CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-903/S-020

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903\S-020

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products Support
Worldwide Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring:

We acknowledge receipt of your June 28, 2002 submission containing final printed labeling in response to our March 6, 2002 letter approving your supplemental new drug application for REBETOL® (ribavirin) capsules for use in combination with the approved biologic product Intron®A (interferon alfa-2b) (REBETRON COMBINATION THERAPY™), and PEG-Intron® (peg-interferon alfa-2b) powder for injection.

We have reviewed the labeling that you submitted in accordance with our March 6, 2002 letter and we find it acceptable.

If you have any questions, call Nitin Patel, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeffrey Murray
6/25/03 05:20:47 PM

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Memorandum of Project Manager's Review: Final Printed Labeling

Date of Review: June 13, 2003

NDA Number: 20-903/S-020

Date of Submission: June 28, 2002

Applicant: The Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Product Name: REBETOL® (ribavirin) capsules
REBETRON COMBINATION THERAPY™, SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin.

Materials Reviewed: June 28, 2002 Final Printed Labeling (FPL)
September 27, 2001 draft labeling
March 6, 2002 approval letter

Background:

This Final Printed Labeling reflects the changes made to the REBETOL® (ribavirin) capsules label regarding its co-administration with PEG-Intron® for the treatment of patients with chronic hepatitis C virus infection, as approved by the Division of Antiviral Drug Products on March 6, 2002. The rationale behind these revisions was to provide consistency between the REBETOL® label and the recently approved PEG-Intron® label.

Summary of Review

The package insert and patient package insert submitted electronically on June 28, 2002 are identical to the September 27, 2001 draft package insert and patient package insert.

An acknowledge and retain letter will be issued to the applicant.

Nitin Patel, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Attachments: June 28, 2002 Final Printed Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nitin Patel
6/23/03 03:23:31 PM
CSO
CSO Labeling Review for NDA 20-903/S-020; PEG-Intron wording
CSO Labeling Review for NDA 20-903/S-020; PEG-Intron wording; Hard copy sign-off by Tony DeCicco - 6/17/03.

Tony DeCicco
7/9/03 09:59:57 AM
CSO

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-903/S-020

PRIOR APPROVAL SUPPLEMENT

Schering Corporation
Attention: Mary Jane Nehring
Senior Director, Marketed Products Support
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Ms. Nehring,

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	REBETOL® (ribavirin) capsules for use in combination with the approved biologic product Intron®A (interferon alfa 2b) (Rebetron Combination Therapy™).
NDA Number:	20-903
Supplement number:	S-020
Date of supplement:	August 13, 2001
Date of receipt:	August 14, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on OCTOBER 13, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room # N115
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, please call Destry M. Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products, HFD-530
Office of Drug Evaluation IV
Center for Drug

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tony DeCicco
1/22/02 02:56:15 PM

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Consumer Safety Officer Labeling Review

NDA: 20-903/S-020

Date submitted: August 13, 2001

Sponsor: The Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

Products: REBETOL® (ribavirin) capsules
REBETRON COMBINATION THERAPY™, SCH 30500 - Intron® A (Interferon alfa-2b, recombinant) for Injection/ SCH 18908 - Ribavirin.

Materials Reviewed: Draft Labeling dated August 13, 2001, and September 27, 2001
Medical Officer's review dated October 15, 2001

Background:

The labeling supplement (SLR) S-020 for NDA 20-903, submitted August 13, 2001, proposes to include information in the REBETOL® (ribavirin) label regarding its co-administration with PegIntron® for the treatment of patients with chronic hepatitis C virus infection. The rationale behind these proposed revisions was to provide consistency between the Rebetol label and the recently approved Peg-Intron® label.

Label Revisions: Package Insert

1. Replacement of the word "six" with the number "6" in the **Boxed Warning**.

2. Deletion of the term "*Ribavirin/Interferon alfa-2b, recombinant*" in the Mechanism of Action section.

3. Deletion of the term "REBETOL and INTRON A" in the Mechanism of Action section, and replacement with the following:

   interferon products

4. Insertion of the words "with REBETOL and INTRON A" in the **CLINICAL PHARMACOLOGY**, *Effect of Food on Absorption of Ribavirin* section, third sentence.

5. Insertion of the following sentence at the end of the **CLINICAL PHARMACOLOGY**, *Effect of Food on Absorption of Ribavirin* section:

During clinical studies with REBETOL/PEG-INTRON, all subjects were instructed to take REBETOL Capsules with food.

