

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-546

MEDICAL REVIEW(S)

Clinical Review

**NDA 21-546
Rebetol® (ribavirin) Oral Solution
For Pediatric Use**

**Schering Plough Research Institute
Kenilworth, New Jersey**

**Russell Fleischer, PA-C, MPH
Senior Clinical Analyst
Acting Medical Team Leader**

**with input from
Kassa Ayalew, MD, MPH
Medical Officer
Division of Antiviral Drug Products**

Table of Contents

Table of Contents 2

I. Recommendations 5

 A. Recommendation on Approvability 5

 B. Recommendation on Phase 4 Studies and/or Risk Management Steps 5

II. Summary of Clinical Findings 6

 A. Brief Overview of Clinical Program 6

 B. Efficacy 6

 C. Safety 7

 D. Dosing 8

I. Introduction and Background 9

 A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups 9

 B. State of Armamentarium for Indication(s) 9

 C. Important Milestones in Product Development 10

 D. Other Relevant Information 11

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Statistics and/or Other Consultant Reviews 11

III. Human Pharmacokinetics and Pharmacodynamics 13

IV. Description of Clinical Data and Sources 14

 A. Overall Data 14

 B. Tables Listing the Clinical Trials 14

 C. Postmarketing Experience 14

CLINICAL REVIEW NDA 21-546

D. Literature Review 14

V. Clinical Review Methods15

A. How the Review was Conducted 16

B. Overview of Methods Used to Evaluate Data Quality and Integrity 16

C. Were Trials Conducted in Accordance with Accepted Ethical Standards 16

D. Evaluation of Financial Disclosure 16

VI. Integrated Review of Efficacy 16

A. Brief Statement of Conclusions 16

B. General Approach to Review of the Efficacy of the Drug 17

C. Detailed Review of Trials by Indication 17

D. Summary of Integrated Efficacy 22

E. Efficacy Conclusions..... 25

VII. Integrated Review of Safety 27

A. Brief Statement of Conclusions 27

B. Description of Patient Exposure..... 27

C. Methods and Specific Findings of Safety Review 28

D. Safety Conclusions..... 34

E. Adequacy of Safety Testing 34

F. Summary of Critical Safety Findings and Limitations of Data..... 34

VIII. Dosing, Regimen, and Administration Issues 35

IX. Use in Special Populations..... 35

A. Evaluation of Sponsor’s Gender Effects Analyses and Adequacy of Investigation..... 35

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy 35

X. Conclusions and Recommendations 36

CLINICAL REVIEW NDA 21-546

A. Conclusions 36

B. Recommendations 37

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW NDA 21-546

Executive Summary Section

I. Recommendations

A. Recommendation on Approvability

The data reviewed in this New Drug Application support the approval of a new dosage form of ribavirin, Rebetol® Oral Solution, and currently available Rebetol® Capsules for use in combination with Intron® A [interferon alfa-2b] in pediatric patients ≥ 25 kilograms with chronic hepatitis C virus (HCV) infection naïve to previous therapy. This recommendation is based on a review of antiviral activity, safety, pharmacokinetic, and dosing information on pediatric patients between 3 and 16 years of age treated with Rebetol Oral solution or Rebetol Capsules for 48 weeks.

Current practice is to treat adults with genotype 2 or 3 virus with combination therapy for 24 weeks. For adults with genotype 1 and fibrosis or advanced inflammation, the recommendation is to assess virologic response after 12-24 weeks of combination therapy. For patients with a virologic response (undetectable HCV RNA or >2 log reduction from baseline HCV RNA), the recommendation is to continue therapy for 36 additional weeks (48 weeks total). If no response by the week 12-24 assessment, it is recommended that therapy be discontinued. These guidelines are the results of numerous epidemiology, viral kinetic, and treatment studies in the adult HCV population.

The natural history of pediatric HCV infection is not as well understood, and there is a paucity of data on response to treatment in this population. The combination of interferon and ribavirin is difficult to tolerate, and the long term impact of treating children (e.g., prevention of cirrhosis, hepatocellular carcinoma, or hepatic failure) is unknown. Therefore, the risks of the therapy (anemia and psychiatric adverse events) should be weighed carefully against the potential but unproven long-term benefit of treatment for all pediatric patients with chronic HCV infection. It may be reasonable, therefore, for some children with more minimal hepatic inflammation or fibrosis to put off treatment until better tolerated and more effective therapies become available or until fibrosis advances to the point that, the risks of disease progression outweigh those of treatment.

If a decision is made to treat a pediatric patient, then duration of treatment based on genotype (1 versus non-1) and early (week 24) virologic response is similar as in adults.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The applicant has committed to follow patients for five years to assess long term effects of Intron A and Rebetol on _____ antiviral response and safety.

Executive Summary Section

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Pursuant to a Pediatric Written Request (WR), the applicant submitted safety, pharmacokinetic and antiviral activity in pediatric patients with chronic HCV infection. The development program involved administration of Rebetol Oral Solution or Rebetol Capsules in combination with IntronA (interferon alfa-2b) to pediatric patients between 3 and 16 years of age for up to 48 weeks in duration.

The applicant designed two studies. The first study (P00018) was conducted in two cohorts. In Cohort 1, 61 pediatric patients with chronic HCV infection were randomized to receive ribavirin 8, 12, or 15 mg/kg/day with Intron A 3 MIU/m² SC TIW for 48 weeks. Assessments of antiviral activity and safety occurred at weeks 4 and 12. The 15 mg/kg/day dose was determined to provide the best balance between efficacy (reduction of HCV RNA) and safety (change from baseline in hemoglobin). Cohort 2 enrolled an additional 35 children at the 15 mg/kg/day dose of ribavirin who also received 48 weeks of combination treatment. A separate study, P00321, enrolled 70 patients. In total, 125 patients received the ribavirin dose proposed for marketing: 15 mg/kg/day for 48 weeks.

In March 2001, the applicant submitted safety and pharmacokinetic data from the two above described studies, which were ongoing, in order to meet certain requirements of the WR (see Medical Review of NDA _____). At that time, all patients had completed the 48-week treatment period but only one-half had completed the required 24 week off therapy follow up period. The current application contains the final sustained virologic response (SVR) data for all children, and one new bioavailability study. No new safety data was included.

B. Efficacy

Response to the antiviral therapy was defined on the basis of virological and biochemical outcome. Sustained virologic response (SVR) is the standard for assessing response to anti-HCV therapy and is defined as HCV RNA below the level of quantification of the assay used 24 weeks following completion of therapy.

The overall SVR for pediatric patients (age 3 to 16 years) with compensated chronic HCV infection and detectable HCV RNA treated with the combination of Rebetol 15 mg/kg/day and Intron A 3 MIU/m² SC TIW was 46%. For pediatric patients with genotype 1, the most prevalent and least responsive to treatment, the SVR was 36%. Conversely, genotype non-1 patients achieved the highest SVRs, 81%. Further patients with the two poor prognostic factors of genotype 1 and HCV RNA >2 million copies/mL achieved only a 26% SVR.

Numerical SVR differences between the Oral Solution and Capsules was likely due to higher drop outs among adolescents who received the Capsule formulation; the differences were not statistically significant.

CLINICAL REVIEW NDA 21-546

Executive Summary Section

All pediatric patients who achieved a SVR exhibited an initial virologic response within the first 24 weeks of treatment.

Analyses by various demographic and disease characteristics suggested that younger children (<13 years of age) Asians, children who weighed <40 kg, females, and children infected for <10 years achieved higher SVRs. However, because the number of children in some of these categories was very small, no specific conclusions could be reached.

Finally, there were only four patients who had received prior interferon therapy, and three were treatment failures. Thus, the small number of patients in this category does not support their specific inclusion in the indication. A post marketing commitment for additional studies in this group of patients was not requested because it is very likely they would not be treated with standard interferon; more likely they would receive a pegylated form of interferon.

C. Safety

The safety database contains data on 166 pediatric patients who received IntronA plus Rebetol Oral Solution or Capsules for up to 48 weeks, 125 of whom received 15 mg/kg/day.

