CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-964

RISK ASSESSMENT and RISK MITIGATION 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:	April 11, 2008
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products, HFD-180
Through:	Linda Kim-Jung, Pharm.D., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention, HFD-420
From:	Tara Turner, Pharm.D., Safety Evaluator Division of Medication Error Prevention, HFD-420
Subject:	Container Label and Carton Labeling 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 #:	2008-611

CONTENTS

EXECUTIVE SUMMARY 1
1 BACKGROUND 1
1.1 Introduction 1
1.2 Regulatory History 1
1.3 Product Information 1
2 METHODS AND MATERIALS 2
2.1 Label and Labeling Risk Assessment 2
3 RESULTS 3
3.1 Label and Labeling Risk Assessment 3
4 DISCUSSION 3
5 CONCLUSIONS 4
6 RECOMMENDATIONS 4
6.1 Comments To the Division 4
6.2 Comments To The Applicant 5
APPENDICES 6

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, we are concerned with the presentation of the proprietary and established names and the location/prominence of other information on the labels/labeling. 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 was written in response to a request from the Division of Gastroenterology Products (HFD-180) to evaluate the revised labeling of Relistor for the potential to contribute to medication errors. The revised labeling includes container label and carton labeling for the vial and the convenience kit.

1.2 REGULATORY HISTORY

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. Most recently, we reassessed and had no objection to the proprietary name, Relistor, in OSE review# 2008-332 dated March 28, 2008 and as part of that review we evaluated the revised container label and carton labeling for the vial forwarded by the review division via e-mail on March 28, 2008.

The review division forwarded revised container label and carton labeling for the vial and convenience kit via e-mail on April 9, 2008. This labeling has not been officially submitted to the NDA as of the signature date of this review.

1.3 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 describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus 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 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.[2]

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

---

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

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

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 April 9, 2008 the following revised labels and labeling for our review (see Appendix A, B, C, D, E, F, G for images):

- Vial Label: 12 mg/0.6 mL
- Sample Vial Label: 12 mg/0.6 mL
- Vial Carton: 12 mg/0.6 mL
- Tray Lidding: 1 vial, 1 syringe with needle, 2 alcohol swabs, 1 physician insert, 1 patient insert
- Sample Tray Lidding: 1 vial, 1 syringe with needle, 2 alcohol swabs, 1 physician insert, 1 patient insert
- Carton: 7 dose trays
- Sample Carton: 2 dose trays

3 RESULTS

3.1 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 presentation of the proprietary and established names and the location/prominence of other information on the labels/labeling.

3.1.1 All Labels and Labeling

In the proprietary name, the letter "O" is presented as a graphic.

The route of administration is included in the established name.

The statements regarding "Sterile Single Use Vial" and "Discard after use" appear above the strength and route of administration.

3.1.2 Trade and Sample Tray Lidding

The statement to "Protect vial from light" is small and difficult to read.

Under the tray contents, the size of the syringe is not indicated.

3.1.3 Trade and Sample Carton Labeling

The statement to "Protect vial from light" is small and difficult to read.

Under the tray contents, the size of the syringe is not indicated.

The word kit is used when referring to the carton contents.

4 DISCUSSION

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, we are concerned with the presentation of the proprietary and established names and the location/prominence of other information on the labels/labeling.

The most important information for the safe and proper use of the drug product is the proprietary name, established name, and product strength. This information should be the most prominent information on the labels and labeling. Although the applicant has prominently displayed the proprietary name, they used a graphic to represent the letter 'O', which is distracting and makes the name difficult to read. Additionally, the route of administration ("subcutaneous") is listed as part of the established name. This is an inappropriate location for the route of administration and is also duplicative. The route of administration is usually presented after the strength on the label and labeling and is not part of the established name. We concur with the presentation of the established name as listed in the CMC review dated February 4, 2008 on page eighty-six as Methylnaltrexone Bromide Injection. Additionally, the strength is separated from the proprietary and established names by various statements such as "Contains one sterile ....." or "Sterile single use vial. Discard after use." The strength should immediately follow the proprietary and established names to ensure that the product is correctly identified.

The presentation of information on the tray lidding and the carton should be prominently displayed and accurate to prevent confusion. The statement "Protect vial from light" is in small font and is difficult to read. This statement should be presented in larger font so that the healthcare practitioner or the patient can store the product appropriately. Also, the size of the syringe is not included on the tray lidding and carton. Finally, the labeling contains terminology such as 'kit' when they are referring to the carton. The use of inconsistent terminology may be confusing to practitioners and lead to medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed container label 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

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention has identified areas of needed improvement. We have provided recommendations in section 6 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-2084.

