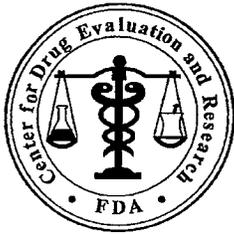


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-964

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: March 28, 2008

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Subject: Proprietary Name Review

Drug Name(s): Relistor (Methylnaltrexone Bromide Injection) 12 mg/0.6 mL

Application Type/Number: NDA # 21-964

Applicant: Progenics Pharmaceuticals, Inc.

OSE RCM #: 2008-332

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Relistor, has some similarity to other proprietary and established drug 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 does not object to the use of the proprietary name Relistor for this product.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Gastroenterology Products (HFD-180) for re-assessment of the proprietary name, Relistor, regarding potential name confusion with other proprietary or established drug names. The sponsor submitted an independent analysis of the name by the _____ a subsidiary of the _____ for review and comment. The Division of Medication Error Prevention previously reviewed and had no objection to the proprietary name, Relistor, in OSE review# 2007-208 dated February 28, 2007 and as part of that review, we evaluated the container labels, carton and insert labeling that were included in the March 30, 2007 submission. The review division forwarded revised container label and carton labeling via e-mail on March 28, 2008. This labeling has not been submitted to the NDA.

1.2 PRODUCT INFORMATION

Relistor (methylnaltrexone bromide) is a peripherally acting mu-opioid receptor antagonist. It is indicated for the treatment of opioid-induced constipation in patients receiving palliative care. Relistor is administered as a subcutaneous injection, no more frequently than one dose in a 24 hour period. The recommended dose is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. The dosage volume calculator below was obtained from the package insert labeling dated March 30, 2007:

The recommended dose of BRANDNAME SC is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). See the table below to determine the correct injection volume.

Patient Weight		Injection Volume	Dose
Pounds	Kilograms		
84 to less than 136	38 to less than 62	0.4 mL	8 mg
136 to 251	62 to 114	0.6 mL	12 mg

Patients whose weight falls outside of the ranges in the table should be dosed at 0.15 mg/kg. The injection volume for these patients should be calculated using one of the following:

- Multiply the patient weight in pounds by 0.0034 and round the volume to the nearest 0.1 mL
- Multiply the patient weight in kilograms by 0.0075 and round the volume to the nearest 0.1 mL

Relistor is supplied as a solution for injection in a single-use vial containing 12 mg/0.6 mL. This allows for the administration of either the 8 mg or the 12 mg dose. It is also packaged as a 'convenience kit' which contains seven dose trays. Each dose tray contains one 12 mg/0.6mL single use vial of Relistor and one 1 cc syringe with a 27-gauge one-half inch needle, two alcohol swabs, one package insert, and one patient instruction leaflet. Relistor should be stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). Relistor should be protected from light.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention 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, Relistor, 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, Relistor, the medication error staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Section 2.1.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). We normally conduct internal CDER prescription analysis studies. However, since this name was previously evaluated, CDER prescription analysis studies were not conducted upon re-review of Relistor. An external prescription analysis study conducted by Drug was considered and incorporated into the overall risk assessment.

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

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We use the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

The Medication Error 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.^{4,5}

To identify drug names that may look similar to Relistor, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (three, capital letter 'R' and lower case letters 'l' and 't'), downstrokes (none), cross-strokes (one, lower case 't') and dotted letters (one, lower case 'i'). Additionally, several letters in Relistor may be vulnerable to ambiguity when scripted, including the capital letter 'R' may appear as capital 'P', 'B', or 'K'; lower case 'el' may look like lower case 'u' or 'd'; lower case 'e' may look like lower case 'i', 'o', 'u', or 'l'; lower case 'l' may look like lower case 'b', 'e', or 't'; lower case 'i' may appear as lower case 'e'; lower case 's' may appear as lower case 'a'; lower case

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

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

't' may appear as lower case 'r' or 'l'; lower case 'o' may appear as lower case 'e'; and lower case 'r' may appear as lower case 'n'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Relistor.

