2.5 to 5 mg daily	LA/SA
Zyloi Isreal	Allopurinol Tablets 100 mg and 300 mg Allopurinol Powder for Injection 500 mg	200 mg to 600 mg daily, in single or divided doses	LA

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Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Ryzolt	Tramadol Hydrochloride Extended-release Tablets 100 mg, 200 mg, and 300 mg	One tablet daily.	
Kefzol (discontinued)	Cefazolin Sodium Injection 250 mg, 500 mg, 1 gram, 10 gram, 20 gram (available: 500 mg/50 mL, 1 gram/50 mL 500 mg, 1 gram, 10 gram, 20 gram powder for solution)	Adults: 250 mg to 1.5 gram every 6, every 8 or every 12 hours. Children: 25 to 50 mg/kg divided into 3 to 4 equal doses. (30 mg to 375 mg every 6 to 8 hours).	LA
Kytril	Granisetron Tablets: 1 mg Granisetron Oral Solution: 1 mg/5 mL Granisetron Injection: 1 mg/mL	2 mg daily or 1 mg twice daily as emotogenic therapy- given up to 1 hour before chemotherapy or radiation. For prevention- 10 mcg/kg IV within 30 minutes before initiation of chemotherapy. For treatment, 1 mg IV over 30 seconds.	LA

*Frequently used, not all-inclusive.
**LA (look-alike)/SA (sound-alike).
*** Proprietary and confidential information that should not be released to the public

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 Ryzolt 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 123 health care professionals (pharmacists, physicians, and nurses). The exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and an outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products with a prescription for Ryzolt (see page 7). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either 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
Outpatient RX: Ryzolt 200g #30 T qd	Ryzolt Quantity thirty Taking one tablet daily
Inpatient RX: Ryzolt 200mg 1 tab daily	

2. Results:

Six of the voice respondents interpreted the proposed name as "Result", which is the proprietary name of two products marketed in South Korea and Canada. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, twenty-three names were identified as having the potential to be confused with the proposed name of Ryzolt. DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that the product could be confused with "Result" which was one of the twenty-three names identified by DMETS. Seven participants from the voice study identified "Result" for the proposed name of Ryzolt. On the verbal order, Ryzolt was pronounced as Rĕzolt, not Rīzolt. Result is a marketed pregnancy test in Canada and an acid pump inhibitor in South Korea. As the South Korean product is limited in marketing and information is not readily available in English on the World-Wide Web, DMETS will not review this further. Moreover, information for the Canadian "Result" pregnancy test is not readily available on the World-Wide-Web and is an over-the-counter product. Thus, a patient or practitioner from the United States would have limited opportunity to be confused by the existence of the Result pregnancy test.

Of the remaining twenty-two names identified by expert panel discussions or independent review, the following sixteen will not be reviewed further due to weak orthographic similarities, weak phonetic similarities, lack of availability in the marketplace, specialty of use, limited distribution, and/or lack of overlapping products characteristics such as dosage form, strength, directions for use: Rizalt, Maxalt, Prialt, Razadyne, Riluzole, Rezulin, Bryrel, Nysert, Nystex, Nystop, Lygen, Tycolet, Xysall, Zylol, and Kytril.

The remaining seven names are discussed in detail below.

1. Xyzal*** was identified as a name with similar appearance and sound to Ryzolt when scripted and spoken. Xyzal is an IND under review by the Agency. Xyzal is an oral H_1-histamine receptor antagonist (levocetirizine) indicated for the treatment of seasonal allergic rhinitis and perennial allergic rhinitis. The usual dosage range is 2.5 mg to 5 mg once daily. Xyzal will be available in 5 mg scored tablets. This drug product is currently marketed in other countries as Xyzal.

   b(4

   The names are phonetically similar as they both contain two syllables and share the "ĭz" or "ĕz" sound. However, the leading "Z" sound of Xyzal compared to the leading "R" of Ryzolt and concluding "t" should differentiate the names. Orthographically, the names share the two consecutive downstrokes of "y" and "z" with a concluding upstroke of "L." However, the leading "X" and "R", plus the existence of the second upstroke ("t") in Ryzolt should differentiate the names.

   Xyzal
   ryzolt

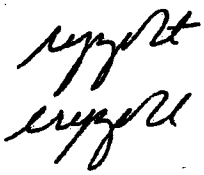
   The drug products share the same route of administration (oral), dosage form (tablet), and dosing frequency (daily). However, they differ in proposed strengths (5 mg compared to 100 mg, 200 mg, and 300 mg). Due to weak orthographic and phonetic similarities and the lack of overlap in product strength, DMETS believes there is limited potential for confusion between the two names.

