

NEW ZEALAND DATA SHEET

REBETOL

NAME OF MEDICINE

ribavirin

PRESENTATION

REBETOL 200 mg capsules are white, opaque capsules imprinted in blue ink with “200mg” and a stripe on the body, and the S-P logo and a stripe on the cap. The capsules are packaged in blisters.

USES

Actions: Ribavirin is a synthetic nucleoside analogue that has shown *in vitro* activity against some RNA and DNA viruses. Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up. However, clinical trials combining ribavirin with peginterferon alfa-2b or interferon alfa-2b resulted in an increased response rate over treatment with pegylated interferon or interferon alfa-2b alone. The mechanism by which ribavirin in combination with peginterferon alfa 2b or interferon alfa-2b exerts its effects against HCV is unknown.

CLINICAL TRIALS

Long-Term efficacy data

Two large long-term follow-up studies enrolled 1,071 patients and 567 patients after treatment in prior studies with non pegylated interferon alfa-2b (with or without ribavirin) and pegylated interferon alfa-2b (with or without ribavirin), respectively. The purpose of the studies was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. At least 5 years of long-term follow-up was completed after treatment in 462 patients and 327 patients, respectively. 12 out of 492 sustained responders and only 4 out of 366 sustained responders relapsed, respectively, in

the studies. The Kaplan-Meier estimate for continued sustained response over 5 years is 97% (95% CI: 95-99%) for patients receiving non pegylated interferon alfa-2b (with or without ribavirin), and is 99% (95% CI: 97-100%) for patients receiving pegylated interferon alfa-2b (with or without ribavirin).

Indications

REBETOL Capsules are indicated in combination with peginterferon alfa 2b or interferon alfa-2b

- for the treatment of chronic hepatitis C in adult patients previously untreated with alpha interferon.

REBETOL Capsules are indicated in combination with interferon alfa-2b

- for the treatment of chronic hepatitis C in adult patients who have subsequently relapsed following alpha interferon therapy.

Patients must be 18 years of age or older and have compensated liver disease.

REBETOL Capsules are to be used only in combination with peginterferon alfa 2b or interferon alfa-2b Solution for Injection.

See the prescribing information for peginterferon alfa-2b or interferon alfa-2b for information on its actions.

DOSAGE AND ADMINISTRATION

REBETOL Capsules must not be used alone because ribavirin is not effective as monotherapy in the treatment of hepatitis C.

REBETOL must be used in combination with either peginterferon alfa-2b (1.5 micrograms/kg/week) or interferon alfa-2b (3 million international units [MIU] three times a week [TIW]). The choice of combination regimen is based on the characteristics of the patient.

REBETOL Capsules in combination with peginterferon alfa-2b solution:

The dose of REBETOL is based on patient body weight (Table 1). REBETOL capsules are to be administered orally each day in two divided doses with food (morning and evening).

REBETOL doses (in combination with peginterferon alfa-2b)		
Table 1 REBETOL dose based on body weight		
Patient weight (kg)	Daily REBETOL dose	Number of 200 mg capsules
< 65	800 mg	4 a
65 – 85	1,000 mg	5 b
>85	1,200 mg	6 c

a: 2 morning, 2 evening

b: 2 morning, 3 evening

c: 3 morning, 3 evening

Duration of treatment – naïve patients:

Predictability of sustained virological response: Patients infected with virus genotype 1 who fail to achieve virological response at Week 12 are highly unlikely to become sustained virological responders.

- Genotype 1: For patients who exhibit virological response at week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks). In the subset of patients with genotype 1 infection and low viral load (<2,000,000 copies/mL) who became HCV RNA negative at treatment week 4 and remain HCV RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration.
- Genotypes 2 or 3: It is recommended that all patients be treated for 24 weeks,
- Genotype 4: In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

REBETOL Capsules in combination with interferon alfa-2b solution:

REBETOL Capsules are administered orally at a dose of 1000 mg or 1200 mg daily in two divided doses (morning and evening), in combination with interferon alfa-2b solution for Injection administered subcutaneously at a dose of 3 million IU three times a week (every other day).

