

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-964

SUMMARY REVIEW



Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick Deputy Director Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director Summary Review
NDA#	21-964 (Original)
Applicant Name	Progenics Pharmaceuticals, Inc.
Date of Submission	May 31, 2007
PDUFA Goal Date	April 30, 2008
Proprietary Name / Established (USAN) Name	Relistor (Methylnaltrexone bromide)
Dosage Forms / Strength	12 mg/0.6 mL solution for subcutaneous injection in a single-use vial
Therapeutic Class	Mu-opioid receptor antagonist
Proposed Indication(s)	Treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.
Action/Recommended Action:	Approval

1. Introduction

This application is for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient with Relistor (methylnaltrexone bromide) subcutaneous injection.

This application was submitted on March 30, 2008. A Major Amendment dated December 7, 2007 was received which included significant information regarding the QT assessment. The PDUFA Goal date was extended by 3 months to April 30, 2008.

Progenics Pharmaceuticals, Inc. submitted two phase 3 studies (MNTX 301 and MNTX 302) that included randomized, double-blind, placebo-controlled periods, and one phase 2, ascending-dose study (MNTX 251) that included a randomized, double-blind, controlled period in support of efficacy of this drug. In each study, double-blind treatment was followed by a period of open-label MNTX treatment (ranging from three weeks to four months). Although the primary intent of open-label treatment with MNTX was to obtain long-term safety data, efficacy was also evaluated. These studies were conducted in patients with advanced illness in the US and one site in Canada.

Methylnaltrexone bromide is a selective antagonist of opioid binding at the mu-opioid receptor. As a quaternary amine, the ability of methylnaltrexone bromide to cross the blood-brain barrier is restricted. This allows methylnaltrexone bromide to function as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

2. Background

The prevalence of opioid-induced constipation (OIC) in patients with advanced medical illness is reported to be nearly 50%. At the present time, there are no FDA approved therapies that are directly targeted to treat the specific cause of OIC. Laxatives are used to treat OIC and work via mechanisms that are unrelated to opioids, i.e. bulk-forming laxatives, osmotically-acting laxatives, and stimulant laxatives). The long-term administration of opioids may be complicated by a number of adverse effects and the most prevalent of these is constipation. Even with the available laxatives, satisfactory relief of constipation is not obtained in many patients. Bulk-forming laxatives cause retention of fluid in colonic contents, thereby increasing bulk and softness and facilitating transit. Osmotically acting laxatives decrease net absorption of water and NaCl. Stimulant laxatives promote accumulation of water and electrolytes in the colonic lumen and increase intestinal motility.

Naltrexone hydrochloride was approved for the indication of alcohol dependence. The drug Suboxone contains naloxone HCl and buprenorphine HCl. Naloxone is also an antagonist at the μ -opioid receptor site. Buprenorphine is a partial agonist which binds at the μ -opioid receptor site and an antagonist at the κ -opioid receptor site. Suboxone is indicated for the treatment of opioid dependence.

Entereg (alvimopan), another investigational opioid antagonist for the treatment of postoperative ileus

- **Advisory Committee:** Relistor™ was not referred to an FDA advisory committee because the safety profile of the product did not pose unique concerns beyond those applicable to other opioid receptor antagonists that are approved and marketed in the U.S. In addition, the primary endpoint, rescue-free laxation response, was non-controversial, and Relistor™ was clearly superior to placebo. Therefore, the benefit-risk profile was favorable for the indicated patient population.

3. CMC

Relistor (methylnaltrexone bromide) Subcutaneous Injection, a peripherally-acting mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (R)-N-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is C₂₁H₂₆NO₄Br, and the molecular weight is 436.36. Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

The Chemistry reviewers concluded the following:

“Adequate data have been submitted to ensure the drug product’s identity, strength, quality, purity, potency, and stability as a subcutaneous product for its intended use. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance. At the completion of this review, labeling review among all disciplines has not taken place. Therefore, from a CMC standpoint, this new drug application may be approved pending resolution of minor labeling issue.”