6. Elimination of all such terms "Trademark of Johnson & Johnson Merck Consumer Pharmaceuticals Co."

7. Insertion of the following paragraph in the **INDICATIONS AND USAGE**, section, second paragraph:

   REBETOL Capsules are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

8. Insertion of the following words in the **INDICATIONS AND USAGE**, section, third paragraph, following the term "INTRON A:"

   or PEG-INTRON products

9. Insertion of the following header in the **INDICATIONS AND USAGE, Description of Clinical Studies section**

   REBETOL/INTRON A Combination Therapy

10. Insertion of the following sections in the **INDICATIONS AND USAGE**, section,

    REBETOL/PEG-INTRON Combination Therapy

    A randomized study compared treatment with two PEG-INTRON/REBETOL regimens [PEG-INTRON 1.5 µg/kg SC once weekly (QW)/REBETOL 800 mg PO daily (in divided doses); PEG-INTRON 1.5 µg/kg SC QW for 4 weeks then 0.5 µg/kg SC QW for 44 weeks/REBETOL 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/REBETOL 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible patients had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

    Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (See **Table 4**).

    Table 4. Rates of Response to Combination Treatment

	PEG-INTRON 1.5µg/kg QW REBETOL 800 mg QD	INTRON A 3 MIU TIW REBETOL 1000/1200mg QD
Overall [1,2] response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75%(123/163)	73% (119/162)

[1]Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
[2] Difference in overall treatment response (PEG-INTRON/REBETOL vs. INTRON A/REBETOL) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

The response rate to PEG-INTRON 1.5→0.5µg/kg/REBETOL was essentially the same as the response to INTRON A/REBETOL (data not shown).

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-INTRON (1.5 µg/kg)/REBETOL combination therapy compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/REBETOL combination therapy.

Patients with lower body weight tended to have higher adverse event rates (see **ADVERSE REACTIONS**) and higher response rates than patients with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PEG-INTRON/REBETOL combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 68% of patients. Compared to baseline approximately 2/3 of patients in all treatment groups were observed to have a modest reduction in inflammation.

11. Insertion of the following sentence at the end of the **CONTRAINDICATIONS**, **Pregnancy** section, previously seen in the **WARNINGS** section:

    Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia) should not be treated with REBETOL Capsules.

12. Insertion of the following words in the **WARNINGS** sections, first two paragraphs (see *italicized* wording for changes. Wording not italicized in action package insert):

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, REBETOL Capsules must not be used alone. The safety and efficacy of REBETOL Capsules have only been established when used together with INTRON A (interferon alfa-2b, recombinant) as REBETRON Combination Therapy *or with PEG-INTRON Injection.*

There are significant adverse events caused by REBETOL/INTRON A *or PEG-INTRON therapy*, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, *autoimmune and infectious disorders*, pulmonary dysfunction, pancreatitis, and diabetes. The REBETRON Combination Therapy *and PEG-INTRON* package inserts should be reviewed in *their* entirety prior to initiation of combination treatment for additional safety information.

13. Removal of the following two paragraphs from the **WARNINGS** sections, and insertion of these same paragraphs in the **PRECAUTIONS** section, first two paragraphs:

    The safety and efficacy of REBETOL/INTRON A and PEG-INTRON therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. REBETOL Capsules should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

    The safety and efficacy of REBETOL/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are nonresponders to interferon therapy, or patients coinfected with HBV or HIV.

14. Removal of the following wording in the **WARNINGS** sections in all CAPS font, and replacement of the same wording as shown:

    The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of rebetol/intron a-treated

15. Insertion of the following wording at the **WARNINGS, Anemia** section, second paragraph:

    Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment

16. Insertion of the following wording at the **WARNINGS, Anemia** section, third paragraph:

    and INTRON A or PEG-INTRON

17. Movement of the following wording in the **PRECAUTIONS, Geriatric Use** section to the end of the section, and consolidation as one paragraph:

    In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%) (See **WARNINGS**).

    In general, REBETOL Capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy.

Consolidated form:

In general, REBETOL Capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%). (See **WARNINGS.**)

18. Deletion of the word "elderly" in the forth line of the **PRECAUTIONS, Geriatric Use** section.

19. Insertion of the heading "REBETOL/INTRON A Combination Therapy" in the **ADVERSE REACTIONS** section.

20. Table 4 becomes Table 5

21. Insertion of the following paragraph in the **ADVERSE REACTIONS** section:

REBETOL/PEG-INTRON Combination Therapy
Overall, in clinical trials, 14% of patients receiving REBETOL in combination with PEG-INTRON, discontinued therapy compared with 13% treated with REBETOL in combination with INTRON A. The most common reasons for discontinuation of therapy were related to psychiatric, systemic (e.g. fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **Table 6** by treatment group.

