SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ribavirine ratiopharm 200 mg filmomhulde tabletten
Ribavirine ratiopharm 400 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of ribavirin.

400 mg
Each film-coated tablet contains 400 mg of ribavirin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Oval, biconvex, ivory film-coated tablets of 14 mm length and 7 mm width.

400 mg
Oval, biconvex, yellow film-coated tablets of 18 mm length and 9 mm width.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Product name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4, and 5.1).
[Product name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) for paediatric patients (children 3 years of age and older and adolescents) not previously treated and without liver decompensation (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Treatment should be initiated, and monitored, by a physician experienced in the management of chronic hepatitis C.

Posology

[Product name] must be used in combination therapy as described in section 4.1.
Please refer to the corresponding Summary of Product Characteristics (SmPC) of medicinal products used in combination with ribavirin for additional prescribing information particular to that product and for further dosage recommendations on co-administration with [Product name].

[Product name] film-coated tablets are to be administered orally each day in two divided doses (morning and evening) with food.

Adults

The recommended dose and duration of [Product name] depends on patient's weight and on the medicinal product that is used in combination. Please refer to the corresponding SmPC of medicinal products used in combination with [Product name].

In the cases in which no specific dose recommendation is made, the following dose should be used: Patient weight: < 75 kg = 1,000 mg and > 75 kg = 1,200 mg.

Paediatric population
No data are available in children below 3 years of age.

Note: For patients who weigh < 47 kg, or are unable to swallow the tablets, ribavirin oral solution may be available and should be used if appropriate.

Dosing of ribavirin for children and adolescent patients is determined by the patient body weight. For example, the body weight dosing used in conjunction with interferon alfa-2b or peginterferon alfa-2b is shown in **Table 1**. Please refer to the corresponding SmPC of medicinal products used in combination with ribavirin as some combination regimens do not adhere to the ribavirin dosing guidance provided in **Table 1**.

Table 1 Ribavirin dose based on body weight when used in combination with interferon alfa-2b or peginterferon alfa-2b in paediatric patients

Patient weight (kg)	Daily ribavirin dose	Number of 200 mg tablets*
47 - 49	600 mg	3 x 200 mg tablets[a]
50 - 65	800 mg	4 x 200 mg tablets[b]
> 65	Refer to adult dose recommendations	

[a]: 1 morning, 2 evening
[b]: 2 morning, 2 evening

[Product name] 400 mg Tablets
*NB: for 800 mg daily dose, 2 x 200 mg tablets can be substituted for 1 x 400 mg tablet.

Dose modification for adverse reactions

Dose modification for adults
Dose reduction of ribavirin depends on the initial ribavirin posology which depends on the medicinal product that is used in combination with ribavirin.

If a patient has a serious adverse reaction potentially related to ribavirin, the ribavirin dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity.

Table 2 provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration, cardiac status and indirect bilirubin concentration.

Table 2 Management of Adverse Reactions		
Laboratory values	Reduce ribavirin dose* if:	Discontinue ribavirin if:
Haemoglobin in patients with No Cardiac Disease	< 10 g/dL	< 8.5 g/dL
Haemoglobin: Patients with History of Stable Cardiac Disease	≥ 2 g/dL decrease in haemoglobin during any 4 week period during treatment (permanent dose reduction)	< 12 g/dL despite 4 weeks at reduced dose
Bilirubin – Indirect	> 5 mg/dL	> 4 mg/dL (adults)

* For patients receiving a 1,000 mg (< 75 kg) or 1,200 mg (> 75 kg) dose, ribavirin dose should be reduced to 600 mg/day (administered as one 200 mg tablet in the morning and two 200 mg tablets in the evening). If the abnormality is reversed, ribavirin may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.
For patients receiving a 800 mg (< 65 kg)-1,000 mg (65-80 kg)-1,200 mg (81-105 kg) or 1,400 mg (> 105 kg) dose, 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets in the evening.

In case of serious adverse reaction potentially related to medicinal products used in combination with ribavirin, refer to the corresponding SmPC of these medicinal products as some combination regimens do not adhere to the ribavirin dose modification and/or discontinuation guidelines as described in **Table 2**.

Dose modification for paediatric patients
Dose reduction in paediatric patients without cardiac disease follows the same guidelines as adult patients without cardiac disease regarding haemoglobin levels (**Table 2**).

There are no data for paediatric patients with cardiac disease (see section 4.4).