The most important safety finding was that pediatric patients, primarily adolescents, appear to be at higher risk for suicidal ideation/attempt than adults (2.4% vs. 1%); three of four pediatric subjects with suicidal ideation or suicidal attempt were adolescents. The Rebetol Oral Solution and Capsule labels will carry a WARNING related to this apparent increased risk among pediatric patients.

The primary toxicity of ribavirin is hemolytic anemia. Pediatric patients experienced anemia with similar frequency and severity as adults. Pediatric patients who received the Capsule formulation experienced greater mean reductions from baseline in hemoglobin levels compared to those who received the Oral Solution, -1.8 g/dL vs. -1.2 g/dL, respectively. The Capsule group also experienced a more pronounced reticulocytosis (3.7%) compared to the Oral Solution group (2.8%); this finding was not unexpected. Seventeen percent of patients who received Rebetol Capsules required a dose modification for anemia vs. 5% among subjects who received the Oral Solution.

Treatment-related reductions in linear growth and weight were observed, which were likely due reduced caloric intake related to gastrointestinal effects of treatment (i.e., nausea, abdominal pain, and anorexia); these effects appeared to be reversing following discontinuation of treatment.

The most common adverse events included flu-like symptoms, particularly headache, fever and fatigue. Gastrointestinal complaints of nausea, vomiting, abdominal pain, and anorexia, were also common. These events are common to interferon. Compared to adult studies some adverse events were reported more commonly in the pediatric population. They included injection site reactions, influenza like symptoms, abdominal pain, diarrhea, vomiting, infections and weight loss.

CLINICAL REVIEW NDA 21-546

Executive Summary Section

For a number of adverse events, there were numerical differences between the Capsule and Oral Solution groups, some of which may have been explained by small numbers of patients influencing outcomes. There were no specific adverse events that require a special mention in the labeling.

D. Dosing

The recommended dosing of ribavirin as Rebetol Oral Solution or Capsules in pediatric patients is based on weight. The recommended dose of ribavirin is 15 mg/kg/day orally in two divided doses. This dose was derived from adequate and well controlled studies demonstrating that 15 mg/kg/day provided reasonable efficacy and safety profiles. Rebetol Capsules are available as 200 mg capsules. The Oral Solution is supplied in a concentration of 40 mg/ml, and is recommended for pediatric patients who weigh <25 kg or who cannot tolerate capsules.

For patients with genotype 1, the recommended duration of treatment is 48 weeks. After 24 weeks, virologic response should be assessed. Patients who have undetectable HCV RNA at that time should receive an additional 24 weeks of therapy. If no response, consideration should be given to discontinuing therapy as essentially no additional patients will respond. For patients with genotype non-1, the duration of dosing is 24 weeks.

E. Special Populations

Use in Pregnancy

Both ribavirin and Intron A are classified as Pregnancy Category X. The following information is included in the labels for currently approved ribavirin and Intron A and will be included in the Rebetol Oral Solution label.

Ribavirin is a teratogen, mutagen, and embryocidal, and Intron A is an abortifacient. Combination Rebetol/Intron A therapy must not be used by females who are pregnant or by males whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking combination Rebetol/Intron A therapy. Combination Rebetol/Intron A therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. Females of childbearing potential and males must use two forms of effective contraception during treatment and during the 6 months after treatment has been concluded.

CLINICAL REVIEW

Clinical Review Section

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name: ribavirin
Trade name: Rebetol® Oral Solution
Proposed indication: Treatment of chronic hepatitis C virus infection
Dose regimen: 15 mg/kg/day in two divided doses
Age groups: 3-16 years of age

B. State of Armamentarium for Indication(s)

Hepatitis C virus infection is the major cause of chronic liver disease in children. It is estimated that 170 million persons worldwide are infected with the hepatitis C virus (HCV). 2.7 million of the people infected with HCV live in the United States.

The seroprevalence of HCV infection is between 0.8-3% in the adult population in most parts of the world, except for some hyperendemic areas. In children, the seroprevalence rate is much lower (mostly 0-0.4%) than that in adults. Among children in the USA, the prevalence rate is 0.2% for those 5-12 years of age and 0.4% for those 12-19 years of age.

Presently, six distinct but related HCV genotypes and multiple subtypes have been identified on the basis of molecular relatedness. In the United States and Western Europe genotypes 1a and 1b are most common, followed by genotypes 2 and 3. Knowledge of the genotype is important because it has predictive value in terms of the response to antiviral therapy, with better responses associated with genotypes 2 and 3 than with genotype 1.

Most adults acutely infected with HCV are asymptomatic and anicteric. Some patients (25 to 35%) develop fatigue, malaise, weakness, nausea, anorexia or become icteric. Most patients develop signs of liver cell injury within 50 days of exposure, as evidenced by elevation of serum alanine transferase (ALT). ALT levels can fluctuate widely, and the relationship between ALT and disease severity as judged by histology is inconsistent. HCV-RNA can usually be detected in the serum within 1-3 weeks. Antibodies to HCV become detectable early in the disease and are present in virtually all patients with chronic HCV infection; anti-HCV is detectable in 50-70% at the onset of symptoms and in 90% three months after onset of infection. HCV infection is self-limited in only about 20% of cases as characterized by the disappearance of HCV-RNA and return of liver enzymes to normal. Approximately 80% of patients fail to clear the virus by 6 months and develop chronic hepatitis with persistent viremia. Although the rate of disease progression is variable, liver damage from chronic HCV infection generally progresses at a slow rate without signs or symptoms in the majority of patients during the first two decades after infection. Fulminant liver failure is relatively rare late manifestation of chronic disease.

Approximately 20% of all chronically infected patients develop cirrhosis. A minority (approximately 20%) of patients with cirrhosis ultimately develops liver failure, portal

CLINICAL REVIEW

Clinical Review Section

hypertension and the associated conditions of ascities, esophageal varicies and encephalopathy. Chronic HCV infection is also associated with increased risk of hepatocellular carcinoma (HCC). Risk factors associated with the development of HCV-related HCC include cirrhosis, male gender and older age.

Less is known about the natural history of HCV infection in children. Although the Centers for Disease Control estimates that the prevalence of anti-HCV antibodies in children in the United States is 0.2 to 0.4%, the incidence of pediatric hepatitis C infection in the United States is still unknown. In the past, most children were infected with HCV after transfusion with blood or blood products. Adolescents are at risk for the acquisition of HCV because of high-risk behaviors such as intravenous or intranasal drug use, body piercing, or tattooing. Currently, the primary mode of HCV transmission is vertical infection from infected mothers to their infants. The rate of mother-to-child transmission of HCV is 5-6% but increases with detectable or increasing plasma HCV RNA levels, or with HIV coinfection. There is no known method of decreasing the rate of perinatal HCV transmission.

The natural history of HCV infection in children is likely influenced by the mode of acquisition, the age at the time of acquisition, concomitant infections, ethanol ingestion, viral genotype, and comorbid diseases. In general, infection with HCV during childhood results in an increase in hepatic transaminases with minimal histopathologic changes, fibrosis, cirrhosis, and other serious complications occur years later during adulthood. However, small studies of children with repeated exposure due to multiple transfusions of blood or blood products suggest that these children can develop serious liver disease during childhood. In this population, hemochromatosis may contribute to the development of liver disease. The natural history of HCV infection after mother-to-child transmission is less well understood. Viremia in the neonate may be transient and not associated with liver disease; however, perinatal HCV infection is more commonly associated with biochemical evidence of liver injury during childhood with clinically significant liver disease developing only after 10 to 20 years. Regardless of the mode of acquisition, liver tissue from children with HCV infection generally exhibits only minimal inflammatory changes and rarely shows fibrosis or cirrhosis, although there are reports of some children with more aggressive liver disease.

C. Important Milestones in Product Development

Following approval of Rebetron™ Combination Therapy (ribavirin capsules with interferon alfa-2a injection) for adults, a Written Request for Pediatric Studies (WR) was issued to the applicant. The WR requested development of an age appropriate formulation of ribavirin, and an assessment of the safety, pharmacokinetics, and activity of the combination of interferon and ribavirin in pediatric patients between 3 and 16 years of age with compensated chronic HCV.