The recommended dose of REBETOL Capsules in combination with interferon alfa-2b depends on the patient's body weight:

Body Weight	Rebetol Capsules, PO	Intron A Injection, SC
≤ 75 kg	2 x 200mg capsules am 3 x 200mg capsules pm	3 million IU 3 times weekly
> 75 kg	3 x 200mg capsules am 3 x 200mg capsules pm	3 million IU 3 times weekly

Duration of treatment:

Predictability of sustained virological response: The recommended duration of treatment is up to 1 year. Duration should be individualized in accordance with the baseline characteristics of the disease, response to therapy and tolerance of the regimen. After 6 months of treatment, virologic response should be assessed. If virologic response has not been achieved by 6 months, discontinuation of REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b Solution should be considered.

- Genotype 1: Treatment should be continued for another six month period (i.e., a total of one year) in patients who exhibit negative HCV-RNA after six months of treatment.
- Genotypes Non-1: The decision to extend therapy to one year in patients with negative HCV-RNA after six months of treatment should be based on other prognostic factors (e.g., age > 40 years, male gender, bridging fibrosis).

Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during therapy with REBETOL and peginterferon alfa-2b or interferon alfa-2b, modify the dosages of each product if appropriate, until the adverse reactions abate. If intolerance persists following dosage adjustment, discontinuation of therapy may be indicated. Guidelines were developed in clinical trials for dose modification (see Dosage modification guidelines, **Table 2**). There is no evidence that switching to another alpha interferon will alleviate intolerance.

<u>Laboratory Values</u>	Reduce only REBETOL Capsule dose <u>to 600 mg/day*</u> , if:	Reduce only interferon alfa-2b dose <u>to one-half dose</u> , if:	Discontinue combination therapy if:
Haemoglobin	< 100g/L	-	< 85 g/L
Haemoglobin in: patients with history of stable cardiac disease	≥ 20g/L decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)		< 120g/L after 4 weeks of dose reduction
White blood cells	-	< 1.5 x 10 ⁹ /L	< 1.0 x 10 ⁹ /L
Neutrophils	-	< 0.75 x 10 ⁹ /L	< 0.5 x 10 ⁹ /L
Platelets	-	< 50 x 10 ⁹ /L	< 25 x 10 ⁹ /L
Bilirubin – Direct	-	-	2.5 x ULN**
Bilirubin – Indirect	> 50mg/L	-	> 40mg/L (for > 4 weeks)
Creatinine	-	-	> 20 mg/L
ALT/AST	-	-	2 x baseline

			and > 10 x ULN**
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* Patients whose dose of REBETOL is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

** Upper limit of normal

Because of the recognized haemolysis associated with ribavirin therapy, separate guidelines are provided for patients with a history of cardiovascular disease. In these patients, a permanent dose reduction is required if the haemoglobin decreases by $\geq 20\text{g/L}$ during any 4 week period. In addition, if the haemoglobin remains $< 120\text{g/L}$ after 4 weeks on a reduced dose, the patient should discontinue REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution (Table 2).

Use in hepatic impairment: No pharmacokinetic interaction appears between ribavirin and hepatic function. Therefore, based on pharmacokinetic activity, no dose adjustment of REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution is required in patients with hepatic impairment. REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution is contraindicated in patients with decompensated liver disease or severe hepatic dysfunction (see CONTRAINDICATIONS and DOSAGE MODIFICATION GUIDELINES table).

Use in renal impairment: The pharmacokinetic activity of ribavirin is altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of REBETOL. Patients with creatinine clearance $< 50\text{ ml/minute}$ must not be treated with REBETOL (see CONTRAINDICATIONS). Subjects with impaired renal function and/or those over the age of 50 should be more carefully monitored with respect to development of anaemia. If serum creatinine rises to $> 20\text{mg/L}$ (see DOSAGE MODIFICATIONS GUIDELINES table),

REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution must be discontinued.

Use in patients under 18 years of age: Safety and effectiveness in these patients have not been established. Therefore, use in children or adolescents under the age of 18 is not recommended (see INDICATIONS AND USAGE).

Use in the elderly: There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to the administration of REBETOL Therapy.

CONTRAINDICATIONS

See peginterferon alfa-2b or interferon alfa-2b prescribing information for additional contraindications.