When searching to identify potential names that may sound similar to Relistor, the Medication Error Staff search for names with similar number of syllables (3), stresses (rel-IS-tor or REL-is-tor), and placement of vowel and consonant sounds. In addition, several letters in Relistor may be subject to interpretation when spoken, including the letter 'e' may be interpreted as 'i'; the letter 'i' may be interpreted as 'e'; or the letters 'or' may be interpreted as 'er' or 'ar'. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Relistor) the established name (methylnaltrexone), proposed indication (treatment of opioid-induced constipation in patients receiving palliative care), strength (12 mg/0.6 mL), dose (8mg, 12 mg, or 0.15 mg/kg), frequency of administration (every 24 hours), route (subcutaneous injection), and dosage form (solution for injection). 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 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, Relistor, was provided to the medication error staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Relistor using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held to gather CDER professional opinions on the safety of the product and the proprietary name, Relistor. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 External Proprietary Name Risk Assessment

For this product, the Sponsor submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. The Division of Medication Error Prevention conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the Medication Error Staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether our risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, we provide a detailed explanation of these differences.

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, we seek to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

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 Relistor 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 Relistor to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety

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

Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

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

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. We identify that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that we object to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns 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, 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 AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton and container labels 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 review division forwarded on March 28, 2008 the following revised label and labeling for our review (see Appendix F, G for images):

- Container Label: 12 mg/0.6 mL vial
- Carton Labeling: 12 mg/0.6 mL vial

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

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

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

were identified as having some similarity to the name Relistor: Restoril, Rifater, Trelstar, Relestat, Neulasta, Nilstat, Rebetol, Refacto, Ritalin, Relaxir, Relenza, Relafen, Rescula, Retisert, Restasis, Relitone, Sulster, Relacore, Relisorm, Rescriptor, Crestor, Resolor, Rebetron, Clistin, Menostar, Prolastin, Reclast, Lipitor, Raniclolor, Relacon, and Relasin.

Twenty-four of these names were previously evaluated. The eight names not previously reviewed are: Clistin, Menostar, Prolastin, Reclast, Lipitor, Raniclolor, Relacon, and Relasin. Four of the eight names were thought to look like Relistor (Clistin, Menostar, Prolastin, and Reclast). The remaining four names (Lipitor, Raniclolor, Relacon, and Relasin) were thought to look and sound similar to Relistor.

3.1.2 CDER Expert panel discussion

The Expert Panel reviewed the pool of names identified by Medication Error Prevention staff (see section 3.1 above) but did not identify any additional names with similarity to Relistor. The Expert Panel indicated that the proposed name Relistor sounds like an antilipidemic drug. Although the Expert Panel did not cite specific reasons, the ending of the Relistor name ('or') looks and sounds similar to the ending of names of antilipidemic drugs such as Lipitor, Crestor, Mevacor, or Zocor. However, the labeling for Relistor clearly states the indication of use for the product and there are other products currently approved that end with the letters 'or' which are not antilipidemic drugs.

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 External Proprietary Name Risk Assessment

In the proposed name risk assessment submitted by the applicant, the _____ identified and evaluated a total of thirty-eight drug names thought to have some potential for confusion with the name Relistor. Twenty-eight of the thirty-eight names were not previously identified in our Staff searches, the Expert Panel Discussion, or our previous review of the proposed name. Thirty of the thirty-eight names identified by _____ did not specifically list whether they share look-alike and/or sound-alike characteristics with Relistor. These thirty names were listed in the Computerized Orthographic and Phonologic Analysis (COPA). The remaining eight names listed look-alike (Relafen), sound-alike (Effexor, Lipitor, Relacore, Relenza), or both look-alike and sound-alike characteristics (Crestor, Relpax, and Restoril) to Relistor.

3.1.4 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator did not identify any additional names thought to look similar to Relistor and represent a potential source of drug name confusion. As such, a total of thirty-six names were analyzed to determine if the drug names could be confused with Relistor and if the drug name confusion would likely result in a medication error.

This analysis determined that the name similarity between Relistor and the identified names was unlikely to result in medication errors for thirty-six product names. Nineteen names were not considered further because they lack convincing orthographic and/or phonetic similarities with Relistor (see Appendix B). Nine names were not considered further because they could not be found in commonly used drug references such as Clinical Pharmacology Online, Facts & Comparisons, Micromedex, STATRef, the Orange Book, or the Red Book and were thus determined by FMEA to pose minimal risk of error in the usual practice setting (see Appendix C). Seven names (Reclast, Relacon, Relasin, Redisol, Menostar, Prolastin, and Respalor) were determined to have some orthographic and/or phonetic similarity to Relistor, and thus determined to present some risk of confusion. For these names, FMEA determined that medication errors were unlikely because they do not overlap in strength or dosage with Relistor (see Appendix D). The remaining name (Celestone) had some numerical overlap with Relistor in dosage and strength. However, analysis of the failure modes did not determine the effects of these similarities to result in medication errors in the usual practice setting (Appendix E).