22. Insertion of a new Table 6 to include PEG-INTRON adverse events, as follows:

Table 6. Adverse Events Occurring in > 5% of Patients

	*Percentage of Patients Reporting Adverse Events**			*Percentage of Patients Reporting Adverse Events**	
Adverse Events	**PEG-INTRON 1.5µg/kg/ REBETOL** (n=511)	**INTRON A/ REBETOL** (n=505)	**Adverse Events**	**PEG-INTRON 1.5µg/kg/ REBETOL** (n=511)	**INTRON A/ REBETOL** (n=505)
Application Site			**Musculoskeletal**		
Injection site Inflammation	25	18	Myalgia	56	50
Injection Site Reaction	58	36	Arthralgia	34	28
Autonomic Nervous Sys.			Musculoskeletal Pain	21	19
Mouth Dry	12	8	**Psychiatric**		
Sweating Increased	11	7	Insomnia	40	41
Flushing	4	3	Depression	31	34
Body as a Whole			Anxiety/Emotional Lability/Irritability	47	47
Fatigue/Asthenia	66	63	Concentration Impaired	17	21
Headache	62	58	Agitation	8	5
Rigors	48	41	Nervousness	6	6
Fever	46	33	**Reproductive, Female**		
Weight Decrease	29	20	Menstrual Disorder	7	6
RUQ Pain	12	6	**Resistance Mechanism**		
Chest Pain	8	7	Infection Viral	12	12
Malaise	4	6	Infection Fungal	6	1
Central/Peripheral Nervous System			**Respiratory System**		

Dizziness	21	17	Dyspnea	26	24
Endocrine			Coughing	23	16
Hypothyroidism	5	4	Pharyngitis	12	13
Gastrointestinal			Rhinitis	8	6
Nausea	43	33	Sinusitis	6	5
Anorexia	32	27	**Skin and Appendages**		
Diarrhea	22	17	Alopecia	36	32
Vomiting	14	12	Pruritus	29	28
Abdominal Pain	13	13	Rash	24	23
Dyspepsia	9	8	Skin Dry	24	23
Constipation	5	5	**Special Senses Other,**		
Hematologic Disorders			Taste Perversion	9	4
Neutropenia	26	14	**Vision Disorders**		
Anemia	12	17	Vision blurred	5	6
Leukopenia	6	5	Conjunctivitis	4	5
Thrombocytopenia	5	2			
Liver and Biliary System					
Hepatomegaly	4	4			

23. Insertion of the heading "REBETOL/INTRON A Combination Therapy" in the **ADVERSE REACTIONS, Laboratory Values** section.

24. Table 5 becomes Table 7.

25. Insertion of the following text in the **ADVERSE REACTIONS, Laboratory Values** section.

REBETOL/PEG-INTRON Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 8.**)

Hemoglobin.

REBETOL induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to < 11g/dL in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-INTRON/REBETOL and INTRON A/REBETOL groups.

Bilirubin and Uric
In the REBETOL/PEG-INTRON combination trial 10-14% of patients developed hyperbilirubenemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

Table 8: Selected Hematologic Values During Treatment with REBETOL plus PEG-INTRON

	Number (%) of Subjects				
	PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)		PEG-INTRON plus REBETOL (N=511)	INTRON A plus REBETOL (N=505)
Hemoglobin (g/dL)			Platelets ($x10^9$/L)		
9.5-10.9	26	27	70-99	15	5
8.0-9.4	3	3	50-69	3	0.8
6.5-7.9	0.2	0.2	30-49	0.2	0.2
<6.5	0	0	<30	0	0
Leukocytes ($x10^9$/L)			Total Bilirubin (mg/dL)		
2.0-2.9	46	41	1.5 -3.0	10	13
1.5-1.9	24	8	3.1-6.0	0.6	0.2
1.0-1.4	5	1	6.1-12.0	0	0.2
<1.0	0	0	>12.0	0	0

Neutrophils ($x10^9$/L)		
1.0-1.49	33	37
0.75-0.99	25	13
0.5-0.74	18	7
<0.5	4	2

ALT (SGPT)		
2 x Baseline	0.6	0.2
2.1-5 x Baseline	3	1
5.1-10 x Baseline	0	0
>10 x Baseline	0	0

26. Deletion the word "combination" as the second word of the OVERDOSAGE section.

27. Insertion of the words "combination therapy" in the first line of the OVERDOSAGE section

28. Insertion of the heading "REBETOL/INTRON A Combination Therapy" in the **DOSAGE AND ADMINISTRATION** section.

29. Table 6 becomes Table 9.

30. Insertion of the heading "REBETOL/PEG INTRON Combination Therapy" in the **DOSAGE AND ADMINISTRATION** section, with the following text:

    The recommended dose of REBETOL Capsules is 800 mg/day in 2 divided doses: two capsules (400 mg) in the morning with food and two capsules (400 mg) with in the evening with food.