6.2 COMMENTS TO THE APPLICANT

6.2.1 All Labels and Labeling

1. In the proprietary name, present the letter "O" without the graphic.
2. Delete the route of administration ("subcutaneous") from the established name so that it reads "methylnaltrexone bromide injection".
3. Relocate the strength to appear directly beneath the established name.
4. Relocate the "Sterile Single Use Vial" and "Discard after use" statements so they appear directly beneath the route of administration statement ("For Subcutaneous Injection Only").

6.2.2 Trade and Sample Tray Lidding

1. Increase the size of the "Protect vial from light" statement.
2. In the tray contents section, add the size of the syringe.

6.2.3 Trade and Sample Carton Labeling

1. Increase the size of the "Protect vial from light" statement.
2. In the tray contents section, add the size of the syringe.
3. Remove the word "kit" from the content statement on the principal display panel. Change the statement to read "Each carton contains 7 trays. Each tray contains one sterile single use vial. Discard after use."

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tara Turner
4/11/2008 01:51:09 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/11/2008 02:42:56 PM
DRUG SAFETY OFFICE REVIEWER

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

Date:	April 4, 2008
To:	Donna Griebel, M.D., Director Division of Gastroenterology Products
Through:	Jodi Duckhorn, M.A., Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Patient Education and Labeling Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)
Drug Name(s):	RELISTOR (methylnaltrexone bromide) Injection
Application Type/Number:	NDA 21-964
Applicant/sponsor:	Progenics Pharmaceuticals, Inc.
OSE RCM #:	2008-421

contains only the Patient Instructions for Use in subsection 17. The [redacted] has been removed from section 17 of the PI.

See the attached document for our recommended revisions to the PPI and Patient Instructions for Use. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI and Patient Instructions for Use. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI and Patient Instructions for Use.

4 CONCLUSIONS AND RECOMMENDATIONS

1. The term "healthcare [redacted]" is vague and should not be used in patient information materials. We have changed "healthcare [redacted]" to "healthcare provider" throughout the PPI and Patient Instructions for Use.
2. [redacted]
3. [redacted]

   The review division has added language to section 17 Patient Counseling Information, in the PI, stating "In approximately 30% of patients in clinical trials, laxation was reported within 30 minutes of a dose of RELISTOR; therefore, advise patients to be within close proximity to toilet facilities once the drug is administered." This information is not found in the clinical trials section of the PI. The review division should clarify where this information comes from.

   We have added suggested language to the section "How should I take RELISTOR?" to address the issue that patients should be near a toilet after taking their dose of RELISTOR: "After taking your dose of RELISTOR, stay near a toilet. You may need to have a bowel movement soon after taking your dose."

4. [redacted] has been deleted. The first two bullets were moved to the section "What are the possible side effects of RELISTOR?" The 3rd bullet was deleted. Pregnancy information is in the section "What should I tell my healthcare provider before taking RELISTOR?" The information in the 4th bullet instructing patients to tell their healthcare provider if they stop their prescription pain medicine, has been moved to the section "How should I take RELISTOR?"
5. We have added the statement, "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." This verbatim statement is

1 INTRODUCTION

The sponsor submitted an original New Drug Application, NDA #21-964 for Relistor (methylnaltrexone bromide) Injection, on March 30, 2007, with the proposed indication "for the treatment of opioid-induced constipation in patients receiving palliative care."

The Patient Labeling and Education Team received a request to review a Patient Package Insert (PPI) for Relistor, which was submitted in subsection 17 ½ of section 17 Patient Counseling Information in the Professional Information (PI) submitted by the sponsor, as part of an amendment to the original NDA, on September 28, 2007. This review is written in response to that request.

2 MATERIAL REVIEWED

- Relistor Professional Information (PI), including ~~~ and Patient Instructions for Use, submitted September 28, 2007
- Relistor Professional Information (PI) and Patient Instructions for Use, as revised by the Review Division, dated March 31, 2008

3 DISCUSSION

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.1, and a Flesch Reading Ease score of 63.3. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the PPI, we have:

- simplified wording where possible,
- made it consistent with the Professional Information,
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question–and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI and Patient Instructions for Use, using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

In the sponsor's submission, dated September 28, 2007, the proposed PI contains a ~~~ ~~~ and Patient Instructions for Use in section 17 Patient Counseling Information, subsection 17 – Patient Labeling. The Review Division's revised PI, dated March 31, 2008,

required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like RELISTOR, we recommend adding this language to all FDA-approved patient labeling for consistency.