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to the proper use of the product, clear communication of the established name, product strength, and route of administration.

3.2.1 Container Label

The proprietary name is presented in multiple colors.

The route of administration is included in the established name.

The dosage form is presented in a different color and size than the rest of the established name.

The product concentration is presented in terms of mg/mL.

The product strength lacks prominence.

The statement regarding "Single Use Vial" appears above the route of administration.

There are no instructions to discard the unused portion of the medication.

3.2.2 Carton Labeling

We identified identical areas of vulnerability as the container label. Additionally, the manufacturer's name has more prominence than the product strength.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The results of the Proprietary Name Risk Assessment found that the proposed name, Relistor, has some similarity to other proprietary and established drug names, but the findings of the FMEA process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, we believe that these limitations are sufficiently minimized by the use of an Expert Panel and, in this case, the data submitted by the Sponsor from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. 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 AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment found that the presentation of the proprietary and established names, strength and route of administration of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, the applicant presented a _____; and a primary strength that lacks prominence. For an injectable product that _____, only the total drug content in the vial should be presented to decrease the risk of confusion. Thus, the only presentation of strength should be 12 milligrams per 0.6 milliliters and this should be presented in a prominence comparable to the proprietary and established name to ensure practitioners can easily identify the product. Although the applicant has prominently displayed the proprietary name; using a graphic to represent the letter 'O' is distracting and makes the name difficult to read. Additionally, presenting the established name in black font and the dosage form in pink font decreases the readability of the established name.

The applicant has prominently presented the route of administration in pink font as a part of the established name. However, this is an inappropriate location for the route of administration. The route of administration is usually presented after the strength on the label and labeling and is not a part of the established name. In contrast the presentation of the secondary route of administration statement is difficult to locate below the "Sterile Single Use Vial" statement. Relocating the route of administration statement to immediately follow the strength will allow for easier readability of this information. The statement "Sterile Single Use Vial" fails to communicate to practitioners that this vial should be discarded after a single use. Since some patients may receive less than 12 mg, practitioners may believe that they can save the remaining drug for another patient or later administration. Thus a "Discard after use" statement would prevent healthcare practitioners from using a single vial for multiple doses.

On the carton labeling, the manufacturer's name (Wyeth and Progenics) are presented in bold font which is more prominent than the product strength and established name. The manufacturer's name should not be as prominent as important information such as the proprietary and established names and the product strength since knowing the manufacturer is not required to safely choose the drug from the shelf for administration.

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 Sponsor 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, Relistor, does not appear to be vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention does not object to the use of the proprietary name, Relistor, for this product. 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. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead

to medication errors. The Division of Medication Error Prevention 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. The Division of Medication Error Prevention has no objections to the use of the proprietary name Relistor for this product.
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.
3. 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 sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

6.2 COMMENTS TO THE APPLICANT

6.2.1 *Proprietary Name*

1. The Division of Medication Error Prevention has no objections to the use of the proprietary name Relistor for this product.
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.

6.2.2 *Labels and Labeling*

6.2.2.1 **Container Label**

1. Present the proprietary name in one consistent color.
2. Delete the route of administration _____ from the established name.
3. Include the dosage form (“injection”) with the established name and present it in the same color and with equal prominence as the established name.
4. Increase the prominence of the product strength.
5. Delete the concentration statement _____
6. _____
7. Revise the statement to _____ to read “Single Use Vial. Discard after Use.”

6.2.2.2 Carton Labeling

1. See Container Label comments 1 to 7.
2. Decrease the prominence of the manufacturer's name.

7 REFERENCES

1. *Adverse Events Reporting System (AERS)*

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

2. *Micromedex Integrated Index (<http://weblern/>)*

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

3. *Phonetic and Orthographic Computer Analysis (POCA)*

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

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

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

5. *AMF Decision Support System [DSS]*

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

6. *Division of Medication Errors and 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.