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability drug substance and drug product. Final labeling was acceptable to the CMC reviewers. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

In animal studies, results were positive for QT prolongation. In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone bromide caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 µM concentrations, respectively). Methylnaltrexone bromide had a hERG IC₅₀ of > 1000 µM. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 µM) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous (SC) doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone bromide (up to 100 µM) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 µM) tested was about 186 and 373 times the human C_{max} at SC doses of 0.3 and 0.15 mg/kg, respectively. In anesthetized dogs, methylnaltrexone bromide caused decreases in blood pressure, heart rate, cardiac output, left ventricular pressure, left ventricular end diastolic pressure, and +dP/dt at ≥ 1 mg/kg. In conscious dogs, methylnaltrexone bromide caused a dose-related increase in QTc interval. After a single IV dosage of 20 mg/kg to beagle dogs, predicted C_{max} and AUC values were approximately 482 and 144 times, respectively, the exposure at human SC dose of 0.15 mg/kg

and 241 times and 66 times, respectively, the exposure at a human SC dose of 0.3 mg/kg. In conscious guinea pigs, methylnaltrexone caused mild prolongation of QTc (4% over baseline) at 20 mg/kg, IV. A thorough QTc assessment was conducted in humans (see section 5).

Long-term carcinogenesis studies in animals have not been performed. Tests for mutagenesis were negative including the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 81 times the recommended maximum human subcutaneous dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats. This supports the Pregnancy Category B classification.

The reviewers recommended approval of Methylnaltrexone for the use in adult patients receiving palliative care.

I concur with the conclusions reached by the pharmacology/toxicology reviewer, and that there are no outstanding preclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The animal data suggested the potential for prolongation of the EKG QT interval. In order to address this issue, the applicant submitted a study in humans. This initial study was deficient in that the positive control arm did not perform as expected in a number of areas. Thus, the question regarding the ability of methylnaltrexone to cause prolongation of the QT interval remained unresolved. Subsequently the sponsor submitted results of an IV methylnaltrexone study developed by their partner Wyeth to this NDA as a major amendment. This thorough QTc clinical study report and summary (3200L2-104 US) was submitted on December 7, 2007 and resulted in a 90 day clock extension in the PDUFA date for the application. The FDA IRT/QT team has reviewed the study report and concluded that this was a well conducted study which addressed the issue. The following is a quote from that review.

“No significant effect of methylnaltrexone was detected in this ‘thorough QT’ study. The largest upper limits of the two-sided 90% CI for the mean difference between the two doses of methylnaltrexone (0.3 mg/kg and 0.64 mg/kg IV infusion) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.”

“The study was a single-center, randomized, double-blind, placebo- and moxifloxacin- (open label) controlled 4-period crossover study in which 56 healthy subjects were administered 0.3 mg/kg, methylnaltrexone 0.64 mg/kg, placebo as a single 20-minute IV infusion. Subjects also received a single oral dose of moxifloxacin 400-mg. Overall findings are summarized in the following table.”

FDA Analysis: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for MOA-728 (0.3 mg/kg and 0.64 mg/kg) and the Largest Lower Bound for Moxifloxacin

Treatment	Time (hour)	$\Delta\Delta\text{QTcN}$ (ms)	90% CI (ms)
MOA-728 0.30 mg/kg	0.67	0.05	(-1.8, 1.9)
MOA-728 0.64 mg/kg	2	0.8	(-1.1, 2.6)
Moxifloxacin*	2	9.4	(6.7, 12.0)

* Multiple time points are adjusted with 3 post-baseline time points.

“The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcN$ for moxifloxacin was greater than 5 ms indicating that the study was adequately designed and conducted to detect an effect on the QT interval.”

The methylnaltrexone doses evaluated in this study are acceptable. The mean peak plasma concentration from the suprathreshold dose (0.64 mg/kg IV) is 9-fold and 2.3-fold greater than those observed from the SC therapeutic dose (0.15 mg/kg SC) and IV therapeutic dose (24 mg). There are no known intrinsic or extrinsic factors that can increase exposure to methylnaltrexone greater than what was observed following the suprathreshold IV dose.

The applicant recommended reducing the dose by one-half in patients with severe renal impairment (creatinine clearance less than 30 mL/min). In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8-to 9-fold and resulted in a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

In *in vitro* drug metabolism studies methylnaltrexone bromide did not significantly inhibit the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2C9, CYP2C19 or CYP3A4, while it is a weak inhibitor of CYP2D6. In a clinical drug interaction study in healthy adult male subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone bromide did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

The clinical pharmacology review team concluded that with the successful closure of the QT issue, there are no outstanding issues from a clinical pharmacology standpoint for this NDA.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer regarding labeling and that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The product reviewers found the manufacturing process results in a sterile product acceptable for subcutaneous injection.

7. Clinical/Statistical-Efficacy

Both the Clinical and Statistical review teams found the efficacy data supported the proposed indication and recommended approval.

I agree with the reviewers' conclusions and recommendation.