Table 3 provides guidelines for discontinuation based on the patient's indirect bilirubin concentration.

Table 3 Management of Adverse Reactions	
Laboratory values	Discontinue ribavirin if:
Bilirubin – Indirect	> 5 mg/dL (for > 4 weeks) (children and adolescents treated with interferon alfa-2b), or > 4 mg/dL (for > 4 weeks) (children and adolescents treated with peginterferon alfa-2b)

Special populations

Elderly (≥ 65 years of age)
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 administration of ribavirin (see section 5.2).

Paediatric patients (children 3 years of age and older and adolescents)
Ribavirin may be used in combination with peginterferon alfa-2b or interferon alfa-2b (see section 4.4). The selection of ribavirin formulation is based on individual characteristics of the patient.
The safety and efficacy of ribavirin used together with direct-acting-anti-virals in these patients has not been established. No data are available.

Please refer to the corresponding SmPC of medicinal products used in combination with ribavirin for further dosage recommendations on co-administration.

Renal impairment
The pharmacokinetics of ribavirin is altered in patients with renal dysfunction due to reduction of apparent creatinine clearance in these patients (see section 5.2). Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of ribavirin. Adult patients with moderate renal impairment (creatinine clearance of 30-50 mL/minute) should be administered alternating daily doses of 200 mg and 400 mg. Adult patients with severe renal impairment (creatinine clearance of < 30 mL/minute) and patients with End Stage Renal Disease (ESRD) or on haemodialysis should be administered ribavirin 200 mg/day. **Table 4** provides guidelines for dose modification for patients with renal dysfunction. Patients with impaired renal function should be more carefully monitored with respect to the development of anaemia. No data are available regarding dose modification for paediatric patients with renal impairment.

Table 4 Dosage Modification for Renal Impairment in Adult Patients	
Creatinine Clearance	**Ribavirin Dose (daily)**
30 to 50 mL/min	Alternating doses, 200 mg and 400 mg every other day
Less than 30 mL/min	200 mg daily
Haemodialysis (ESRD)	200 mg daily

Hepatic impairment
No pharmacokinetic interaction appears between ribavirin and hepatic function (see section 5.2). For use in patients with decompensated cirrhosis, see the corresponding SmPC of the medicinal products used in combination with ribavirin.

Method of administration
[Product name] should be administered orally with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see sections 4.4, 4.6 and 5.3). In females of childbearing potential, ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- Breast-feeding.
- History of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months (see section 4.4).
- Haemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).

Please refer to the corresponding SmPC of medicinal products used in combination with [Product name] for contraindications specific to these products.

4.4 Special warnings and precautions for use

Ribavirin must be used in combination with other medicinal products (see section 5.1).

Please refer to the SmPC of (peg)interferon alfa for details on the recommendations of monitoring and management regarding the adverse reactions listed below before initiating therapy and other precautions associated with (peg)interferon alfa.

There are several serious adverse reactions associated with the combination therapy of ribavirin with (peg)interferon alfa. These include:
- Severe psychiatric and central nervous system effects (such as depression, suicidal ideation, attempted suicide and aggressive behaviour, etc.)
- Growth inhibition in children and adolescents that may be irreversible in some patients
- Increased thyroid stimulating hormone (TSH) in children and adolescents

- Severe ocular disorders
- Dental and periodontal disorders.

Paediatric population
When deciding not to defer combination treatment with peginterferon alfa-2b or interferon alfa-2b until adulthood, it is important to consider that this combination therapy induced a growth inhibition that may be irreversible in some patients. The decision to treat should be made on a case by case.

Haemolysis
A decrease in haemoglobin levels to < 10 g/dL was observed in up to 14 % of adult patients and 7 % of children and adolescents treated with ribavirin in combination with peginterferon alfa-2b or interferon alfa-2b in clinical trials. Although ribavirin has no direct cardiovascular effects, anaemia associated with ribavirin may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, ribavirin must be administered with caution to patients with pre-existing cardiac disease (see section 4.3). Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy must be stopped (see section 4.2).

Cardiovascular
Adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities 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. There are no data in children or adolescents with a history of cardiac disease.

Teratogenic risk
Prior to initiation of treatment with ribavirin the physician must comprehensively inform both male and female patients of the teratogenic risk of ribavirin, the necessity of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during or following treatment with ribavirin (see section 4.6). For laboratory monitoring of pregnancy, please refer to Laboratory tests.