31. Insertion of the following wording in the **HOW SUPPLIED** section:

    42 capsules (NDC 0085-1327-04), 56 capsules (NDC 0085-1351-05), 70 capsules. (NDC 0085-1385-07, and...(NDC 0085-1194-03).

32. Table 7 becomes Table 10

Label Revisions: Medguide:

1. Deletion of the words "this medicine".and replacement with "REBETOL" at the end of the first paragraph of the Medguide.

2. Insertion of the following words in the "**What is the most important information I should know about therapy with REBETOL Capsules?**" section, second sentence:

   pregnant or your sexual partner is

3. Deletion of the words "you must" in the "**What is the most important information I should know about therapy with REBETOL Capsules?**" section, second sentence, and replacement with the word "do."

4. Replacement of the words six and two with the numbers 6 and 2 (entire Medguide).

5. Insertion of the words "you must" in the "**What is the most important information I should know about therapy with REBETOL Capsules?**" section, second paragraph, first bullet.

6. Insertion of the following sentence in the "**What is the most important information I should know about therapy with REBETOL Capsules?**" section, third paragraph, first bullet:

(See What should I avoid while taking REBETOL?"

7. Overall re-write of the third bullet for the "**What is the most important information I should know about therapy with REBETOL Capsules?"** section, as follows:

   - **Do not take REBETOL Capsules alone to treat hepatitis C infection.** REBETOL Capsules should be used in combination with interferon alfa-2b (INTRON A) or in combination with peginterferon alfa-2b (PEG-INTRON) for treating chronic hepatitis C infection. . REBETOL Capsules and INTRON A when used together are called REBETRON Combination Therapy. Your health care provider or pharmacist should give you a copy of the REBETRON Combination Therapy or PEG-INTRON Medication Guide. They have additional important information about combination therapy not covered in this guide.

8. Deletion of all terms "INTRON A" in the "**What is REBETOL (ribavirin)**?" section, and replacement with the term interferon alpha-2b

9. Insertion of the following words in the "**What is REBETOL (ribavirin)**?" section, first paragraph:

   ...some patients with...**(see the REBETRON Combination Therapy or PEG-INTRON Medication Guide)**.

10. Deletion of the following words in the "**What is REBETOL (ribavirin)**?" section, first paragraph:

    ...made by Schering

11. Insertion of the following word in the "**What is REBETOL (ribavirin)**?" section, second paragraph:

    ...an...

12. Deletion of the third paragraph in the "**What is REBETOL (ribavirin)**?" section

13. Deletion of the word "Please" and the words "at the beginning of this Medication Guide." in the "**Who should not take REBETOL capsules?**" section, and replacement with the sentence, "**What should I avoid while taking REBETOL Capsules**?"

14. Deletion of the words "health care" in the "**Who should not take REBETOL capsules?**" section, third bullet.

15. Deletion of the words "Intron A (see also the Rebetron Medication Guide)" in the "**Who should not take REBETOL capsules?**", section , subsection "**Tell your health care provider...**," and replacement with the following:

    Interferon alfa-2b

16. Deletion of all terms "Intron A" in the "**Who should not take REBETOL capsules?**" section, and replacement with the term "interferon alfa-2b."

17. Deletion of the words "for a mental illness" and "...psychosis. Psychosis is..."in the "**Who should not take REBETOL capsules?**", section , subsection "**Tell your health care provider**...," first bullet.

18. Insertion of the following in the "**Who should not take REBETOL capsules?**", section , subsection "**Tell your health care provider**...," first bullet:

    (psychosis). Tell your health care provider if you take any medicines for these problems.

19. Deletion of the following words in the "**Who should not take REBETOL capsules?**", section , subsection "**Tell your health care provider**...," seventh bullet:

    abnormalities...medication.

    And replacement with the following:

    problems... medicine.

20. Insertion of the following at the end of the "**Who should not take REBETOL capsules?**" section:

    For more information see the Rebetron Combination Therapy or PEG-INTRON Medication Guides.