- a history of hypersensitivity to ribavirin or any component of REBETOL Capsules.
- a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months (see PRECAUTIONS).
- pregnant women. REBETOL plus INTRON A or PEG-INTRON Combination Therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy;
- men whose female partners are pregnant;
- women who are breastfeeding
- hemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).
- severe, debilitating medical conditions, including patients with chronic renal failure or creatinine clearance <50 ml/minute.
- severe hepatic dysfunction or decompensated cirrhosis of the liver
- autoimmune hepatitis; or history of autoimmune disease

WARNINGS AND PRECAUTION

(See peg-interferon alfa-2b or interferon alfa-2b prescribing information for additional precautions.)

Based on results of clinical studies, the use of ribavirin as monotherapy is not effective and REBETOL Capsules must not be used alone. The safety and efficacy of combination therapy have been established only using REBETOL Capsules together with peginterferon alfa-2b or interferon alfa-2b Solution for Injection. Variations in dosage, routes of administration and adverse reactions exist among different brands of interferon. Therefore, only peginterferon alfa 2b or interferon alfa-2b Solution for Injection should be used in combination with REBETOL Capsules.

Teratogenic risk:

Preclinical data: Significant teratogenic and/or embryocidal potential has been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses one tenth to one twentieth of the recommended human dose. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of fetuses and offspring was reduced. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose.

Female patients: Ribavirin therapy must not be used by women who are pregnant (see CONTRAINDICATIONS). Extreme care must be taken to avoid pregnancy in female patients. REBETOL therapy should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their partners must each use an effective contraceptive during treatment and for 6 months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time (see USAGE DURING PREGNANCY AND LACTATION). If pregnancy does occur during treatment or within 6 months from stopping

treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking REBETOL Therapy. Ribavirin accumulates intracellularly and is cleared from the body very slowly. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilization of the ova. Male patients and their female partners of childbearing age must, therefore, be counselled to each use an effective contraceptive during treatment with ribavirin and for 6 months after treatment has been concluded.

Carcinogenicity and Mutagenicity: Conventional carcinogenicity studies in rodents with low exposures compared to human exposure under therapeutic conditions (factor 0.1 in rats and 1 in mice) did not reveal tumorigenicity of ribavirin. In addition, in a 26 week carcinogenicity study using the heterozygous p53(+/-) mouse model, ribavirin did not produce tumours at the maximally tolerated dose of 300 mg/kg (plasma exposure factor approximately 2.5 compared to human exposure). These studies do not suggest a carcinogenic potential of ribavirin in humans.

Ribavirin is mutagenic in some *in vivo* and *in vitro* genotoxicity assays.

Haemolysis/Anaemia: A decrease in haemoglobin levels to <100 g/L was observed in up to 14% of patients treated with REBETOL in combination with interferon alfa-2b solution in clinical trials. Although ribavirin has no direct cardiovascular effects, anaemia associated with REBETOL Capsules may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution must be administered with caution to patients with pre-existing cardiac disease (see CONTRAINDICATIONS). Cardiac status should be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy should be stopped (see DOSAGE AND ADMINISTRATION).

Acute hypersensitivity: If an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, REBETOL in combination with peginterferon alfa 2-b or interferon alfa-2b solution should be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Liver function: Hepatotoxicity, including fatalities, has been observed rarely with interferon alfa-2b. Any patient developing significant liver function abnormalities during treatment should be monitored closely. The treatment should be discontinued if signs and symptoms progress. REBETOL in combination with peginterferon alfa-2b or interferon alpha-2b is contraindicated in the presence of severe hepatic dysfunction or decompensated liver disease (see CONTRAINDICATIONS).

Renal function: Renal function should be evaluated in all patients prior to initiation of REBETOL (see CONTRAINDICATIONS AND DOSAGE AND ADMINISTRATION for specific guidelines.)

Psychiatric and Central Nervous System (CNS): *Patients with existence of or history of severe psychiatric conditions, or with substance use disorders:* If combination treatment with REBETOL Capsules and peg-interferon alfa-2b or interferon alfa 2-b is judged necessary in adult patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualized diagnostic and therapeutic management of the psychiatric condition.