Acute hypersensitivity
If an acute hypersensitivity reaction (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) develops, ribavirin must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Liver function
Any patient developing significant liver function abnormalities during treatment must be monitored closely. Please refer to the corresponding SmPC of medicinal products used in combination with ribavirin for discontinuation or dose modification recommendations.

Renal impairment
The pharmacokinetics 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 ribavirin. Due to substantial increases in ribavirin plasma concentrations in patients with moderate and severe renal impairment, ribavirin dose adjustments are recommended in adult patients with creatinine clearance < 50 mL/minute. No data are available regarding dose modification for paediatric patients with renal impairment (see sections 4.2 and 5.2). Haemoglobin concentrations should be monitored closely during treatment and corrective action taken as necessary (see section 4.2).

Potential to exacerbate immunosuppression
Pancytopenia and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the administration of a peginterferon and ribavirin concomitantly with azathioprine. This

myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see section 4.5).

HCV/HIV Co-infection

Mitochondrial toxicity and lactic acidosis: Caution should be taken in HIV-positive subjects co-infected with HCV who receive nucleoside reverse transcriptase inhibitor (NRTI) treatment (especially ddI and d4T) and associated interferon alfa/ribavirin treatment. In the HIV-positive population receiving an NRTI regimen, physicians should carefully monitor markers of mitochondrial toxicity and lactic acidosis when ribavirin is administered. For additional details see section 4.5.

Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis

Co-infected patients with advanced cirrhosis receiving combined anti-retroviral therapy (cART) may be at increased risk of hepatic decompensation and death. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentrations.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Please refer to the corresponding SmPC of medicinal products used in combination with ribavirin for discontinuation or dose modification recommendations. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

Haematological abnormalities in HCV/HIV co-infected patients

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and cART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with ribavirin and zidovudine are at increased risk of developing anaemia; therefore, the concomitant use of ribavirin with zidovudine is not recommended (see section 4.5).

Patients with low CD4 counts

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/μL. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the corresponding SmPC of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with ribavirin.

Laboratory tests

Standard haematologic tests, blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, serum creatinine, liver function tests, uric acid) and pregnancy tests must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of ribavirin therapy:

- Haemoglobin — Adult: ≥ 12 g/dL (females); ≥ 13 g/dL (males)
  Children and adolescents: ≥ 11 g/dL (females); ≥ 12 g/dL (males)

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

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

Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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.

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of pegylated alpha interferons and ribavirin concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these medicines should be stopped (see section 4.4).

No interaction studies have been conducted with ribavirin and other medicinal products, except for peginterferon alfa-2b, interferon alfa-2b and antacids.

No pharmacokinetic interactions were noted between ribavirin and peginterferon alfa-2b or 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_{tf} 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
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 analogs (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 (see section 4.4).
The exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment (ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine induced anaemia.

Any potential for interactions may persist for up to two months (five half-lives for ribavirin) after cessation of ribavirin therapy due to the long half-life (see section 5.2).

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

Conflicting findings are reported in literature on co-administration between abacavir and ribavirin. Some data suggest that HIV/HCV co-infected patients receiving abacavir-containing ART may be at

risk of a lower response rate to pegylated interferon/ribavirin therapy. Caution should be exercised when both medicines are co-administered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Female patients
Ribavirin must not be used by females who are pregnant (see sections 4.3, 4.4 and 5.3). Extreme care must be taken to avoid pregnancy in female patients (see section 5.3). Ribavirin therapy must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Females of childbearing potential must use an effective contraceptive during treatment and for nine months after treatment has been concluded; routine monthly pregnancy tests must be performed during this time (see section 4.4). If pregnancy does occur during treatment or within nine months from stopping treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the foetus (see section 4.4).

Male patients and their female partners
Extreme care must be taken to avoid pregnancy in partners of male patients taking ribavirin (see sections 4.3, 4.4 and 5.3). 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 potential teratogenic or genotoxic effects on the human embryo/foetus. Although data on approximately 300 prospectively followed pregnancies with paternal exposure to ribavirin have not shown an increased risk of malformation compared to the general population, nor any specific pattern of malformation, either male patients or their female partners of childbearing age must be advised to use an effective contraceptive during treatment with ribavirin and for six months after treatment. Routine monthly pregnancy tests must be performed during this time. Men whose partners are pregnant must be instructed to use a condom to minimise delivery of ribavirin to the partner.