The efficacy and safety of Relistor in the treatment of opioid-induced constipation in advanced illness patients receiving palliative care was demonstrated in two randomized, double blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51% were females. In both studies, patients had advanced illness with a life expectancy of less than 6 months and received care to control their symptoms. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other

advanced illnesses. Prior to screening, patients had been receiving palliative opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid induced constipation (either <3 bowel movements in the preceding week or no bowel movement for >2 days). Patients were on a stable opioid regimen ≥ 3 days prior to randomization (not including PRN or rescue pain medication) and received their opioid medication during the study as clinically needed. Patients maintained their regular laxative regimen for at least 3 days prior to study entry, and throughout the study. Rescue laxatives were prohibited from 4 hours before to 4 hours after taking an injection of study medication

Study 301 compared a single, double-blind, subcutaneous dose of Relistor 0.15 mg/kg, or Relistor 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label 4 week dosing period, where Relistor could be used as needed, no more frequently than 1 dose in a 24 hour period. Throughout both study periods, patients maintained their regular laxative regimen. A total of 154 patients (47 Relistor 0.15 mg/kg, 55 Relistor 0.3 mg/kg, 52 placebo) were enrolled and treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medication. Relistor-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo treated patients (14%); $p < 0.0001$ for each dose versus placebo.

Study 302 compared double-blind, subcutaneous doses of Relistor given every other day for 2 weeks versus placebo. Patients received opioid medication ≥ 2 weeks prior to receiving study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg Relistor or placebo. In the second week the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the patient's assigned dose could be reduced based on tolerability. Data from 133 (62 Relistor, 71 placebo) patients were analyzed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medication and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of study medication. Relistor-treated patients had a higher rate of laxation within 4 hours of the first dose (48%) than placebo-treated patients (16%); $p < 0.0001$. Relistor-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52%) than did placebo-treated patients (9%); $p < 0.0001$. In both studies, in approximately 30% of patients, laxation was reported within 30 minutes of a dose of Relistor.

In both studies, there was no evidence of differential effects of age or gender on safety or efficacy. No meaningful subgroup analysis could be conducted on race because the study population was predominantly Caucasian (88%). The rates of discontinuation due to adverse events during the double blind placebo controlled clinical trials (Study 1 and Study 2) were comparable between Relistor (1.2%) and placebo (2.4%).

The efficacy and safety of methylnaltrexone bromide was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 1, and in two open-label extension studies (Study 301 EXT and Study 302 EXT) in which Relistor was given as needed for up to 4 months. During open-label treatment, patients maintained their regular laxative regimen. A total of 136, 21, and 82 patients received at least 1 open-label dose in studies 1, 301 EXT, and 302 EXT, respectively. Laxation response rates observed during double-blind treatment with RELISTOR were maintained over the course of 3 to 4 months of open-label treatment.

There was no relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients in these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either Relistor-treated patients or in placebo treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

8. Safety

The total safety data base from the studies conducted by the Applicant is 286 patients and 144 volunteers who received SC MNTX. Of the 286 patients who took MNTX, 225 had a primary diagnosis of cancer, 174 had renal dysfunction, 120 had CNS disease, 54 had heart failure, and 60 had COPD.

The longest study submitted to this NDA was MNTX 301/301EXT in which SC MNTX was given for up to four months.

A review of deaths for patients receiving Relistor and with advanced illness is difficult to interpret given the nature of the underlying illnesses. The applicant reported the following findings. A total of 159 deaths were reported among patients who participated in the clinical studies. A total of 41 deaths occurred during double-blind treatment (23 on MNTX and 18 on placebo), one death occurred in a placebo-treated patient who entered an open-label phase but did not receive MNTX, and an additional 117 deaths occurred during open-label MNTX treatment (two patients died after the study period and 12 patients died more than 30 days after the last dose of study drug was administered).

No healthy volunteer or other subject in a phase 1 study died. In the phase 2 and phase 3 studies submitted for review, only one death was reported as being related to MNTX therapy.

Of the 140 MNTX treated patients who died, the reported cause of death were the underlying disease or a complication relating to the underlying disease except in one case.

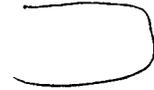
The medical officer concluded the following regarding the safety of Relistor.

“The one reported study death that was probably related to MNTX therapy was due to dehydration and diarrhea. The patient’s underlying terminal breast cancer however may have played a confounding role.”

“The incidence of non-fatal, serious adverse events was lower in the MNTX arm than in the placebo arm. Most of these adverse events were related to the gastrointestinal system and, more specifically, most were probably related to MNTX effects on the obstipated colon.”

“Four of the five most common adverse events in the MNTX Pool (abdominal pain, nausea, vomiting and flatulence) were also related to the gastrointestinal tract. The fifth event was malignant neoplasm progression which was not unexpected in this patient population.”