21. Insertion of the following at the end of the "**How should I take REBETOL capsules?**" section, second paragraph:

    ...when used with INTRON A...

22. Removal of the following sentence, and reinsertion of it at the end of the "**How should I take REBETOL capsules?**" section, second paragraph:

    You can take REBETOL Capsules with or without food, but you should take them the same every day.

23. Insertion of a new paragraph in the "**How should I take REBETOL capsules?**" section, as follows:

24. Insertion of a two new bullets in the "**How should I take REBETOL capsules?**" section, as follows:

    - Tell your provider before taking REBETOL Capsules if you have ever had any heart or breathing problems. Your provider should check your red blood cell count before starting therapy and often during the first 4 weeks of therapy. Your red blood cell count may be checked more frequently if you have had heart or breathing problems.
    - Females taking REBETOL Capsules or female sexual partners of male patients taking REBETOL Capsules must have a pregnancy test before treatment begins, every month during treatment, and for 6 months after treatment ends to make sure there is no pregnancy.

25. Insertion of a new subheading in the "**What should I avoid while taking REBETOL Capsules?**" section, as follows:

    Avoid the following during REBETOL Capsule treatment:

26. Deletion of the word "becomes" in the "**What should I avoid while taking REBETOL Capsules?**" section, first bullet, first paragraph, and replacement with the following:

    ...gets pregnant during treatment with REBETTOL Capsules or in the 6 months after treatment ends,

27. Deletion of the words "at the beginning of this Medication Guide." in the "**What should I avoid while taking REBETOL Capsules?**" section, first bullet, first paragraph.

28. Deletion of the words "becomes." in the "**What should I avoid while taking REBETOL Capsules?**" section, first bullet, second paragraph, and replacement with the word "gets."

29. Deletion of the words "toll-free." in the "**What should I avoid while taking REBETOL Capsules?**" section, first bullet, second paragraph, and replacement with the following:

    Schering, the company that makes REBETOL at...

30. Insertion of the following sentence in the "**What should I avoid while taking REBETOL Capsules?**" section, second bullet:

    The medicine may pass through your milk and harm the baby.

31. Insertion of a new bullet (third bullet) in the "**What should I avoid while taking REBETOL Capsules?**" section, as follows:

    - **Drinking alcohol**, including beer, wine, and liquor. This may make your liver disease worse.

32. Revision of the final bullet in the "**What should I avoid while taking REBETOL Capsules?**" section, as follows:

    - **Taking other medicines.** Take only medicines prescribed or approved by your health care provider. These include prescription and non-prescription medicines and herbal supplements.

33. Revision of the entire "**What are the most common side effects of REBETOL Capsules?**" section, as follows:

    What are the most common side effects of REBETOL Capsules?
    The most serious possible side effects of REBETOL Capsules are:

    - **Harm to unborn children.** REBETOL Capsules may cause birth defects or death of an unborn child. (For more details, see "**What is the most important information I should know about REBETOL Capsules?**")
    - **Anemia.** Anemia is a reduction in the number of red blood cells you have which can be dangerous, especially if you have heart or breathing problems. Tell your health care provider right away if you feel tired, have chest pain or shortness of breath. These may be signs of low

red blood cell counts.

Tell your provider right away if you have any of the following symptoms. They may be signs of a serious side effect:

- **trouble breathing**
- **hives or swelling**
- **chest pain**
- **severe stomach or low back pain**
- **bloody diarrhea or bloody stools (bowel movements). These may appear black and tarry.**
- **bruising**
- **other bleeding**

The most common side effects of REBETOL Capsules are:

- **feeling tired**
- **nausea and appetite loss**
- **rash and itching**
- **cough**

This summary does not include all possible side effects of REBETOL therapy. Talk to your health care provider, if you do not feel well while taking REBETOL. Your health care provider can give you more information about managing your side effects.

34. Revision of the last heading "**How do I store my medicine?**" to read, "**How do I store my REBETOL Capsules?**

35. Revision of the first sentence in the, "**How do I store my REBETOL Capsules?**" section to read:

Store REBETOL Capsules at room temperature 77°F (25°C).

Conclusions/Recommendations:

It should be conveyed to the applicant that the Final Draft Labeling is acceptable, and an approval letter should be sent.

Destry M. Sillivan, MS

Regulatory Project Manager

Attachment: 1. Clean copy of September 27, 2001 Final Draft Labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Destry Sillivan
3/6/02 04:27:38 PM
CSO

Tony, this is my CSO label review, S-020, NDA 20903

Tony DeCicco
3/15/02 04:13:45 PM
CSO

Appears This Way
On Original