CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125196

MEDICAL REVIEW(S)

CLINICAL REVIEW

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

BLA/S:	125196/0
RECEIVED:	07-03-2006
PRODUCT:	PegIntron (peginterferon alfa-2b) and Rebetol (ribavirin)
SPONSOR:	Schering Corporation
REVIEWER:	Scott Proestel, M.D.
REVIEW DATE:	05-01-2008

Summary

This submission requested co-packaging of PegIntron and Rebetol for the treatment of patients with chronic hepatitis C, using the proprietary name [redacted] Additionally, the proposed label includes clinical efficacy and safety data from a different supplement, BLA/S 103949/5123.

A consult was obtained from the Division of Medication Errors and Technical Support (DMETS) on August 21, 2006, regarding the proposed name [redacted] DMETS objected to this name as it [redacted]. The Applicant subsequently proposed the name "PegIntron/Rebetol Combo Pack." On January 12, 2007, DMETS determined that while the proposed name is long and could result in abbreviations to fit prescribing and dispensing systems, it was acceptable from a promotional perspective.

While no clinical data was submitted in the current supplement, the proposed label included the Applicant's requested revisions based on efficacy supplement 103949/5123. That supplement provided weight-based dosing of Rebetol and a shorter duration of treatment (24 weeks) for patients with HCV genotype 2 or 3. Review of that supplement was delayed due to instances of underreporting of serum HCV RNA levels for the clinical trial. In a letter dated March 2, 2007, the Applicant was informed that the supplement review could not continue because of inadequate data to take an action in light of the assay problem. The Applicant took remedial action that included re-assaying the samples and re-analyzing the study efficacy results. The supplement was resubmitted September 25, 2007, and the revised HCV RNA data did not have a substantive impact on the efficacy findings. BLA/S 103949/5123 was subsequently approved on March 26, 2008. As BLA 125196 proposed a label that incorporated clinical data from the delayed efficacy supplement, review of BLA 125196 was also delayed.

With respect to labeling format, FDA provided the Applicant with faxed comments on January 12, 2007, regarding issues with their proposed revisions to the package insert, carton, and medication guide. Recommendations included the need to use terms that are

less likely to be confused ("mcg" instead of "μg," and "daily" instead of "QD"), the appropriate use of bolded font and capitalization, and the need to use terms such as "adverse reactions" instead of "adverse events." Appropriate labeling revisions based on these comments have been submitted by the Applicant.

Due to the Food and Drug Administration Amendments Act of 2007, FDA now requires submission of a Risk Evaluation and Mitigation Strategy (REMS) for an approved drug if a determination is made that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. As one element of a REMS, FDA has determined that a Medication Guide is required for distribution with the PegIntron/Rebetol Combo Pack. 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.

Information needed for assessment of the REMS should include:

a. Survey of patients' understanding of the serious risks of Intron A
b. Report on periodic assessments of the distribution and dispensing of the Medication Guide
c. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Conclusions

In light of the fact that PegIntron and Rebetol are intended to be used in combination for the treatment of chronic hepatitis C, co-packaging is appropriate. Based on the results of the DMETS consult, the proposed proprietary name of "PegIntron/Rebetol Combo Pack" is acceptable. The clinical safety and efficacy data from BLA/S 103949/5123 have already been incorporated into the PegIntron label, and should be used for the PegIntron/Rebetol Combo Pack label.

Recommendation

Approval of this supplement is recommended. The REMS requirements will be provided to the Sponsor.