Based on the expected date of Rebetol's patent expiration, June 1, 2001, the date for submission of data from the studies outline in the WR was March 1, 2001, which was met. On May, 9, 2001, the Pediatric Exclusivity Board granted SPRI an additional six months of marketing exclusivity through January 1, 2002. At the time the supplement was submitted, it was assigned a 10 month review period. Because the length of the studies, 48 weeks of treatment with 24

CLINICAL REVIEW

Clinical Review Section

weeks of off-therapy follow-up, it was recognized that the applicant was not able to submit sustained response rates for all patients by either the March 1 deadline or by the end of the 10 month review period (January 1, 2002). Consequently, only safety and pharmacokinetic results from the 70 patients who received the capsule formulation of ribavirin were included in the Rebetol® and Rebetron® Combination Therapy labels.

The current application provides complete SVR data. This application was granted a priority (6-month) review because it contained pediatric clinical data.

D. Other Relevant Information

Ribavirin is a purine analog that is approved in combination with Intron A and PEG-Intron for the treatment of chronic HCV infection in adults. Neither the mechanism for antiviral activity against HCV-RNA or for synergistic activity observed with interferon is known. The only currently available strength and formulation are oral 200 mg capsules. At the present time, because of this limitation, Rebetol Capsules are only labeled for children >25 kg who are able to swallow capsules. This application provides for a new Oral Solution formulation of ribavirin that will allow more flexible dosing to younger children.

Rebetol Oral Solution is not currently approved in any other country. There are two approved ribavirin products in the US: (Rebetol® Capsules, Schering Plough) and (Copegus® Tablets, Roche Pharmaceuticals). Both formulations are approved for use with standard (alfa-2a and alpha 2b) and pegylated (PegIntron® and Pegasys®) formulations of interferon for treatment of adults with chronic HCV infection.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Statistics and/or Other Consultant Reviews

A. Chemistry, Manufacturing and Controls

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Kambhyampati's review.

Rebetol® Oral Solution will be supplied as

Rebetol Oral Solution, is a clear, colorless to pale or light yellow liquid. Each bottle contains approximately 100 mL of the solution containing a total of 4 g of ribavirin. The composition of each 1 mL are listed in Table 1.

CLINICAL REVIEW

Clinical Review Section

Table 1 Composition of Rebetol® Oral Solution

Component	Mg/1 mL of Solution
Ribavirin	40.0
Sucrose	
Sorbitol solution	
Glycerin	
Propylene glycol	
Sodium citrate	
Citric acid	
Sodium benzoate	
Natural and artificial bubble gum flavor	
Purified water	

Source: CMC review.

Rebetol Oral Solution (40 mg/mL) is packaged in 4 oz size amber glass bottles (100 mL/bottle) with child resistant closures. The Rebetol Oral Solution bottles should be stored at 2° □ and 8° C (36° □ and 46° F) or at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) and they have an expiration dating period of 36 months.

Three of the four facilities manufacturing, packaging, and/or testing of the drug substance and drug product were found to be acceptable by DMPQ (HFD-324). The inspection of the fourth facility, Schering, Las Piedras, Puerto Rico, a drug substance release testing facility, is pending.

B. Pharmacology and Toxicology

This section was cross-referenced to NDA 20-903. No new Pharmacology/Toxicology data submitted.

Both ribavirin and Intron A are classified as Pregnancy Category X. The following information is included in the labels for currently approved ribavirin and Intron A and will be included in the Rebetol Oral Solution label.

CLINICAL REVIEW

Clinical Review Section

C. Microbiology

This section was cross-referenced to NDA 20-903. No new Microbiology data was submitted.

III. Human Pharmacokinetics and Pharmacodynamics

Please see Dr. Derick Zhang and Dr. Jooran Kim's review for details.

Tables 1 and 2 present pharmacokinetic data in children and comparisons between children and adults. These data were previously submitted and reviewed in NDA _____ and supported adding pediatric dosing information for the Capsule.

Table 1. Ribavirin pharmacokinetic parameters in pediatric patients

Parameter	12 mg/kg/day (n=19)	15 mg/kg/day (n=19)
T _{max} (hr)	1.4 (60)	1.9 (81)
C _{max} (ng/mL)	2705 (17)	3243 (24)
AUC _{tr} (ng*h/mL)	25049 (16)	29620 (25)
Apparent Clearance (L/hr)	0.49 (16)	0.54 (26)

Table 2. Pharmacokinetics in pediatric patients compared to adults

Dose	C _{max} , ng/mL	AUC, ng*h/mL
	Pediatric (%CV)	
12 mg/kg	2705 (17)	25049 (16)
15 mg/kg	3243 (24)	29620 (25)
	Adults (range)	
1000 mg/day	3230 (1680-6760)	27800 (16500-45900)
1200 mg/day	3480 (2020-7200)	30300 (16300-59350)

Pharmacokinetic analysis also demonstrated that the pharmacokinetics of Rebetol Oral Solution and Capsules were comparable between adults and children.

The current application contains results from a single dose bioavailability study comparing the pharmacokinetics of the Capsule and Oral Solution in healthy adults. Ribavirin was rapidly absorbed following oral administration as the Oral Solution formulation. Maximum plasma concentrations were achieved within 0.5 to 2 hr post-dose. Ribavirin C_{max} and AUC values after administration of the Oral Solution were comparable to data obtained in previous ribavirin Capsule studies in healthy adults.

Comment: Pharmacokinetic parameters in children appeared generally dose proportional, and comparable to adults, and supported the selection of the 15 mg/kg/day dose of ribavirin. The Intron A dose was chosen based on available safety data in pediatric patients with chronic hepatitis B virus infection (see Intron A label); therefore, no dose ranging of Intron A was requested. The design of the studies, 48 weeks of treatment followed by a 24

CLINICAL REVIEW

Clinical Review Section

week off therapy period was considered standard study design at the time the clinical studies were initiated.

IV. Description of Clinical Data and Sources

A. Overall Data

The material reviewed in this NDA was derived from clinical studies conducted by the applicant.

B. Tables Listing the Clinical Trials

Table 3 presents a schematic overview of the completed pediatric studies conducted to demonstrate the safety and efficacy of ribavirin capsules and oral solution for treatment of pediatric patients with chronic HCV infection.

Table 3. Studies of Rebetol plus Intron A in pediatric patients with chronic HCV infection

Protocol No.	Design	Treatment Dose Frequency Duration	No. Patients Treated
P00018 (Cohort 1)	Open-label, / randomized, parallel group, dose finding	INTRONA 3 MIU/m ² SC TIW plus Rebetol 8, 12, or 15 mg/kg/day PO for 48 weeks; 24 weeks follow-up	N=61 8 mg/kg=21 12 mg/kg=20 15 mg/kg=20
P00018 (Cohort 2)	Open-label, single arm	INTRONA 3 MIU/m ² SC TIW plus Rebetol 15 mg/kg/day PO for 48/ weeks; 24 weeks follow-up	N=35
P00321	Open-label, single arm	INTRONA 3 MIU/m ² SC TIW plus Rebetol 15 mg/kg/day PO for 48 weeks; 24 weeks follow-up	N=70

C. Postmarketing Experience

Use of ribavirin for treatment of pediatric patients with chronic HCV infection is not approved in any country.

D. Literature Review

The applicant submitted the results of a comprehensive literature search. The literature included articles on the epidemiology, diagnosis, treatments, and outcomes of patients treated with ribavirin. Articles describing treatment of pediatric patients with combinations of interferon and ribavirin were included and reviewed. None of the articles raised safety concerns that were inconsistent with the data provided and reviewed in this NDA. A search by FDA identified a report of a small study of pediatric patients treated with pegylated interferon and ribavirin, of

CLINICAL REVIEW

Clinical Review Section

which 61% (25/41) had an SVR. No references to treatment of pediatric patients specifically with Rebetol Oral Solution were found.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Clinical Review Section

V. Clinical Review Methods

A. How the Review was Conducted

The clinical review of NDA 21-546 (Rebetol® Oral Solution) was conducted using clinical study reports and electronic SAS transport files of the NDA submission. The current indication being considered is treatment of chronic HCV infection in pediatric patients. As noted in Table 3 above, the development program to support the safety and efficacy of Rebetol Oral Solution and Capsules in the pediatric population consisted of two clinical studies.