Treatment with interferons may be associated with exacerbated symptoms of psychiatric disorders in HCV infected patients with co-occurring psychiatric and substance use disorders. If treatment with interferons is judged necessary in patients with prior history or existence of psychiatric condition or with substance use disorders, in order to reach successful adherence to treatment with interferons, adequate management of psychiatric symptoms and substance use requires individualized screening strategies and frequent psychiatric symptom monitoring. Early intervention

for re-emergence or development of neuropsychiatric symptoms and substance use is recommended.

If severe neuropsychiatric effects, particularly depression, are observed, REBETOL Capsules in combination with peginterferon alfa 2-b or interferon alfa 2-b should be discontinued. Severe central nervous system (CNS) effects particularly depression, suicidal ideation, suicide or attempted suicide have been observed in some patients during treatment with REBETOL Capsules in combination with peg-interferon alfa-2b or interferon alfa 2-b. Other CNS effects including aggressive behaviour, sometimes directed towards others, psychosis including hallucinations, confusion and alterations of mental status also have been observed.

If patients develop psychiatric or CNS problems, including clinical depression, it is recommended that the patient be carefully monitored by the prescribing physician during treatment and in the 6-month follow-up period. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician. If psychiatric symptoms persist or worsen, or suicidal ideation or aggressive behaviour towards others is identified, it is recommended that treatment with REBETOL combination therapy be discontinued, and the patient followed with psychiatric intervention as appropriate.

Cardiovascular: Patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders should be closely monitored. Those patients who have pre-existing cardiac abnormalities should have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. (Also see PRECAUTIONS: Haemolysis/Anaemia).

Patients co-infected with HIV/HCV: Patients taking NRTI treatment in association with ribavirin and interferon alfa-2b or peginterferon alfa-2b may be at increased risk of mitochondrial toxicity, lactic acidosis and hepatic

decompensation. Please refer also to the relevant product information for antiviral medicinal products.

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Dental and periodontal disorders: Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of REBETOL and interferon alfa-2b or pegylated interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition, some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Laboratory tests: Standard haematological tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid), and a test of thyroid function should be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of REBETOL in combination with peg-interferon alfa-2b or interferon alfa-2b solution are:

- o Haemoglobin ≥ 120 g/L (females) ≥ 130 g/L (males)
- o Platelets $\geq 100,000/\text{mm}^3$
- o Neutrophil Count $\geq 1,500/\text{mm}^3$
- o TSH Levels must be within normal limits

These laboratory evaluations should be conducted during pretreatment and at weeks 2, 4 and 8 of therapy and periodically thereafter as clinically appropriate.

For women of childbearing potential: Female patients must have a routine pregnancy test performed monthly during treatment and for 6 months thereafter. Female partners of male patients must have a routine pregnancy test performed monthly during treatment and for six months thereafter (see **Precautions**).

Uric acid may increase with REBETOL due to haemolysis; therefore, the potential for development of gout must be carefully monitored in pre-disposed patients

DRIVING AND OPERATING MACHINERY: Patients who develop fatigue, somnolence, or confusion during treatment with REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b Solution should be cautioned to avoid driving or operating machinery.

USAGE DURING PREGNANCY AND LACTATION: Ribavirin was embryotoxic and/or teratogenic in conventional embryotoxicity/mutagenicity studies in rats and rabbits at dose levels well below those proposed for clinical use. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of foetuses and offspring was reduced. Foetal abnormalities occurred at ribavirin doses as low as 0.3 mg/kg/day in rats and rabbits. Ribavirin had no effect on fertility or peri- or post- natal reproductive performance.

***Female patients:* REBETOL Capsules must not be used by women who are pregnant (see Contraindications and Precautions). Extreme care must be taken to avoid pregnancy in female patients. Therapy with REBETOL Capsules must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and their partners must each use an effective contraceptive during treatment and for six months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time (see Precautions). If pregnancy does occur during treatment or within six months from stopping treatment,**

the patient must be advised of the significant teratogenic risk of ribavirin to the foetus.