“Among the MNTX treated patients there were no clinically significant changes over time with respect to liver function, renal function or hematologic test results. The only laboratory parameter associated with MNTX use was a mild lymphopenia that was present in 20/199 (10.1%) of the patients. The mean changes in absolute lymphocyte counts were small (-0.1 x 10⁹/L). The clinical significance of this change is uncertain.”



- **Final labeling recommendations:**
 - **CONTRAINDICATIONS:** RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.
 - **WARNINGS AND PRECAUTIONS:** If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.
- **REMS/RiskMAPs :**
None were recommended.

9. Pediatrics

Safety and efficacy of RELISTOR have not been established in pediatric patients.

Studies in pediatric patients birth to 5 years of age are waived due to the small numbers of patients available and the impracticability of conducting such studies in order to obtain meaningful information. Studies in pediatric patients > 5 years to 17 years of age are deferred because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The study "A Multicenter, Open-label, Multistage Single and Multiple Dose Study of the Pharmacokinetics and Safety of Subcutaneous Methylnaltrexone Bromide in Children and Adolescents Aged 5 through 17 Years with Opioid Induced Constipation and Advanced Illness Receiving Care that is Primarily Palliative". The waiver/deferral requests and above pediatric study plan were presented to Pediatric Review Committee (PeRC) on March 19, 2008 and the PeRC generally concurred this plan.

The deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required pediatric postmarketing study. The status of these required postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA.

10. Other Relevant Regulatory Issues

- **DSI Audits:**
The clinical audits of four clinical sites revealed minor violations and the DSI summary states the following:
"The violations listed above, some of them due to the nature of the study being studied in terminally ill patients, would not affect the validity and acceptability of the data in support of this NDA."
- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** a formal consult was not obtained, but brief discussions were held regarding technical aspects of the PLR and its application to this label.

"There are no other unresolved relevant regulatory issues"

11. Labeling

- **Physician labeling:**

DMEP recommended deleting subcutaneous from the name; however, the medical review team felt that it was important to make the distinction so that this drug was not injected intravenously. Therefore, the Medical team recommended retaining the following name: Relistor™ (methylnaltrexone bromide) Subcutaneous Injection. The name Relistor™ was acceptable to DMEP, as well as the Division of Gastroenterology Products.

The indication is for short term use in patients who are terminally ill. Therefore, it is important to note that the risk benefit evaluation was based upon this specific indication: “RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.” With specific wording regarding the fact that the “Use of RELISTOR beyond four months has not been studied.”

- **Carton and immediate container labels:**

Recommendations from DMEP regarding the carton and container labeling was sent to the sponsor. Only, departure was the recommendation for the name (see above).

- **Patient labeling/Medication guide:**

Section 17 of the label, PATIENT COUNSELING INFORMATION, includes information regarding how to prepare the injection and administer it subcutaneously. In addition there is Patient Package Insert information. The Medical Review Team agreed with retaining this information as helpful to the patient, but not required for safe use. Therefore it is NOT deemed a Medication Guide and as such is not subject to FDAAA.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend approval of this supplement with the agreed upon labeling changes for the agreed upon indication. This is agreement with review team recommendations.
 - **Risk Benefit Assessment:**
Given the second-line nature of the indication, for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient, and the patient population for which it is intended, the risk benefit profile is acceptable for short term use of Relistor.
 - **Recommendation for Postmarketing Risk Management Activities:**
None are recommended
 - **Recommendation for other Postmarketing Study Requirements or Commitments**
None are recommended
-

Material Reviewed/Consulted: OND Action Package	Reviewer
Medical Officer Review	R. Orleans (3/6/08)
Medical Team Leader Review	R. He (3/28/2008)
Statistical Review	K. Dwyer (3/7/2008)
Pharmacology Toxicology Review	T. Chakraborti (11/29/2007)
Clinical Pharmacology Review	I. Kim (12/12/07, 3/11/08)
CMC Review	J. Chang (February 4, 2008) B. Fraser (February 5, 2008) V. Pawar (11/30/07, micro)
Intredisciplinary Review for QT Studies	S. Grant, C Garnett, J. Zhang, K.Dwyer (8/28/07)
DSI Clinical Site Inspection summary	C. Lewin, K. Malek (12/3/08)
OSE/Division of Risk Management Review	S. Mills (4/4/2008)
OSE/Division of Medication Error Prevention Review	T. Turner (April 11, 2008, March 28, 2008)

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

SEALD=Study Endpoints and Label Development Division

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/s/

Joyce Korvick
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