6. We have added the sections "General information about RELISTOR" and "What are the ingredients in RELISTOR?" to the PPI. The sponsor's name and address should be added at the end of the PPI.

7. We have re-named the Patient Instructions for Use as follows:

   From: Section A: PATIENT INFORMATION FOR VIAL AND SYRINGE WITH RETRACTABLE NEEDLE IN TRAY

   To: Patient Instructions for Use for RELISTOR Vial and Syringe with Retractable Needle in Tray

   From: Section B: PATIENT INFORMATION FOR VIAL AND STANDARD SYRINGE

   To: Patient Instructions for Use for RELISTOR Vial and Standard Syringe and Needle

   We were unable to remove the all capital letters. For improved readability, please request that the sponsor correct this.

8. We have made the content of the two Patient Instructions for Use as consistent as possible.

9. The sponsor should add a figure to both Patient Instructions for Use showing all the supplies needed to give an injection of RELISTOR. The sponsor should add a figure showing the syringe and needle and label each part. Each figure should be labeled and referenced in the corresponding text. For the syringe with retractable needle, the sponsor should provide a close up figure of the syringe with the needle in the position for injection and retracted so that patients know what the syringe looks like when the needle is properly retracted.

10. We recommend that the sponsor add the cotton ball or gauze pad, and bandage to the RELISTOR tray so that patients have all the needed supplies. Patients may not routinely have gauze pads or cotton balls at home.

11. The dose selection table has been removed from both Patient Instructions for Use. The patient should not be determining the correct dose of RELISTOR; they should be taking it as prescribed by their healthcare provider. Dose adjustments should be made by the healthcare provider.

12. The last statement in both Patient Instructions for Use has been deleted. There is a statement in the PPI under the section "General information about RELISTOR" in which patients are instructed that "If you would like to know more information about RELISTOR, talk to your healthcare provider. You can ask your doctor or pharmacist for information about RELISTOR that is written for healthcare professionals."

Please let us know if you have any questions.

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Risk 1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Mills
4/4/2008 11:12:37 AM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/4/2008 12:33:13 PM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 21-964

Name of Drug: Relistor (methylnaltrexone bromide) [redacted] Injection

Applicant: Progenics Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): 3/30/07, 9/28/07

Receipt Date(s): 3/30/07, 9/28/07

Submission Date of Structure Product Labeling (SPL): 3/30/07, 9/28/07

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights Section:

- The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

  Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

- Use command language whenever possible (i.e., use "Advise" rather than "Patients should be advised"). [See **WARNINGS AND PRECAUTIONS**]

- Add adverse reaction inclusion criterion (e.g., incidence rate greater than X%). [21 CFR 201.57(a)(11)]

- A revision date must appear at the end of the highlights. However, for a new NDA, the revision date should be left blank at the time of submission and will be edited to the month/year of application approval. [21 CFR 201.57(a)(3)]

Full Prescribing Information: Contents:

- If the Highlights and Table of Contents do not fit on one page, insert Table of Contents on page 2.

- Only section and subsection headings should appear in Contents. Delete

- Delete

Full Prescribing Information (FPI):

- **12.3 Pharmacokinetics** is a required sub-heading. Please re-order sub-headings 12.3 and 12.4. [21 CFR 201.56(d)(1)]

- Please add subheading **13.2 Animal Toxicology and/or Pharmacology**. [21 CFR 201.56(d)(1)]

- Avoid using internal company study titles (e.g. Study 301, 301EXT).

- Patient Counseling Information must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)] Please use command language and provide subheadings and numbering for each item in this section. **[See 17 for PATIENT COUNSELING INFORMATION].**

Recommendations

The sponsor will be issued and advice letter asking it to address the identified deficiencies/issues and re-submit labeling by March 31, 2008. This updated version of labeling will be used for further labeling discussions.

Matthew Scherer
Regulatory Project Manager

Supervisory Comment/Concurrence:

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: MCS/March 11, 2008
Revised/Initialed: JD/ March 17, 2008
Finalized: MCS/ March 17, 2008

CSO LABELING REVIEW OF PLR FORMAT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Matthew Scherer
3/17/2008 02:18:47 PM
CSO

Julieann DuBeau
3/17/2008 02:25:45 PM
CSO