Male patients and their female partners: Extreme care must be taken to avoid pregnancy in partners of male patients taking REBETOL Capsules. Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilization of the ova. Male patients and their female partners of childbearing age must, therefore, be counselled to each use an effective contraceptive during treatment with REBETOL Capsules and for six months after treatment has been concluded.

REBETOL is recommended for use in fertile women only when they are using effective contraception during the treatment period.

Lactation: It is not known whether either component of REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b solution is excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing must be discontinued prior to initiation of treatment.

ADVERSE REACTIONS

(See the prescribing information for peginterferon alfa-2b or interferon alfa-2b for additional adverse effects.)

The safety of REBETOL is evaluated from data from three clinical trials in patients with no previous exposure to interferon (interferon-naïve patients): two trials studied REBETOL in combination with interferon alfa-2b, one trial studied REBETOL in combination with peginterferon alfa-2b.

Patients who are treated with interferon alfa-2b and ribavirin after previous relapse from interferon therapy or who are treated for a shorter period are likely to have an improved safety profile than that described below.

Table 3 describes the regimens and patient exposure from the trial experience for one year of treatment in interferon-naïve patients. The most common undesirable effects reported for each of these treatment groups is presented in **Table 4**.

Table 3 Regimens and patient exposure		
Treatment	Regimen	Number of patients treated for one year
REBETOL + peginterferon alfa-2b	REBETOL (> 10.6 mg/kg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week)	188
REBETOL + interferon alfa-2b	REBETOL (1,000/1,200 mg/day) + interferon alfa-2b (3 MIU three times a week)	505

Table 4 Undesirable effects reported in a clinical trial ($\geq 10\%$ of patients receiving REBETOL Combination Therapy)		
Organ system	REBETOL Combination Therapy	Interferon alfa-2b + ribavirin
Application site disorder		
Injection site inflammation	20 %	17 %
Injection site reaction	54 %	36 %
Body as a whole		
Headache	58 %	57 %
Fatigue	56 %	59 %
Rigors	42 %	40 %
Fever	39 %	32 %
Flu-like symptoms	21 %	23 %
Asthenia	28 %	17 %
Weight decrease	30 %	19 %
Gastrointestinal		
Nausea	43 %	31 %
Anorexia	35 %	26 %
Diarrhoea	20 %	13 %
Abdominal pain	12 %	9 %
Vomiting	16 %	10 %
Musculoskeletal		
Myalgia	49 %	49 %
Arthralgia	31 %	26 %
Musculoskeletal pain	15 %	11 %
Psychiatric		
Depression	34 %	32 %
Irritability	32 %	34 %
Insomnia	37 %	41 %
Anxiety	14 %	14 %
Concentration impaired	18 %	21 %
Emotional lability	11 %	10 %
Skin and appendages		
Alopecia	45 %	32 %
Pruritus	27 %	27 %
Skin dry	23 %	21 %
Rash	21 %	21 %
Respiratory system		
Pharyngitis	10 %	7 %
Coughing	14 %	11 %
Dyspnoea	26 %	22 %
Other		
Dizziness	17 %	16 %
Infection viral	10 %	5 %
Mouth dry	10 %	8 %

Undesirable effects reported between 5 and 10 % in the treatment group receiving the recommended dose of REBETOL + peginterferon alfa-2b were increased sweating, chest pain, right upper quadrant (RUQ) pain, paresthesia, hypothyroidism, constipation, dyspepsia, tachycardia, agitation, nervousness, menorrhagia, menstrual disorder, nonproductive cough, rhinitis, taste perversion, and blurred vision.

Undesirable effects reported between 2 and 5 % in the treatment group receiving the recommended dose of REBETOL + peginterferon alfa-2b were injection site pain, flushing, hypotension, lacrimal gland disorder, erythema, malaise, hypertension, syncope, confusion, hyperesthesia, hypoesthesia, hypertonia, decreased libido, tremor, vertigo, hyperthyroidism, flatulence, gingival bleeding, glossitis, loose stools, stomatitis, ulcerative stomatitis, hearing impairment/loss, tinnitus, palpitation, thirst, thrombocytopenia, aggressive behavior, somnolence, herpes simplex, fungal infection, amenorrhea, prostatitis, otitis media, bronchitis, nasal congestion, respiratory disorder, rhinorrhea, sinusitis, eczema, abnormal hair texture, photosensitivity reaction, erythematous rash, maculopapular rash, migraine, conjunctivitis, and lymphadenopathy.