Study reports, line listings, and Case Report Forms were reviewed for all efficacy endpoints and demographic subgroups. The safety review also consisted of a review of all adverse events by summary tables and line listings, along with review of physical examination line listings. 'Clinically significant' laboratory abnormalities were defined as falling outside the 'normal' range values for the parameter by a specified amount defined in the study reports.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

The applicant reported discrepancies in the management and reporting of data from one site for study P00018 (_____). The discrepancies were raised due to inaccurate reporting on severity of adverse events, relationship adverse events to study drug as well as start and stop dates of adverse events. As a result, certain safety and dosing data from that site could not be verified. Ten subjects were enrolled at site 10: 1 to the 8 mg/kg/day arm, 1 to the 12 mg/kg/day arm, and 3 to the 15 mg/kg/day arm of cohort 1, and five were in cohort 2. Site 10 did not participate in study P00321. Therefore, the applicant presented summary results both including and excluding site 10.

Comment: Since the overall efficacy results were not impacted by the inclusion/exclusion of data from Site 10, FDA decided to present efficacy results after excluding data from Site 10. Patients from Site 10 are discussed in the analysis of safety.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

There was no evidence to suggest that the studies contained in this NDA were not conducted in accordance with accepted ethical standards and under good clinical practices.

D. Evaluation of Financial Disclosure

Financial disclosure information was submitted to NDA _____

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The overall SVR for pediatric patients (age 3 to 16 years) with compensated chronic HCV infection and detectable HCV RNA treated with the combination of Rebetol 15 mg/kg/day and Intron A 3 MIU/m² SC TIW was 46%. For pediatric patients with genotype 1, the most prevalent

CLINICAL REVIEW

Clinical Review Section

and least responsive to treatment, the SVR was 36%. Conversely, genotype non-1 patients achieved the highest SVRs, 81%. Further patients with the two poor prognostic factors of genotype 1 and HCV RNA >2 million copies/mL achieved only a 26% SVR.

All pediatric patients who achieved a SVR exhibited an initial virologic response within the first 24 weeks of treatment.

There was no significant difference in sustained virologic response rates whether patients had baseline HCV RNA \leq 2 million copies/mL or >2 million copies/mL, or whether they received Rebetol Capsules or Oral Solution.

Analyses by various demographic and disease characteristics suggested that younger children (<13 years of age) Asians, children who weighed <40 kg, females, and children infected for <10 years achieved higher SVRs. However, because the number of children in some of these categories was very small, no absolute conclusions could be reached.

B. General Approach to Review of the Efficacy of the Drug

The principal focus of the review was studies P00018 and P000321. No other clinical study information was submitted.

C. Detailed Review of Trials by Indication

The database to support approval of Rebetol Oral Solution for treatment of chronic HCV infection in pediatric patients consisted of two major studies, P00018 and P00321. These studies are reviewed below.

Study P00018

The study was conducted in two parts with two cohorts of patients. The objective of Cohort 1 was to select Rebetol dose for further evaluation of safety and efficacy. The objective of Cohort 2 was to assess the safety and efficacy of the combination of Intron A plus Rebetol at the dose selected from Cohort 1 in pediatric subjects with chronic HCV infection.

• Cohort 1

Design

Cohort 1 was a multiple-dose, open label evaluation of safety and pharmacokinetics/pharmacodynamics of the combination Intron A and Rebetol Capsules in pediatric patients with chronic HCV infection.

Patients were randomized to one of three doses of Rebetol (8, 12, or 15 mg/kg/day) administered in two divided doses using a 50 mg capsule. All patients also received Intron A 3 MIU/m² SC thrice weekly. Pharmacokinetic assessments occurred at week 4, with safety and preliminary

CLINICAL REVIEW

Clinical Review Section

anti-HCV activity assessed at week 12. Based on the week 4 and 12 data, the 15mg/kg/day dose was selected for further study.

Patients in the 8 and 12 mg/kg/day dose groups who had not achieved at least a 2-log decrease in HCV RNA after 12-weeks of treatment were permitted to have their ribavirin dose increased to 15 mg/kg/day.

Population

Sixty-two pediatric patients were randomized, and 61 subjects were treated. As noted above, Site 10 participated in this study. With patients from Site 10 are excluded the total number of patients was 57, with 56 subjects receiving study treatments.

Eligible subjects included children 5-16 years of age with documented HCV-RNA infection and a liver biopsy compatible with diagnosis of chronic HCV infection with no evidence of cirrhosis on liver biopsy obtained within 2 years prior to enrollment. Patients were either treatment naïve or had previously received and responded to interferon, but had lost that response. They were required not to have received previous ribavirin or other immunomodulator treatment. In addition they were required to be HIV and HBV negative.

- Cohort 2

Design

Cohort 2 was an open-label single treatment group. In Cohort 2 an additional 35 patients received Rebetol at the 15 mg/kg/day level to increase the number of patients in whom safety could be assessed. The study was open label. All subjects in Cohort 2 were treated with the 15 mg/kg/day (in two divided doses) in combination with Intron A 3 MIU/m² SC TIW for 48 weeks followed by a 24-week post treatment period. Two Rebetol formulations were used in this trial: capsules (50 mg and 200 mg) and oral solution (40mg/ml).

Population

The patients enrolled in Cohort 2 met the same inclusion/exclusion as those in Cohort 1.

Study P00321

Objectives

The objective of the study was evaluation of the safety and efficacy of the combination of Intron A and Rebetol in pediatric patients with chronic HCV infection.

CLINICAL REVIEW

Clinical Review Section

Design

Study P00321 was an open-label, multicenter, multinational trial in which pediatric patients with chronic HCV infection received Rebetol 15 mg/kg/day in two divided doses as either the 200 mg capsule or the Oral Solution in combination with Intron A 3 MIU/m² SC TIW. Patients who weighed <47 kg received Rebetol Oral Solution. Treatment was for 48 weeks followed by a 24 week off therapy period.

An interim assessment of virologic response was conducted following 24 weeks of treatment; patients who remained HCV-RNA positive were withdrawn from the study and analyzed as treatment failures.

Population

Pediatric subjects age 3 to 16 years with chronic HCV infection who had not been previously treated with interferon, ribavirin, or combination interferon plus ribavirin were eligible for the study. Eligible subjects were required to have chronic HCV infection confirmed in during the screening by a liver biopsy obtained within the previous 12 months with findings consistent with a diagnosis of chronic hepatitis and no evidence of cirrhosis. Eligibility was further confirmed by certain minimum hematologic and biochemical criteria. Because the majority of pediatric patients with HCV have relatively normal ALT levels, elevated ALT levels were not required for eligibility.

Demographics

Table 4 presents the demographic and disease characteristics of enrollees in studies P00018 and P00321 who received Rebetol 15 mg/kg/day. Patients in the 8 and 12 mg/kg/day dose cohorts of study P00018 had similar disease and demographic characteristics.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Clinical Review Section

Table 4. Demographic and disease characteristics of patients in studies P00018 and P00321

	All 15 mg/kg/day* (n=125)	Capsules* (n=70)	Oral solution (n=55)
Age (years)			
Median	11	12	10
Range	3-16	5-16	3-16
Age range			
3-6	21 (17%)	4 (6%)	17 (31%)
7-9	26 (21%)	16 (23%)	10 (18%)
10-12	32 (26%)	16 (23%)	16 (29%)
13-15	33 (26%)	24 (34%)	9 (16%)
>15	13 (10%)	10 (14%)	3 (5%)
Gender			
Male	69 (55%)	43 (61%)	26 (47%)
Female	56 (45%)	27 (39%)	29 (53%)
Race			
Caucasian	101 (81%)	58 (83%)	43 (78%)
Non-Caucasian	24 (19%)	12 (17%)	12 (22%)
Body weight (kg)			
Median	40.6	50.8	35
Range	10-95	18-95	10-87
Weight range			
<46 kg	77 (62%)	31 (44%)	46 (84%)
>46-55 kg	14 (11%)	7 (10%)	7 (13%)
>55 kg	34 (27%)	32 (46%)	2 (4%)
HCV genotype			
1	97 (78%)	55 (79%)	42 (76%)
2/3/4	28 (22%)	15 (21%)	13 (24%)
Viral load (HCV RNA)			
Geometric mean	1,975,976	2,455,349	1,498,730
≤2 million c/mL	58 (46%)	27 (39%)	31 (56%)
>2 million c/mL	67 (54%)	43 (61%)	24 (44%)
ALT (x ULN)			
Median	1.2	1.1	1.3
Range	0.45-3.10	0.45-3.10	0.50-2.70
Source of exposure			
Transfusion associated/parenteral	53 (42%)	31 (44%)	22 (40%)
Vertical	67 (54%)	35 (50%)	32 (58%)
Other	4 (3%)	3 (4%)	1 (2%)
Years since exposure			
Median	10.7	11.9	9.2
Range	0.8-17.0	1.3-17.0	0.8-16.4

* Includes enrollees from site 10.