2. Eryzole was identified as a name with similar appearance and sound to Ryzolt when scripted and spoken. Eryzole contains 200 mg of erythromycin ethylsuccinate and 600 mg of sulfisoxazole acetyl per teaspoonful (5 mL) as an oral suspension. The drug product is indicated for treatment of acute otitis media in children and is available as 100 mL, 150 mL, and 200 mL bottles for reconstitution. The recommended dosage is weight based (50 mg/kg for erythromycin and 150 mg/kg for sulfisoxazole) and typically ranges from 2.5 mL to 10 mL four times daily for ten days.

   The phonetic similarities stem from the shared central "zŏl" sound. However, the leading "ery" of Eryzole compared to the "ry" of Ryzolt and the concluding "t" of Ryzolt should differentiate the names in speech. Orthographically, the products share the central letters of "ryzol." However, the leading and concluding "E" of Eryzole and concluding "t" of Ryzolt should differentiate the names upon scripting.

   ERYZOLE
   RYZOLT

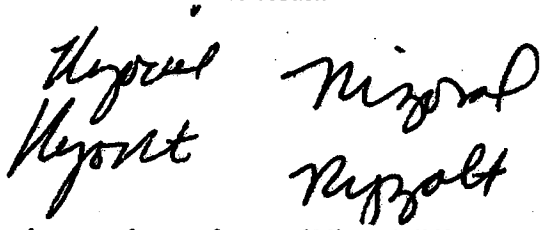
*** This review contains proprietary and confidential information that should not be released to the public.



The drug products share a similar route of administration (oral). However, the products differ in dosage form (oral suspension compared to tablets), strength (200 mg/600 mg compared to 100 mg, 200 mg, and 300 mg), frequency of dosing (four times daily compared to once daily), indication (otitis media in children compared to management of pain), and patient populations (children compared to adults). In addition, the method of ordering the products differ in that Eryzole will be ordered as teaspoonful or milliliter compared to tablets of Ryzolt. Additionally, since Eryzole is a combination product with two strengths, it is unlikely that there could be an overlap at 200 mg because health care practitioners will prescribe as teaspoonsful or milliliters. DMETS believes the possibility for drug name confusion is limited.

3. Nizoral was identified as a name with similar appearance to Ryzolt when scripted. Prescription strength Nizoral contains ketoconazole in tablet (200 mg), cream (2%), and shampoo (2%) dosage forms. Nizoral is indicated for the treatment of fungal infections and severe recalcitrant cutaneous dermatophyte infections. The recommended dosage for the tablet dosage form is 200 mg daily, which may be dosed up to 400 mg daily. The cream is applied once to twice daily for two to four weeks. Lastly, the shampoo should be used twice weekly for four weeks.

   The orthographic similarities stem from the possibility for the leading "N" and "R" to resemble each other when scripted, compounded by the shared downstroke of the "z" in Nizoral and "y" of Ryzolt. However, Ryzolt concludes with two upstrokes ("lt") compared to the single upstroke (l) of Nizoral. The likelihood that the "z" of Ryzolt will be scripted with a downstroke creates consecutive downstrokes that should differentiate the names. The concluding "t' of Ryzolt may serve to differentiate the two names as there are two consecutive upstrokes. Lastly, the central "ra" of Nizoral may lengthen the name in comparison to the single letter of "o" between the upstrokes and downstrokes; thus, differentiating the names. Therefore, there must be multiple scripting anomalies for confusion to result.



   The shampoo and cream dosage forms of Nizoral differ in product strength (2% compared to 100 mg, 200 mg, and 300 mg) and dosage form from Ryzort; thus, limiting the possibility for confusion on prescriptions. However, the tablet formulations share a similar route of administration (oral), dosing frequency (daily), and strength (200 mg). Although the products share product characteristics, the orthographic differences should help alleviate name confusion.

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*** proprietary and confidential information that should not be released to the public.

b(4)

5. Drysol was identified as a name with similar appearance to Ryzolt when scripted. Drysol contains 20% aluminum chloride in 93% SD alcohol for the treatment of hyperhidrosis. Drysol is available as 37.5 mL bottles or 35 mL and 60 mL with Dab-O-Matic applicator. Patients should apply to affected area(s) once daily, at bedtime.

