CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-903/S-008, S-011, S-012, S-016

MEDICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service
Food and Drug Administration
Rockville, MD 20857

DATE: **July 25, 2001**

TO: **NDA 20-903/Rebetron™ Combination Therapy**

FROM: **Russell Fleischer, PA-C, MPH**
Senior Clinical Analyst, DAVDP

Therese Cvetkovich, MD
Medical Team Leader, DAVDP

THROUGH: **Debra Birnkrant, MD**
Acting Director, DAVDP

RE: **Medical Review of Request to Provide a Stand-Alone Package of Rebetol® (ribavirin) (SLR-008)**

Background

In this SLR, Schering Corporation (the Applicant) submitted a request to market a stand-alone 84 capsule container of Rebetol® (ribavirin). Rebetron™ Combination Therapy (Rebetol and Intron A) was approved in June 1998 for treatment of adults with chronic HCV infection who had responded to a previous course of interferon monotherapy but subsequently relapsed. In December 1998, the combination was approved for treatment of therapy-naïve patients.

At the time of initial approval, the Applicant requested that Rebetol and Intron A be co-packaged. The Applicant cited various safety reasons for not providing Rebetol in a stand-alone package. It was the Division's position that Rebetol could be appropriately labeled and provided in its own container. However, the Office of Chief Counsel advised us that there was no regulatory basis that would preclude co-packaging. Therefore, nine package configurations of Rebetron were approved.

The Applicant now proposes to market a stand-alone 84 capsule container of ribavirin 200-mg capsules, along with appropriate labeling. The Applicant has stated that all currently approved package configurations of the Rebetron Combination Therapy would remain on the market (see November 7, 2000 letter from Schering to DAVDP).

The Applicant was asked to provide safety data that would support the proposed stand-alone package of Rebetol. The Applicant was asked to address the specific safety concerns that they had outlined to support co-packaging of Rebetol and Intron A. These included, potential safety problems associated with monotherapy use of Rebetol and the safety of Rebetol when used with interferons other than Intron A. The Division consulted

The Office of Postmarketing Drug Risk Assessment (OPDRA) of the Center for Drug Evaluation and Research to evaluate the same concerns as raised by the Applicant.

Data Review

Safety of Monotherapy Use

In September 1998, the Applicant raised a concern that it would be inappropriate to market ribavirin alone because it might encourage monotherapy use in HCV-infected patients, a use for which it was not effective. To this end, the following statement was included in the Rebetron label: "REBETOL Capsule monotherapy is not effective for the treatment of chronic hepatitis C and should not be used for this indication."

The Applicant reviewed their Drug Safety Surveillance database for oral ribavirin monotherapy use between May 1999 and March 2001. According to Schering, the data demonstrate minimal use of oral ribavirin monotherapy in the US for either treatment of chronic hepatitis C virus infection; and virtually no monotherapy use for other indications. Schering identified 13 US reports of serious adverse events among persons who reported use of oral ribavirin monotherapy: six involved accidental ingestion but did not report any adverse events, one female treated for influenza became pregnant, two females being treated for chronic HCV became pregnant, one female in a pharmacology study experienced a miscarriage, one male enrolled in a pharmacology study experienced pneumonia, one female treated for lupus experienced gastrointestinal symptoms and dizziness, and one patient treated for an unknown indication experienced cough.

Finally, Schering submitted a literature search to identify monotherapy use of ribavirin. The search identified a few articles in which ribavirin was used as monotherapy in post-liver transplant patients, the results of which demonstrated no benefit and no new or different issues of safety beyond what is currently known for ribavirin.

The OPDRA consult supported the Applicant's assessment and conclusions and determined, based on data available to the Agency, that it does not appear that oral ribavirin is being used as monotherapy to any great degree. Further, OPDRA concluded that there does not appear to be any new or specific safety issues associated with the few cases of oral ribavirin monotherapy that were identified.

Safety of Use with Other Interferons

Another of the Applicant's concerns was that the availability of ribavirin outside of being co-packaged with Intron A might encourage use for other infections for which ribavirin was not approved. The Applicant was also concerned that the separate availability of ribavirin might encourage use with interferons other than Intron A since there was no data to support such use. It was the Applicant's position that all interferons are not interchangeable and that use of oral ribavirin with other interferons might raise significant safety concerns.

The Applicant submitted and reviewed copies of several meeting abstracts describing use of oral ribavirin with other interferons. The available safety data did not appear to be substantially different than that which is seen with the Rebetol/Intron A combination. The Applicant also conducted a comprehensive search of the MEDLINE, Scholar, and ICON databases for publications in which ribavirin was administered in combination with interferons other than Intron A, e.g., interferon alpha-2a, consensus interferon, natural leukocyte interferon, or interferon alpha-n3. The searches spanned the years between 1995 and early 2001. The citations were reviewed. For those that included safety information, reported adverse events appeared to be consistent with the known toxicity profile of ribavirin. There did not appear to be any new or different adverse events reported when ribavirin was used with other interferons.

Assessment and Recommended Regulatory Action

Analysis of the data supplied by the Applicant demonstrates no apparent safety concerns that would preclude the provision of a stand-alone package of Rebetol. The OPDRA review also appears to confirm this conclusion. The label and Medication Guide provide all relative cautionary information about the appropriate use of Rebetol. Therefore, this supplement to provide a stand-alone package of Rebetol should be approved.

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/s/

Russell Fleischer
7/26/01 10:00:18 AM
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7/26/01 10:12:56 AM
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Debra Birnkrant
7/26/01 10:46:33 AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

DATE: July 23, 2001

TO: NDA 20-903 (Rebetron™ Combination Therapy)

FROM: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVDP

THROUGH: Therese Cvetkovich, MD
Medical Team Leader, DAVDP

RE: Medical Review of Labeling Supplement-Revisions to the Multidose Pen Medication Guide (SLR-011)

Background

Schering Corporation submitted this labeling supplement to revise the Medication Guide for the Intron® A multidose pen injector to provide instructions to patients about the correct method for using the pen. This revision was prompted by consumer complaints of pink tinged solution remaining in the pen following injection. The pink tinge was determined to be likely due to blood that had entered the syringe. Schering proposed to revise the patient information to instruct patients to pinch a 2-inch fold of skin, hold the pen at a 45° angle, to release the push button slowly after injection, and to contact their physician/pharmacist if blood comes into the syringe.

Assessment and Recommended Regulatory Action

No issues of clinical concern were identified in this review. The revised instructions to patients for administration of Intron A appear reasonable. Therefore, this labeling supplement should be approved.

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/s/

Russell Fleischer
7/24/01 07:21:42 AM
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Labeling supplement to revise the multidose pen Med Guide

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8/2/01 03:10:28 PM
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8/7/01 02:32:33 PM
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