

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125196

SUMMARY REVIEW

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ANTIMICROBIAL PRODUCTS
DIVISION OF ANTIVIRAL PRODUCTS

BLA: 125196/0
PRODUCT: PegIntron/REBETOL Combo Pack (peginterferon alfa-2b and ribavirin)
SPONSOR: Schering Corporation
REVIEWER: Scott Proestel, M.D.
DATE: 04-30-2008

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity.

We are aware of safety information associated with PegIntron, indicating that there are cases of cerebrovascular complications due to stroke in patients with few or not expected risk factors for stroke. After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of the PegIntron/REBETOL Combo Pack outweigh the risks.

- A. The number of patients chronically infected with hepatitis C virus (HCV) in the United States, and therefore potentially eligible for combination therapy with PegIntron and REBETOL, is estimated at greater than 2.7 million.
- B. PegIntron and REBETOL combination therapy is approved to treat chronic infection with HCV, a serious medical condition. Complications of chronic infection with HCV can include cirrhosis, hepatocellular carcinoma, and hepatic failure. These complications, when they arise, frequently necessitate inpatient hospitalization and may lead to liver transplantation or death.
- C. Use of PegIntron and REBETOL combination therapy has been shown to lead to long term undetectable blood levels of HCV, which may lead to a decrease in the

complications associated with chronic HCV infection or slow progression of liver disease.

- D. The expected duration of therapy with PegIntron and REBETOL is up to 48 weeks.
- E. Known serious risks associated with the use of interferon alphas such as PegIntron include fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Serious risks associated with Rebetol include hemolytic anemia, worsening of cardiac disease due to anemia, and teratogenicity.
- F. The term new molecular entity (NME) is generally not used with respect to biologics. Nevertheless, we have considered the fact that PegIntron is a member of the class of therapeutics known as interferon alphas. Rebetol is a member of the class of therapeutics known as nucleoside analogs. The use of PegIntron in combination with Rebetol (not co-packaged) for the treatment of chronic HCV was approved on August 7, 2001.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Under 21 CFR Part 208, the sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed the PegIntron/REBETOL Combo Pack. Pursuant to 21 CFR Part 208, FDA has determined that the PegIntron/REBETOL Combo Pack is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use the PegIntron/REBETOL Combo Pack. In addition, patient labeling could help prevent serious adverse events. A timetable for submission of assessments of the REMS is also required, and shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved.

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.



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