   Orthographically, the beginning letters (D vs. R) have the potential to appear similar when scripted in upper case. In addition, the names share the downstroke of "y" followed by "ol" in similar locations. However, the concluding "t" of Ryzolt may differentiate the name if scripted with prominence, which will create two consecutive upstrokes to assist in visual identification.

   Dysol
   Ryzolt

   The products share once daily dosing. However, they differ in all remaining characteristics as shown by the following: route of administration (topical compared to oral), dosage form (solution compared to tablets), strength (20% compared to 100 mg, 200 mg and 300 mg), different storage locations, and indication of use (hyperhidrosis compared to pain management). Due to the differing strengths and dosage forms, DMETS believes the possibility for confusion to be minimal.

*** proprietary and confidential information that should not be released to the public.

6. Kefzol was identified as a name with similar appearance to Ryzolt when scripted. Kefzol is a drug product that was discontinued, but this name is well known amongst medical practitioners and generics are available. Kefzol contains cefazolin sodium for injection in five strengths: 250 mg, 500 mg, 1 g, 10 g and 20 g. Cefazolin is indicated for the treatment of infections (respiratory, urinary tract, skin, skin structure, biliary, bone and joint, genital, endocarditis and septicemia). It is also used in perioperative prophylaxis. The dosing ranges from 250 mg to 1.5 g every 6 to 12 hours.

   The orthographic similarities stem from the potential for the leading "K" and "R" to resemble each other when scripted. In addition, the names share two consecutive downstrokes in a similar position ("fz" and "yz") and the letter combination of "zol." However, the concluding "t" of Ryzolt may differentiate the name if scripted with prominence, which will create two consecutive upstrokes to assist in visual identification.

   The drug products do not share any product characteristics as shown by the following: route of administration (intravenous compared to oral), strength (250 mg, 500 mg, 1 g, 10 g, 20 g compared to 100 mg, 200 mg, and 300 mg), dosing frequency (every 6 to 12 hours compared to daily), duration of therapy (limited to time needed to treat infection compared to unlimited), and indication of use (infection requiring injectable drug product compared to pain management). Although the dosing for children is weight based, DMETS believes the possibility for overlap with the three strengths of Ryzolt would be limited. Kefzol will likely be used in an inpatient setting; thus, the route of administration is required for order completion. DMETS believes the possibility for confusion to be minimal due to the differing dosing frequency and route of administration.

7. Reyataz was identified as a name with similar appearance to Ryzolt when scripted. Reyataz contains atazanavir sulfate for the treatment of human immunodeficiency virus type 1 with other antiretroviral agents. Reyataz is available as 100 mg, 150 mg, and 200 mg capsules to be taken as 400 mg daily with food for therapy-naïve patients and 300 mg daily with ritonavir for therapy experienced patients.

   The orthographic similarities stem from the shared leading "R" followed by the downstroke of "y." However, the names may be differentiated by the remaining "ataz" of Reyataz and "zolt" of Ryzolt. Furthermore, the likelihood that the "z" of Ryzolt will be scripted with a downstroke creates consecutive downstrokes that should differentiate the names.

3. Relocate the product strength to appear immediately following the established name. However, assure the strength is not in close proximity to the net quantity result in confusion. Thus, after moving the strength, the sponsor needs to relocate the net quantity to the upper right corner to prevent confusion.

4. We note that the blue colors used for the boxing of the 200 mg and 300 mg strengths are almost identical. Please adjust accordingly to assure that the strengths are differentiated appropriately. Additionally, the dark blue print on the blue background of these two strengths is difficult to read. Revise this color scheme to provide greater contrast between strengths and the background to allow for greater readability and differentiation.

5. For all three strengths, delete the bolding of "30 Tablets" to assure that the strength has the most prominence.

6. Decrease the prominence and remove the bolding of the "Rx only" statement to assure the strength has prominence.

B. INSERT LABELING

1. See Container Comment A1 with reference to the presentation of the established name.

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A. Appendix A: Prescription Study Results for Ryzolt

Inpatient	Outpatient	Voice
Ryzolt	Ryznt	Result
Nyzolt	Ryzint	Result
Nyzolt	Repint	Result
Ryzalt	Rytint	Result
Ryzolt	Ryant	Resalt
Ryzolt	Ryzort	Result
Ryzolt	Ryzint	Result
Ryzolt	Rigrivit	Zesult
ryzoit	Nyzert	Ryzolt
Ryzolt	Regzirt	
Repint	Ryzert	
	Ryzolt	
	Ryzint	
	Ryrint	

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/s/

Alina Mahmud
9/22/2006 04:15:23 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/22/2006 04:25:52 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/22/2006 04:36:12 PM
DRUG SAFETY OFFICE REVIEWER