Four patients who received Rebetol 15 mg/kg/day, one in Cohort 1 and three in Cohort 2 of study P00018, had received previous interferon monotherapy. All other patients were treatment naïve at the time of enrollment.

CLINICAL REVIEW

Clinical Review Section

Comment: No publicly available database of demographic and disease characteristics was available for comparison to study patients. Compared to adults, pediatric patients were more often female, non-Caucasian, and more often infected with HCV genotype 1. Vertical and parenteral transmission of HCV was the dominant mode of acquisition of infection in children compared to parenteral in adults.

Patient Disposition

The disposition of patients is presented in Table 5.

Table 5. Patient disposition

	All 15 mg/kg/day With Site 10 (n=125)	All 15 mg/kg/day Without Site 10 (n=118)	Capsules With Site 10 (n=70)	Capsules Without Site 10 (n=63)	Oral Solution (n=55)
Completed 12 Wk of Tx	97% (121)	98% (115)	97% (68)	98% (62)	96% (53)
Discontinued During Wk 1-12	3% (4)	3% (3)	3% (2)	2% (1)	4% (2)
Adverse Events	2% (3)	3% (3)	1% (1)	2% (1)	4% (2)
Noncompliance	<1% (1)	0	1% (1)	0	0
Completed 24 Weeks of Tx	94% (117)	96% (113)	91% (64)	95% (60)	96% (53)
Discontinued Wk 13-24	3% (4)	2% (2)	6% (4)	3% (2)	0
Adverse Events	2% (2)	<1% (1)	3% (2)	2% (1)	0
Treatment Failure	<1% (1)	<1% (1)	1% (1)	2% (1)	0
Consent Withdrawal	<1% (1)	0	1% (1)	0	0
Completed 48 Wk of Tx	58% (73)	59% (69)	53% (37)	52% (33)	66% (36)
Discontinued Wk 25-48	35% (44)	37% (44)	39% (27)	43% (27)	31% (17)
Adverse Events	2% (3)	3% (3)	0	0	6% (3)
Treatment Failure	30% (38)	32% (38)	36% (25)	40% (25)	24% (13)
Consent Withdrawal	2% (2)	2% (2)	1% (1)	2% (1)	2% (1)
Noncompliance	<1% (1)	<1% (1)	1% (1)	2% (1)	0
Completed Treatment & FU	58% (73)	59% (69)	53% (37)	52% (33)	66% (36)

Data Source: Applicant submission.

Comment: The exclusion of patients from Site 10 did not impact the overall similarity of disease or demographic characteristics. Lack of virologic efficacy and adverse events were the most common reasons for premature discontinuations, similar to the causes observed in adult studies.

CLINICAL REVIEW

Clinical Review Section

D. Summary of Integrated Efficacy

One hundred twenty-five patients received the 15 mg/kg/day ribavirin dose. The assessments of efficacy were conducted without the data from Site 10. Therefore, the efficacy population is 118 patients.

The primary efficacy endpoint was SVR, defined as absence of plasma HCV RNA using a research based RT-PCR assay, 24 weeks following completion of 48 weeks of therapy. SVR by genotype and baseline viral load, and assessment of ALT levels were secondary endpoints. FDA also evaluated time to virologic response.

Comment: In study P00018 and early in study P00321, an assay produced by _____ with a reported detection limit of 100 copies of HCV RNA/ml was used. Subsequently, the applicant replaced the _____ assay with an in-house assay _____ Quantification of the detection limit for either assay could not be validated. Therefore, the assays were used to qualify whether HCV RN was present or absent, and not to determine the actual amount of virus present.

• Assessment Virologic Response

Overall SVR was 46%. As to be expected, patients with poor prognostic factors such as genotype 1 and high baseline viral load levels had lower virologic responses (see Table 6).

Table 6 Sustained virologic response by genotype and baseline viral load level

	All 15 mg/kg/day	Capsules	Oral Solution
All Genotypes			
Overall SVR	46% (54/118)	25% (40/63)	53% (29/55)
≤2 million c/mL	52% (28/54)	35% (8/23)	65% (20/31)
>2 million c/mL	41% (26/64)	43% (17/40)	38% (9/24)
Genotype 1			
Overall SVR	36% (33/92)	15% (30/50)	43% (18/42)
≤2 million c/mL	48% (20/42)	29% (5/17)	60% (15/25)
>2 million c/mL	26% (13/50)	30% (10/33)	18% (3/17)
Genotype non-1			
Overall SVR	81% (21/26)	83% (10/12)	85% (11/13)
≤2 million c/mL	67% (8/12)	60% (3/5)	83% (5/6)
>2 million c/mL	93% (13/14)	100% (7/7)	86% (6/7)

The response rate for Capsules appears numerically higher than that for the Oral Solution. The applicant believes that this difference is mainly due to eight patients who received Capsules who were negative at end of treatment but who were missing at the end of follow-up data; seven of the eight were between 11-16 years of age and were classified as "lost to follow-up." FDA typically treats missing values as failures. An analysis comparing response rates demonstrates that the numbers are not statistically significantly different (p-value=0.214). Therefore, we do

CLINICAL REVIEW

Clinical Review Section

not have sufficient evidence to conclude that the difference between Capsules and Oral Solution is real.

Eleven patients (seven in the 8 mg/kg/day and four in the 12 mg/kg/day dose groups) in Cohort 1 of study P00018 had their dose of ribavirin increased after week 12 due to lack of virologic activity. One patient who was in the 12 mg/kg/day dose group was a sustained responder. Overall, approximately 35% of patients in the 8 and 12 mg/kg/day dose groups achieved an SVR, compared to 47% in the 15 mg/kg/day group, suggesting that the higher dose is a more effective dose.

Analyses of SVR by various demographic and disease characteristics were conducted. The data suggest that younger children (<13 years of age) Asians, children who weighed <40 kg, females, and children infected for <10 years achieved higher SVRs (see Table 7). The numbers of patients in some cells is very small; therefore, no definite conclusions about efficacy in some subgroups can be reached.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Clinical Review Section

Table 7 SVR by selected demographic and disease characteristics

	All 15 mg/kg/day (n=118)	Capsules (n=63)	Oral Solution (n=55)
Age (years)			
<5	50% (4/8)	-	50% (4/8)
5-6	46% (6/13)	25% (1/4)	56% (5/9)
7-9	64% (16/25)	67% (10/15)	60% (6/10)
10-12	59% (17/29)	54% (7/13)	63% (10/16)
13-15	25% (8/32)	22% (5/23)	33% (3/9)
>15	27% (3/11)	25% (2/8)	33% (1/3)
Race			
Caucasian	47% (44/94)	41% (21/51)	53% (23/43)
Black	0% (0/5)	0% (0/4)	0% (0/1)
Asian	100% (4/4)	100% (1/1)	100% (3/3)
Hispanic	36% (5/14)	43% (3/7)	29% (2/7)
Other	100% (1/1)	-	100% (1/1)
Body Weight			
<40 kg	56% (32/57)	46% (11/24)	64% (21/33)
>40 kg	36% (22/61)	36% (14/39)	36% (8/22)
Gender			
Male	43% (29/67)	39% (16/41)	50% (13/26)
Female	49% (25/51)	41% (9/22)	55% (16/29)
Source of Exposure			
Transfusion	43% (18/42)	25% (5/20)	59% (13/22)
Vertical	42% (27/64)	38% (12/32)	47% (15/32)
Parenteral	71% (5/7)	71% (5/7)	-
Sporadic/other	80% (4/5)	75% (3/4)	100% (1/1)
Years Since Exposure			
<10	58% (33/57)	62% (16/26)	55% (17/31)
>10	34% (21/61)	24% (9/37)	50% (12/24)

Only one of the four patients who had previously received monotherapy were sustained virologic responders.