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. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also 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 (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, we 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, we also consider a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		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	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Names lacking convincing look-alike and/or sound-alike similarities with Relistor

Proprietary Name	Similarity to Relistor
Lipitor	Look/Sound
Raniclor	Look/Sound
Acyclovir	COPA
Effexor	Sound
Elestat	COPA
Evista	COPA
Orlistat	COPA
Precision	COPA
Raloxifene	COPA
Reli On	COPA
Relief	COPA
Relion	COPA
Relpax	Look/Sound
Trecator	COPA
Trileptal	COPA
Zocor	COPA
Clistin*	Look
Renovist*	COPA
Trilisate*	COPA

*These products have been discontinued and are no longer commercially available in the US. Generic formulations are available.

Appendix C: Identified product name(s) with little or no product information.

Proprietary Name	Similarity to Relistor
Gelhist	COPA
Helistat	COPA
Orestol	COPA
Prehist	COPA
Prehist D	COPA
Prelestrin	COPA
Ranestol	COPA
Rectorx	COPA
Rhulicort	COPA

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

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Relistor (methylalntrexone) injection		12 mg/0.6 mL	8 mg, 12 mg, or 0.15 mg/kg once daily via subcutaneous injection
Reclast (zoledronic acid injection)	Look	5 mg/100 mL	5 mg intravenously over at least 15 minutes (one time dose for Paget's disease; once a year dose for postmenopausal osteoporosis)
Relacon DM NR (dextromethorphan/guaifenesin/pseudoephedrine) *Other Relacon products have been discontinued (Relacon DM, Relacon HC, Relacon HC NR, Relacon LAX)	Look and Sound	(dextromethorphan 15 mg/ guaifenesin 200 mg/ pseudoephedrine 32 mg per 5 mL)	10 mL orally 2 to 3 times daily ; not to exceed 3 doses in 24 hours
Relasin DM (dextromethorphan/guaifenesin/pseudoephedrine) Relasin HC (chlorpheniramine/hydrocodone/phenylephrine) Relasin HCX (guaifenesin /hydrocodone)	Look and Sound	Relasin DM (dextromethorphan 15 mg/ guaifenesin 175 mg/ pseudoephedrine 32 mg per 5 mL) Relasin HC (chlorpheniramine 2.5 mg/hydrocodone 3.25 mg/ phenylephrine 8 mg per 5 mL) Relasin HCX (guaifenesin 200 mg/hydrocodone 7.5 mg per 5 mL)	Relasin DM – 10 mL orally 2 to 3 times daily; not to exceed 3 doses in 24 hours Relasin HC – 10 mL orally every 4 to 6 hours; not to exceed 40 mL in 24 hours Relasin HCX – 5 to 10 mg hydrocodone component orally every 4 to 6 hours as needed; not to exceed 30 mg hydrocodone component in 24 hours
Redisol (cyanocobalamin) *discontinued product; generic formulations available	COPA	1 mg/mL injection	30 micrograms intramuscularly or subcutaneously once daily for 5 to 10 days, then 100 to 200 micrograms intramuscularly or subcutaneously once monthly
Menostar (estradiol extended release transdermal film)	Look	0.014 mg/24 hr	Apply 1 patch once per week
Prolastin (alpha proteinase inhibitor injection powder for reconstitution)	Look	500 mg or 1 gram vials	60 mg/kg intravenously once weekly
Respalar (liquid nutrition for pulmonary patients)	COPA	No information available.	No information available.

Appendix E: Potential confusing name with numerical overlap in strength or dose

Relistor (methylnaltrexone injection)	12 mg/0.6 mL	8 mg, 12 mg, or 0.15 mg/kg once daily via subcutaneous injection
Failure Mode: Name confusion	Causes (could be multiple)	Effects
Celestone (betamethasone)	Numerically similar strengths (12 mg/0.6 mL vs. 0.6 mg/5mL syrup or 6 mg/mL injection) Orthographic similarity (‘elistor’ vs. eleston’)	Orthographic differences, as well as differences in product characteristics minimize the likelihood of medication errors in the usual practice settings. <i>Rationale:</i> Although the names share a similar middle section (‘elistor’ vs. ‘eleston’), they begin with different letters (‘R’ vs. ‘C’) which bear no resemblance to each other. These letters have not been shown to be confused with each other according to a list of commonly confused drug names compiled from reports to the MEDMARX and USP/ISMP medication error reporting programs. This difference will help to distinguish the names. The most likely area of confusion is in the inpatient setting because patients are unlikely to be given a prescription for Celestone.Injection. However, JCAHO standards require that the route of administration is specified on inpatient medication orders. This lessens the risk of confusion between Relistor and the injectable formulation of Celestone. .

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