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Office of Surveillance and Epidemiology

Memo

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-550

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology HFD-420

From: Linda Wisniewski, RN
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420

Date: July 10, 2006

Re: ODS Consult 06-0050-1 & 06-0050-2 ——— and Ryzolt; NDA#: 21-745

b(4)

This memorandum is in response to a June 12, 2006 request from the Division of Anesthesia, Analgesia, and Rheumatology Products, to review the proprietary names ——— and Ryzolt. Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) had promotional concerns with the proprietary names. Specifically, they stated:

b(4)

Ryzolt

"DDMAC objects to the proposed trade name Ryzolt because it overstates the effectiveness of the drug product. Depending on the pronunciation, Ryzolt sounds like "result." Result is defined as "something that happens or exists because of something else (www.dictionary.cambridge.org accessed 06/19/06) or "an outcome; a favorable or concrete outcome or effect" (www.bartleby.com (American Heritage) accessed 06/19/06). The proposed trade name Ryzolt suggests a guaranteed favorable or concrete outcome (pain relief) for the typical patient taking tramadol, thus creating an unrealistic expectation for patients and healthcare providers. In absence of substantial evidence to support such a treatment response, the proposed trade name is misleading. Please note that 21 CFR 201.10(c)(3) states that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(6)(i)]."

Per e-mail communication with the Division of Anesthesia, Analgesia, and Rheumatology Products, they concur with DDMAC's comments (e-mail on Monday, July 10, 2006). Therefore, DMETS will not proceed with the safety review of the proposed proprietary names, [redacted] and Ryzolt. We recommend the sponsor be notified immediately of the decision to reject the names based on the promotional concerns and request submission of an alternative proprietary name/s for NDA# 21-745. Please forward the alternate name for DMETS review upon submission. b(4)

If you have any questions for DDMAC, please contact the Regulatory Review Officer, Suzanne Berkman. If you have any questions or need clarification, please contact the medication errors Project Manager, Diane Smith at 301-796-0538.

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/s/

Linda Wisniewski
7/14/2006 03:19:04 PM
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Alina Mahmud
7/14/2006 04:07:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/14/2006 04:13:54 PM
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Carol Holquist
7/14/2006 04:26:11 PM
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Office of Surveillance and Epidemiology

Memo

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

From: Felicia Duffy, RN, BSN, MSEd
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology, HFD-420

Through: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology, HFD-420, WO22, Mail Stop 4447

Date: May 30, 2006

Re: ODS Consult 06-0050
Tramadol Contramid OAD (Tramadol HCl Controlled-release) Tablets; 100 mg, 200 mg, 300 mg
NDA# 21-745

This memorandum is in response to CMC comments from the Division about the proprietary name in an email on May 10, 2006. The chemist provided the following comments:

The proprietary name proposed by the NDA applicant is "Tramadol Contramid OAD", which may not be appropriate for one of the following reasons:

1. Tramadol is a non proprietary name (generic name, USAN name).
2. Contramid is the trade name for a pregelatinized modified starch (one of the excipients).
3. OAD stands for once-a-day.
4. The nonproprietary name of the drug product should be "tramadol hydrochloride extended-release tablets." The NDA proposed term "controlled-release" should not be used. Refer to Appendix C of the Orange Book for Uniform Terms.

In support of the CMC comments, DMETS response is as follows:

1. Tramadol is an established name designated by USAN which is currently marketed. Thus, the sponsor cannot submit Tramadol as a proprietary name as it is the established name of the product.
2. The sponsor describes Contramid® as a new technology that is a "highly compressible excipient with excellent flow and binding characteristics, ideal for efficient tablet and capsule manufacture." Since this technology may be used in future drug products, we do not recommend the use of technology in the proprietary name.
3. DMETS does not recommend the use of modifiers, such as OAD, because practitioners will not understand what the modifier represents. DMETS has post-marketing reports where modifiers may be misinterpreted leading to medication errors.
4. We acknowledge that the dosage form "controlled-released" is not a recognized dosage form by the USP. We recommend consulting the CDER Labeling and Nomenclature Committee (LNC) on the appropriate designation of the established name.

In summary, DMETS concurs with the Division that Tramadol Contramid OAD is not an appropriate proprietary name, and we request the sponsor submit an alternate name for review. If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-796-0538.

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/s/

Felicia Duffy
6/9/2006 08:59:59 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/9/2006 09:32:34 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/12/2006 08:00:10 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS in her absence

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