- **Assessment of ALT Levels**

Seventy-seven patients had abnormal ALTs at baseline, and 33 of these were sustained responders. Of the 44 non-responders who had abnormal ALTs at baseline only 20% (9/44) had normal ALTs at the end of follow-up.

Among the 21 sustained responders who had normal baseline ALT levels, 90% (19/21) had normal levels at the end of follow-up. Of the 16 non responders who had normal ALTs at baseline, 70% had normal ALTs at the end of follow-up.

CLINICAL REVIEW

Clinical Review Section

Comment: These data suggest a correlation between a sustained virologic response and normalization of ALT among patients with baseline ALT elevations.

- Time to Virologic Response

Current treatment guidelines data suggests that adult patients with genotype non-1 virus achieve very high SVRs with only 24 weeks of therapy. Adults with genotype 1 virus, however, may take longer to have a virologic response. For these patients, the recommendation is to assess virologic response between weeks 12 and 24. If the patient has not achieved at least a ≥ 2 log₁₀ reduction from baseline in HCV RNA, therapy should be discontinued. If a virologic response has been achieved, the patient may receive a full 48-week course of therapy.

Interferon and ribavirin are toxic and difficult to tolerate, and there is no reason to expose patients to these agents if they will not benefit. FDA conducted an analysis of time to initial virologic response to attempt to determine if pediatric patients respond similarly as adults. If so, appropriate dosing recommendations could be made.

The analysis demonstrated that 100% and 91% of patients with genotype non-1 and 1 who achieved a SVR had a virologic response by week 24 of therapy. Adult patients with genotype 1 who have responded by week 24 appear to benefit from an additional 24 weeks of therapy. Patients with genotype non-1 do not have a similar benefit. Thus, the pattern of response among pediatric patients is similar to the pattern observed in adults.

Comment: The pattern of response by genotype between children and adults is very similar. It is reasonable to advise clinicians that an assessment of virologic response in patients with genotype 1 should be made at week 24. Patients who have achieved a virologic response may go on to receive a full 48 weeks of therapy. Conversely, patients who have not responded by week 24, the clinician should consider discontinuing therapy. Patients with genotype non-1 should receive only 24 weeks of therapy since an additional 24 weeks did not increase SVR rates.

E. Efficacy Conclusions

The treatment of HCV with the combination of Intron A plus ribavirin 15 mg/kg/day for 48 weeks resulted in sustained virologic response in 46%, which is comparable to sustained response rates achieved in adults. The numerical difference in response rates between the Oral Solution and Capsules was not statistically significant, and was likely due to a high rate of drop outs among adolescents.

Pediatric patients, like adults, infected with HCV genotype 1 regardless of viral load had lower virologic response rates. Patients with HCV genotype 1 and high viral load had the least robust response to treatment. A correlation between normalization of ALT and sustained virologic response was observed.

CLINICAL REVIEW

Clinical Review Section

In summary, the efficacy results support the proposed indication for treatment with Rebetol Oral Solutions or Capsule (15 mg/kg/day) with Intron A in pediatric patients naïve to previous anti-HCV therapy.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Clinical Review Section

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The primary dose-limiting toxicity of ribavirin is hemolytic anemia. Most adult patients experience a reduction from baseline in hemoglobin between 1-3 gm/dL within the first four weeks of treatment. The resulting anemia has been demonstrated to exacerbate symptoms of coronary disease and result in the deterioration of cardiac function. The anemia is reversible once the dose of ribavirin is reduced or is discontinued. In adult clinical trials, over 10% of patients required dose modifications for anemia. In general, the pattern of hemoglobin reductions in pediatric patients followed the same pattern as in adults, but the overall mean reductions from baseline were lower in pediatric patients, -1.5 g/dl versus -2.6 g/dl in adults. Patients who received the Capsule formulation experienced greater reductions of hemoglobin levels compared to those who received the Oral Solution, however, no pediatric patient discontinued ribavirin due to anemia. As in adults, pediatric patients experienced reversal of anemia within 4 weeks of discontinuation of ribavirin.

Interferon therapy is associated with the potential for significant psychiatric abnormalities including, but not limited to depression, insomnia, irritability, abnormal dreams, suicidal ideation/attempt, and homicidal ideation/attempt. In comparison to previous adult trials of interferon with ribavirin, children experienced more insomnia (52% vs. 39%), but less depression (14% vs. 28%). Suicidal behavior (ideation, attempt, or suicide), however, occurred more often in children than adults (2.4% vs. 1%).

The most common adverse events included flu-like symptoms, particularly headache, fever and fatigue; these were reported by 59-70% of subjects. Gastrointestinal complaints were also common, with 35-52% of subjects reporting nausea, vomiting, abdominal pain, and anorexia. Compared to adult studies some adverse events were reported more commonly in the pediatric population. They included injection site reactions, influenza like symptoms, abdominal pain, diarrhea, vomiting, infections and weight loss.

B. Description of Patient Exposure

This summary includes safety information for 166 subjects who received at least one dose of Intron A plus ribavirin, of which 125 received the 15 mg/kg/day ribavirin dose. These 125 are the focus of the safety review. Important safety findings from patients who received 8 and 12 mg/kg/day are also described.

Table 8 presents exposure data for the two clinical trials.

Table 8 Pediatric exposure to interferon and ribavirin

Week	P00018		P00321	
	Capsules (n=55)		Capsules (n=15)	Oral Solution (n=55)
12	53 (96%)		15 (100%)	53 (96%)
24	49 (89%)		15 (100%)	53 (96%)
48	30 (55%)		7 (47%)	36 (66%)

CLINICAL REVIEW

Clinical Review Section

Approximately 50% of subjects completed 48 weeks of treatment. As noted in Table 5, the most common reason for non-completion of treatment was virologic failure.

C. Methods and Specific Findings of Safety Review

The safety review focuses on 118 of the 125 pediatric patients who received the 15 mg/kg/day dose of ribavirin. The difference is accounted for by the 7 patients enrolled at Site 10. The safety information for this population has currently been reviewed (see Safety Review of NDA 20-903/SLR-15), and no new safety information was submitted in the current application. Of note, the safety of Rebetol in the 7 patients from Site 10 was reviewed; their adverse event profiles were consistent with the adverse event profile in the larger pediatric population. The following discussion provides a review of the safety data.

Deaths

There were no deaths reported.

Serious Adverse Events

Seven children had SAEs during treatment and 2 had SAEs during follow-up.

The events that occurred during therapy included one each of dehydration, suicidal ideation, suicide attempt, infection after a surgical procedure, depression, diabetes mellitus, vomiting, and diarrhea. The psychiatric events and diabetes mellitus are consistent with the known adverse event profile of interferon.

Two events of appendicitis and one of asthma were reported by two children during the off-therapy follow-up period. Review of these cases demonstrated no relationship to study medication.

There were no differences between patients who received Capsules and Oral Solution.

Discontinuations Due to Adverse Events

Eight (6%) patients who received ribavirin 15 mg/kg/day discontinued therapy due to adverse events. The events included neutropenia (n=2), depression (n=2), headache (n=1), elevated AST/ALT (n=1), injection site pain (n=1), and suicide attempt (n=1).

Two patients discontinued from the 8 mg/kg/day dose group of Cohort 1 of study P00018: one for severe depression and suicidal ideation and one for hyperglycemia.

All of these events are known to be related to therapy with interferon. No patients discontinued because of anemia.

CLINICAL REVIEW

Clinical Review Section

Dose Modifications Due to Adverse Events

Dose modifications were required in 30% (37/125) and were more common in children who received Capsules compared to Oral Solution (44 % vs. 16%). Dose modification of Intron A was more frequent than dose modification of Rebetol. Consistent with adult data, the most common reasons for dose modifications were anemia (Rebetol) and neutropenia and depression (Intron A) (see Table 9).

