CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-964

OFFICE DIRECTOR MEMO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 24, 2008

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 21-964 Relistor (methylnaltrexone bromide) Subcutaneous Injection; Progenics Pharmaceuticals, Inc.

Summary

Relistor (methylnaltrexone bromide) Subcutaneous Injection is a mu-opioid receptor antagonist that has been evaluated in patients with advanced illness experiencing opioid-induced constipation. Relistor is a quarternary derivative of naltrexone, which is approved for the treatment of alcohol dependence. Naltrexone is marketed as Revia and as Vivitrol, as oral and intramuscular formulations, respectively. The addition of a methyl group to naltrexone forms a compound that is less lipid soluble and, therefore, less likely to cross the blood-brain barrier. Thus, Relistor has the potential to block undesired peripherally-mediated side effects of opioids in the gastrointestinal tract without affecting their centrally-mediated analgesic effects. Relistor was investigated in patients with advanced illness (cancer, HIV/AIDS, Alzheimer's, late stage pulmonary or cardiac disease) who did not obtain satisfactory relief from available laxatives for their opioid-induced constipation. The subcutaneous route of administration was selected to provide a more rapid and predictable onset of action compared to available alternatives.

This memo documents my concurrence with the Division of Gastroenterology Product's recommendation for the approval of Relistor 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. Use of Relistor beyond four months has not been studied.

Dosing

Relistor is administered by subcutaneous injection. The recommended dose of Relistor is weight-based: 8 mg for patients who weigh between 38 and 62 kg, and 12 mg for patients who weigh between 62 and 114 kg. Patients outside of these weight ranges will be dosed at 0.15 mg/kg. A dose reduction by one-half is recommended for patients with severe renal impairment. The recommended dosing schedule is one dose every other day, as needed. Dosing should not exceed more than one dose in a 24 hour period.

Regulatory History

NDA 21-964 was submitted on March 30, 2007 and was granted a standard review. A clinical trial evaluating the effects of Relistor on cardiac repolarization was submitted at FDA's request on December 7, 2007. This submission was considered a major amendment and triggered a three-month clock extension. The PDUFA goal date was extended to April 30, 2008.

This application was not referred to an FDA advisory committee for the following reasons. Relistor is a member of the class of previously approved opioid receptor antagonists marketed in the US, and it did not pose unique concerns beyond those applicable to other opioid receptor antagonists.

Efficacy

The efficacy of Relistor was evaluated in patients with advanced illness and a life expectancy of 6 months or less enrolled in two multicenter, randomized, double-blind, placebo-controlled clinical trials and in one randomized, double-blind, dose-ranging phase 2 trial. The duration of double-blind treatment in these trials was brief: one day (one dose), two weeks (7 doses), and one week (3 doses), respectively. Open-label treatment with Relistor following completion of the double-blind period in these trials was permitted but did not exceed 4 months.

Results from these studies demonstrated that the 0.15 mg/kg and 0.30 mg/kg doses of Relistor administered subcutaneously were both more effective than placebo in the treatment of opioid-induced constipation when assessed in terms of rescue-free laxation response within 4 hours of dosing. When the results of the double-blind phases of the two phase 3 trials are pooled, 54% of Relistor-treated patients (n=109, 0.15mg/kg) reported a positive rescue-free laxation response within four hours of dosing as compared to 15% of placebo-treated patients (n= 123). Fifty-five patients administered the 0.30 mg/kg dose experienced a similar laxation response as those administered the 0.15 mg/kg dose. In both studies, in approximately 30% of patients, laxation in Relistor-treated patients was reported within 30 minutes of dosing consistent with the drug's C_{max} of 0.5 hours.

Other measures of laxation, including laxation response within 24 hours after the first dose and laxation after two of the first four double-blind doses, also showed a consistent advantage for Relistor over placebo. Durability of response to Relistor was observed in the double-blind and open-label portions of these trials.

Safety

The safety profile of Relistor at recommended doses administered subcutaneously no more than once daily appears acceptable. In the submitted trials, a total of 286 patients received at least one dose of Relistor. As might be anticipated from a patient population with advanced illness, clinical worsening or death related to the underlying disease process was noted in many patients. Only one death was thought to be related to study drug in a patient with metastatic breast cancer who developed severe diarrhea, dehydration and cardiovascular collapse.

Serious non-fatal gastrointestinal adverse events were reported in 4.9% of Relistor-treated patients as compared to 2.4% of placebo-treated patients. Serious adverse events on Relistor included nausea, vomiting, abdominal pain, constipation, ileus, and diarrhea. The WARNINGS AND PRECAUTIONS section of the label advises that patients experiencing severe or persistent diarrhea during treatment should not continue therapy and consult their physician. Use of Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Use of Relistor has not been studied in patients with peritoneal catheters.

Overall, the most common adverse events in Relistor-treated patients were referable to the gastrointestinal tract; this is not unexpected for a drug that increases bowel motility.

Severe renal impairment was found to decrease the renal clearance of methylnaltrexone bromide by 8- to 9-fold and to increase the AUC by 2-fold. No change in C_{max} was noted. A dose reduction by one-half is recommended for patients with severe renal impairment (i.e., creatinine clearance < 30 mL/min).

Mild to moderate hepatic impairment was not shown to affect the AUC or C_{max} of methylnaltrexone bromide. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone bromide has not been studied.

Use of Relistor did not appear to interfere with opioid analgesic effects or to result in opioid antagonism centrally.

Relistor was found to have concentration-dependent effects on hERG current *in vitro*, and caused dose-related increases in QTc interval in conscious dogs. A trial in 207 healthy volunteers contained in the

original NDA submission was deemed inconclusive with respect to assay sensitivity. FDA requested and received results from a second clinical trial, a randomized, double-blind, placebo- and moxifloxacin-controlled crossover trial, in 56 healthy volunteers. This trial demonstrated no effect on the QT/QTc interval in subjects receiving Relistor doses of either 0.3 mg/kg or 0.64 mg/kg.

Tradename Review

The tradename "Relistor" [redacted] has been found acceptable.

Labeling

Product labeling will include a Patient Package Insert that provides instructions for preparing and administering subcutaneous injections of the product.

Postmarketing Requirements under PREA

We are waiving the pediatric requirement for ages 0 months to up to 5 years because necessary studies are impossible or highly impracticable in that age group. In addition, we are deferring submission of pediatric studies for ages 5 to 17 years because this product is ready for approval for use in adults and the pediatric studies have not been completed.

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 this required postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This requirement is listed below.

1. Conduct a pharmacokinetics and safety study of Relistor in pediatric patients ages 5 to 17 years with opioid induced constipation and advanced illness receiving palliative care.

Postmarketing Requirements under 505(o)

The Division has determined, and I concur, that analysis of postmarketing adverse events reports will be sufficient to address known serious risks, signals of serious risks, or unexpected serious risks that, based on available data, have the potential to occur with Relistor. No postmarketing studies or clinical trials have been agreed to, or will be required under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

Julie Beitz, MD
Office Director,
Office of Drug Evaluation III
CDER, FDA

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/s/

Julie Beitz
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DIRECTOR