A reduction in haemoglobin concentrations by > 40g/L was observed in 30 % of patients treated with REBETOL and peginterferon alfa-2b and 37 % of patients treated with REBETOL + interferon alfa-2b. Haemoglobin levels dropped below 100g/L in up to 14 % of patients treated with REBETOL in combination with either peginterferon alfa-2b or interferon alfa-2b.

Most cases of anaemia, neutropenia, and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with REBETOL in combination with peginterferon alfa-2b (WHO grade 3: 39 of 186 (21 %); and WHO grade 4: 13 of 186 (7 %)).

In a clinical trial, approximately 1.2 % of patients treated with REBETOL in combination with peginterferon alfa-2b or interferon alfa-2b reported life-threatening psychiatric events during treatment. These events included suicidal ideation, aggressive behaviour, sometimes directed towards others, and attempted suicide.

Pancreatitis has been reported with the combination of REBETOL and interferon alfa-2b.

Very rarely, REBETOL used in combination with alfa interferons, including Intron A and PegIntron, may be associated with aplastic anaemia or pure red cell aplasia. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis also have been reported with REBETOL Capsules in combination with peginterferon alfa-2b.

An increase in uric acid and indirect bilirubin values associated with haemolysis was observed in some patients treated with REBETOL used in combination with peginterferon alfa-2b or interferon alfa-2b in clinical trials, but values returned to baseline levels by four weeks after the end of therapy. Among those patients with elevated uric acid levels, very few patients treated with the combination developed clinical gout, none of which required treatment modification or discontinuation from the clinical trials.

INTERACTIONS

Results of *in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

No interaction studies have been conducted with REBETOL Capsules and other medicinal products, except for peg interferon alfa-2b or interferon alfa-2b and antacids.

Peginterferon alfa-2b and Interferon alfa-2b: No pharmacokinetic interactions were noted between REBETOL Capsules and interferon alfa-2b in a multiple-dose pharmacokinetic study.

Antacid: The bioavailability of ribavirin 600 mg was decreased by co-administration with an antacid containing magnesium aluminium and simethicone; AUC_{0-∞} decreased 14 %. It is possible that the decreased bioavailability in this study was due to delayed transit of ribavirin or modified pH. This interaction is not considered to be clinically relevant.

Nucleoside analogues: Ribavirin was shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in vitro* findings raise the possibility that concurrent use of REBETOL Capsules with either zidovudine or stavudine might lead to increased HIV plasma viremia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with REBETOL Capsules concurrently with either of these two agents. If HIV RNA levels increase, the use of REBETOL Capsules concomitantly with reverse transcriptase inhibitors must be reviewed.

Use of nucleoside analogues, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogues (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported.

Patients co-infected with the Human Immunodeficiency Virus (HIV) and are receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding treatment with REBETOL Combination Therapy to HAART.

Any potential for interactions may persist for up to 2 months (5 half-lives for ribavirin) after cessation of REBETOL therapy due to the long half life.

There is no evidence that ribavirin interacts with non-nucleoside reverse transcriptase inhibitors or protease inhibitors.

(See the prescribing information for peginterferon alfa-2b or interferon alfa-2b for additional information on drug interactions.)

OVERDOSAGE

In clinical trials with REBETOL capsules in combination with peginterferon alfa-2b or interferon alfa-2b solution, the maximum overdose reported was a total dose of 10 g of REBETOL Capsules (50 x 200 mg capsules) and 39 million units of interferon alfa-2b Solution for Injection (13 subcutaneous injections of 3 million IU each) taken in one day by a patient in an attempt at suicide. The patient was observed for two days in the emergency room, during which time no adverse event from the overdose was noted.

PHARMACEUTICAL PRECAUTIONS

Store Rebetol capsules at or below 25°C, protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

PRESENTATIONS

REBETOL Capsules are marketed in packs of 84 Capsules. Other presentations registered but not marketed are 112, 140 and 168 capsules.

NAME AND ADDRESS

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DATE OF PREPARATION

20 January 2011