Table 9 Dose modifications in pediatric patients

	All 15 mg/kg/day (n=118)	Capsule (n=63)	Oral Solution (n=55)
Total	31% (37)	44% (28)	16% (9)
Intron A, not Rebetol	19% (22)	24% (15)	13% (7)
Rebetol, not Intron A	6% (7)	11% (7)	0
Intron A and Rebetol	6% (8)	10% (6)	4% (2)

Comment: The frequency of dose modifications and the reasons for those modifications were consistent with the reasons and frequencies seen in adult clinical trials.

Adverse Events of Special Concern

The following events were evaluated because they are known to be of clinical concern among patients treated with interferon and ribavirin.

Psychiatric Events

Interferon therapy is associated with the potential for significant psychiatric abnormalities including, but not limited to depression, insomnia, irritability, abnormal dreams, suicidal ideation/attempt, and homicidal ideation/attempt.

The overall incidence of psychiatric adverse events was 52%, higher among subjects who received Rebetol Oral Solution compared to those who received Capsules (67% vs 40%). A higher frequency of somnolence, behavior disorder, and insomnia accounted for the difference. There did not appear to be relationship between age and these events.

In comparison to previous adult trials of interferon with ribavirin, pediatric patients experienced suicidal behavior (ideation, attempt, or suicide) more often (2.4% vs. 1%). Four patients had suicidal ideation or attempt, three of whom were adolescents (13, 13, and 14 years of age). All four patients were in study P00018, one each received 8 and 12 mg/kg/day and two received 15 mg/kg/day.

Patient P00018-16/0070 was an 8 year old female in the 8 mg/kg/day dose group. She complained of increasing agitation and depression during the treatment period. She stated she

CLINICAL REVIEW

Clinical Review Section

wanted to kill herself but later claimed she did not really mean it. Study medications were discontinued on day 232 of dosing.

Patient P00018-16/0010 was a 13 year old female in the 12 mg/kg/day dose group. She complained of increasing depression during the treatment period and received Celexa. She completed 48 weeks of combination therapy. On day 132 of follow-up she called her psychiatrist with a plan to commit suicide, but did not make any attempt to carry it out. She was placed on additional anti-psychotic medications.

Patient P00018-13/0214 was a 14 year old female in the 15 mg/kg/day Capsule group. She complained of depression and suicidal ideation on study day 71. She was subsequently started on Prozac, and had her dose of Intron A reduced. Suicidal ideation resolved and on study day 89 she resumed the full dose of Intron A and completed the study.

Patient P00018-17/0227 was a 13 year old female in the 15 mg/kg/day Capsule group. This patient had a history of attention deficit disorder and learning disabilities. She complained of depression on day 43, placed on Paxil, and had her dose of Intron A reduced. On day 65 she attempted suicide consisting of superficial cuts to both wrists. Study medications were stopped. The suicidal ideation resolved without further incidence.

Comment: Exposure to interferon produces psychiatric adverse events likely to negatively effect physical, emotional, social and intellectual development, which could increase the risk for school failure, dropout, excitement seeking behavior (such as drug abuse, reckless driving) as well as the risk for suicide and physical endangerment. The higher frequency of suicidal behavior in pediatric patients noted in the previous review resulted in a precautionary statement being added to the Pediatric Use section of the Rebetol Capsules and Rebetron Combination Therapy labels. A decision was made during this review cycle to add the same information to the WARNINGS section.

Neutropenia

Interferon is myelosuppressive, and can cause neutropenia. In adult ribavirin/Intron A combination therapy trials, between 30-40% experienced reductions of neutrophil counts. The mean maximum decrease was approximately $-1.6 \times 10^9/L$. Neutrophil counts generally returned to pretreatment levels within four weeks of cessation of therapy in most patients.

Pediatric patients exhibited a similar pattern. The mean neutrophil counts decreased $-1.4 \times 10^9/L$ during the first four weeks of treatment, stabilized, and returned to baseline following discontinuation of interferon.

Neutropenia was the most common cause of Intron A dose modification in children. The dose modification rate for neutropenia was higher among subjects receiving Capsules compared with those receiving Oral Solution (17% vs. 9%). This was consistent with the higher incidence of Grade 3-4 neutropenia with Capsules compared with Oral Solution (23% vs. 13%). The majority of cases were managed with dose modifications and only two patients discontinued therapy.

CLINICAL REVIEW

Clinical Review Section

Anemia

The primary toxicity of ribavirin is hemolytic anemia. In adults, reductions in hemoglobin levels occur within 1-2 weeks of initiation of therapy and generally return to baseline levels within four weeks of ribavirin discontinuation. In general, the pattern of hemoglobin reductions in pediatric patients followed the same pattern as in adults, but the overall mean reductions were lower in pediatric patients. Pediatric patients experienced lesser mean reduction from baseline in hemoglobin level (-1.5 g/dl) in comparison to adults (-2.6 g/dl) (see Table 10).

Table 10 Mean change from baseline in hemoglobin after four weeks of ribavirin

		Ribavirin dose (daily)		
Pediatric dose		8 mg/kg	12 mg/kg	15 mg/kg
Median Δ in Hgb (g/dL)		-1.1	-1.1	-1.5
Adult dose		600 mg	800 mg	1,000-1,200 mg
Median Δ in Hgb (g/dL)		-1.17	-1.37	-2.23

Pediatric patients who received the Capsule formulation experienced greater mean reductions from baseline in hemoglobin levels compared to those who received the Oral Solution, -1.8 g/dL vs. -1.2 g/dL, respectively. The Capsule group also experienced a more pronounced reticulocytosis (3.7%) compared to the Oral Solution group (2.8%).

Seventeen percent of patients who received Rebetol Capsules required a dose modification for anemia vs. 5% among subjects who received the Oral Solution. A higher proportion of subjects receiving Capsules had Grade 1 (33%) and Grade 2 (7%) anemia than subjects who received Oral Solution, Grade 1 (13%) and Grade 2 (0%).

Growth

During childhood, the child's body changes in both weight and height. Many drugs given during this period may alter the normal physical, emotional and cognitive growth, and reproductive potential; interferon is one such drug. The prolonged use of such drugs may affect muscle development, bone remodeling and growth.

The evaluation in height and weight data based on change in percentile showed a decrease in linear growth rate during treatment (-7.22 percentile) followed by smaller compensatory increase during follow up (+1.84 percentile). Decreases in the rate of weight gain during treatment (-9.43 percentile) followed by equivalent increase in the rate of weight gain during follow up (+9.24 percentile) were observed. These growth decreases may have been due to Intron A-related decreased caloric intake secondary to anorexia, nausea and other gastrointestinal events. During the off therapy follow-up period, a general trend toward normalization of height and weight was observed.

CLINICAL REVIEW

Clinical Review Section

General Adverse Events

The types of adverse events were similar among the Rebetol Capsule and Oral Solution groups. All subjects reported at least one adverse event during the treatment period. The majority, more than 80%, were considered by the investigator to be mild or moderate in severity, and there was only one event considered to be life threatening. Table 11 presents the frequency of selected adverse events, regardless of attribution of causality or grade.

**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW

Clinical Review Section

Table 11 Selected adverse events, all grades

	All 15 mg/kg/day n=118	Capsules n=63	Oral Solution n=55
Total Reporting AE	100%	100%	100%
Application site	36%	49%	20%
Fatigue	58%	57%	58%
Fever	61%	46%	78%
Headache	69%	65%	73%
Flu-like symptoms	31%	44%	15%
Malaise	11%	6%	16%
Rigors	25%	24%	25%
Weight decrease	25%	25%	24%
Dizziness	20%	24%	16%
Abdominal pain	39%	33%	45%
Anorexia	51%	49%	53%
Diarrhea	25%	24%	27%
Nausea	33%	33%	33%
Vomiting	42%	38%	47%
Arthralgia	15%	8%	24%
Musculoskeletal pain	21%	19%	24%
Myalgia	32%	32%	33%
Aggressive reaction	3%	2%	5%
Agitation	7%	8%	5%
Behavior disorder	5%	0	11%
Impaired concentration	5%	3%	7%
Depression	13%	13%	13%
Emotional lability	16%	14%	18%
Insomnia	14%	10%	18%
Irritability	10%	8%	13%
Somnolence	9%	5%	15%
Viral infection	25%	35%	15%
Coughing	11%	6%	16%
Epistaxis	13%	14%	11%
Pharyngitis	27%	24%	31%
Alopecia	23%	27%	18%
Pruritis	12%	8%	16%
Rash	17%	14%	20%
Skin dry	7%	6%	7%
Hypothyroidism	4%	3%	5%

Comment: The overall adverse event profile was similar between Oral Solution and Capsules and between children and adults. The adverse event profile among 7 patients from Site 10 and patients who received 8 and 12 mg/kg/day was similar to the overall 15 mg/kg/day profile.

CLINICAL REVIEW

Clinical Review Section

D. Safety Conclusions

The safety data reviewed herein has previously been reviewed (). Therefore the safety data reviewed with this NDA does not change the overall safety conclusion with respect to use of either Rebetol Capsules or Oral Solution in pediatric patients. Both studies demonstrated comparable and acceptable safety of Rebetol Oral Solution and Capsule. Adverse events were generally mild to moderate.

The primary dose-limiting toxicity of ribavirin is hemolytic anemia. In general, the pattern of hemoglobin reductions in pediatric patients followed the same pattern as in adults, but mean reductions from baseline were lower in pediatric patients, -1.5 g/dl versus -2.6 g/dl in adults. Patients who received the Capsule formulation experienced greater reductions of hemoglobin levels compared to those who received the Oral Solution, however, no pediatric patient discontinued ribavirin due to anemia. As in adults, pediatric patients experienced reversal of anemia within four weeks of discontinuation of ribavirin.

In comparison to previous adult trials of interferon with ribavirin, children experienced more insomnia (52% vs. 39%), but less depression (14% vs. 28%). Suicidal behavior (ideation, attempt, or suicide), however, occurred more often in children than adults (2.4% vs. 1%).

The most common adverse events included flu-like symptoms, particularly headache, fever and fatigue; these were reported by 59-70% of subjects. Gastrointestinal complaints were also common, with 35-52% of subjects reporting nausea, vomiting, abdominal pain, and anorexia. Compared to adult studies some adverse events were reported more commonly in the pediatric population. They included injection site reactions, influenza like symptoms, abdominal pain, diarrhea, vomiting, infections and weight loss.

It is interesting to note that for some adverse events patients who received the Capsule formulation had a higher frequency compared to Oral Solution recipients, and vice versa, although pharmacokinetic data demonstrate that ribavirin exposures are similar when it is administered as the Capsule or Oral Solution. Thus, since pharmacokinetics did not explain these findings, other explanations are not apparent.

E. Adequacy of Safety Testing

The applicant submitted the results of two open label trials in support of Rebetol Oral Solution safety and efficacy in the treatment of chronic HCV infection in children. The methods that were used to monitor safety in both trials were adequate.

F. Summary of Critical Safety Findings and Limitations of Data

The applicant provided data on 125 patients exposed to interferon plus ribavirin for up to 48 weeks duration. Although a relatively small database, it was deemed sufficient to adequately characterize the safety profile of this combination in pediatric patients. The safety analyses conducted by the applicant and FDA resulted in similar conclusions. Overall, the safety data-

CLINICAL REVIEW

Clinical Review Section

reviewed in this NDA does not change the assessment of safety previously described. The label will provide a WARNING related to the potential increased risk of suicidal ideation among pediatric patients, primarily adolescents.

VIII. Dosing, Regimen, and Administration Issues

The recommended dose of ribavirin is 15 mg/kg/day orally in two divided doses. This dose was derived from an adequate and well controlled study demonstrating that 15 mg/kg/day provided comparable efficacy between pediatric and adult patients, and an acceptable safety profile.

Rebetol Oral Solution is supplied in a concentration of 40 mg/ml, and is recommended for pediatric patients who weigh <25 kg or who cannot tolerate capsules. The following table provides the recommended pediatric doses of Intron A and Rebetol Capsules.

Table 12 Dosing of Rebetol Capsules and Intron A for pediatric patients

Body weight	Rebetol Capsules	Intron A Injection
25-36 kg	1 x 200 mg capsules AM 1 x 200 mg capsules PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
37-49 kg	1 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
50-61 kg	2 x 200 mg capsules AM 2 x 200 mg capsules PM daily p.o.	3 million IU/m ² 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

It will be recommended that patients with genotype non-1 receive 24 weeks of therapy. For patients with genotype 1, the recommendation is to assess virologic response at week 24. If the patient has responded, an additional 24 weeks of therapy is warranted. If they have not responded, treatment discontinuation should be considered.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

An efficacy analysis by gender was conducted. Female patients had a overall SVR approximately 6% higher than males, with no difference based on ribavirin formulation administered. Further there were no differences in the safety profile between males and females and ribavirin formulation.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The overall SVR for the entire study population was 46%. Patients who received the Oral Solution had higher SVRs compared to those who received the Capsules, 53% vs. 25%. No clear reason(s) for this difference was identified. Patients ranged between 3 and 16 years of age, the median age was 11. Eight patients were younger than 5 years of age. All eight received the Oral

CLINICAL REVIEW

Clinical Review Section

Solution formulation and 50% (4/8) achieved a SVR. Children between 5 and 10 years of age generally had higher SVRs than those >10 years of age.

The majority of patients were Caucasian. The number of patients of other ethnicities was relatively small. Only four patients were Black, and none achieved an SVR. This finding is consistent with adult data demonstrating that Black patients are more likely to have genotype 1 and typically respond less well than Caucasians or Asians.

Patients treated with the Oral Solution experienced more fever, fatigue, abdominal pain, vomiting, irritability, somnolence, coughing and rash. Capsule recipients had higher rates of anemia, flu-like symptoms, alopecia, and viral infections.

Ribavirin exposures are similar between Capsules and Oral Solution. Therefore, the reason(s) for the differences in safety are not clear.

X. Conclusions and Recommendations

A. Conclusions

The data reviewed from two adequate and well-controlled pediatric trials support the conclusion that the combination of Intron A 3 MIU/m² TIW plus Rebetol Capsules or Oral Solution 15 mg/kg/day provides SVRs in children similar to adults with chronic HCV infection.

In general, the adverse event profile is also similar between pediatric and adult patients. Of note, there is a higher incidence of suicidal ideation and attempts in pediatric subjects compared with adults.

Current practice is to treat adults with genotype 2 or 3 virus with combination therapy for 24 weeks. For adults with genotype 1 and fibrosis or advanced inflammation, the recommendation is to assess virologic response after 12 weeks of combination therapy. For those who have a virologic response (undetectable HCV RNA or >2 log reduction in HCV RNA), it is recommended that therapy be continued for 36 additional weeks (48 weeks total). If no response by week 12-24, therapy should be discontinued. These guidelines are the results of many years and studies worth of epidemiology and treatment data in the adult population.

The natural history of pediatric HCV infection is not as well understood, and there is a paucity of data on response to treatment in this population. The combination of interferon and ribavirin is difficult to tolerate, and the long term impact on treating children (e.g., prevention of cirrhosis, hepatocellular carcinoma, or hepatic failure) is unknown. Therefore, it is not unreasonable, therefore, to balance the risks (anemia and psychiatric adverse events) against the potential but unknown long-term benefits of treatment for all pediatric patients with chronic HCV infection

CLINICAL REVIEW

Clinical Review Section

Specifically, patients with genotype 1 who have not achieved a virologic response by week 24 are highly unlikely to achieve a SVR. Therefore, for those who have achieved a virologic response, a full 48 weeks of therapy is recommended. Conversely, patients who have not responded by week 24, the clinician should consider discontinuing therapy. Patients with genotype non-1 do not appear to benefit from more than 24 weeks of therapy.

B. Recommendations

Based on the review of the data submitted in NDA 21-546, and the data previously submitted and reviewed in _____ it is recommended that the application for Rebetol Oral Solution for pediatric patients naïve to previous anti-HCV therapy be approved.

**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/

Russell Fleischer
7/28/03 03:26:20 PM
MEDICAL OFFICER

Debra Birnkrant
7/29/03 09:06:59 AM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**