Pregnancy

The use of ribavirin is contraindicated during pregnancy. Ribavirin has been shown in preclinical studies to be teratogenic and genotoxic (see section 4.4 and 5.3).

Breast-feeding

It is not known whether ribavirin is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding must be discontinued prior to initiation of treatment.

Fertility

Preclinical data:
- Fertility: In animal studies, ribavirin produced reversible effects on spermatogenesis (see section 5.3).
- Teratogenicity: Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses as low as one twentieth of the recommended human dose (see section 5.3).
- Genotoxicity: Ribavirin induces genotoxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

[Product name] has no or negligible influence on the ability to drive and use machines; however, other medicinal products used in combination may have an effect. Thus, patients who develop fatigue, somnolence, or confusion during treatment must be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The salient safety issue of ribavirin is haemolytic anaemia occurring within the first weeks of therapy. The haemolytic anaemia associated with ribavirin therapy may result in deterioration of cardiac function and/or worsening of pre-existing cardiac disease. An increase in uric acid and indirect bilirubin values associated with haemolysis were also observed in some patients.

The adverse reactions listed in this section are primarily derived from clinical trials and/or as adverse drug reactions from spontaneous reports when ribavirin was used in combination with interferon alfa-2b or peginterferon alfa-2b.

Use of Ribavirin in combination with direct antiviral agents (DAA)
Based on the review of safety data derived from clinical studies in adults with DAA in combination with ribavirin, the most frequent adverse reactions identified as associated with ribavirin were anaemia, nausea, vomiting, asthenia, fatigue, insomnia, cough, dyspnoea, pruritus and rash. Except anaemia, the majority of these adverse reactions were not serious and resolved without treatment discontinuation.

Please refer to the corresponding SmPC of medicinal products that are used in combination with ribavirin for additional undesirable effects reported with these products.

Adults

Bitherapy with peginterferon alfa-2b or interferon alfa-2b
The safety of ribavirin is evaluated from data from four clinical trials in patients with no previous exposure to interferon (interferon-naïve patients): two trials studied ribavirin in combination with interferon alfa-2b, two trials studied ribavirin 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.

Tabulated list of adverse reactions for adults

The adverse reactions listed in **Table 5** are based on experience from clinical trials in adult naïve patients treated for 1 year and post-marketing use. A certain number of adverse reactions, generally attributed to interferon therapy but that have been reported in the context of hepatitis C therapy (in combination with ribavirin) are also listed for reference in **Table 5**. Also, refer to peginterferon alfa-2b and interferon alfa-2b SmPCs for adverse reactions that may be attributable to interferon monotherapy. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 5 Adverse reactions reported during clinical trials or following the marketing use of ribavirin with pegylated interferon alfa-2b or interferon alfa-2b	
System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Viral infection, pharyngitis
Common:	Bacterial infection (including sepsis), fungal infection, influenza, respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis, urinary tract infection
Uncommon:	Lower respiratory tract infection
Rare:	Pneumonia*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Neoplasm unspecified
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Haemolitic anaemia, leukopenia, thrombocytopenia, lymphadenopathy, lymphopenia
Very rare:	Aplastic anaemia*
Not known:	Pure red cell aplasia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura
Immune system disorders	
Uncommon:	Drug hypersensitivity
Rare:	Sarcoidosis*, rheumatoid arthritis (new or aggravated)
Not known:	Vogt-Koyanagi-Harada syndrome, systemic lupus erythematosus, vasculitis, acute hypersensitivity reactions including urticaria, angioedema, bronchoconstriction, anaphylaxis
Endocrine disorders	
Common:	Hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
Very common:	Anorexia
Common:	Hyperglycaemia, hyperuricaemia, hypocalcaemia, dehydration, increased appetite
Uncommon:	Diabetes mellitus, hypertriglyceridemia*
Psychiatric disorders	
Very common:	Depression, anxiety, emotional lability, insomnia
Common:	Suicidal ideation, psychosis, aggressive behaviour, confusion, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, decreased libido apathy, abnormal dreams, crying
Uncommon:	Suicide attempts, panic attack, hallucination
Rare:	Bipolar disorder*
Very rare:	Suicide*
Not known:	Homicidal ideation*, mania*, mental status change
Nervous system disorders	
Very common:	Headache, dizziness, dry mouth, concentration impaired
Common:	Amnesia, memory impairment, syncope, migraine, ataxia, paraesthaesia, dysphonia, taste loss, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia
Uncommon:	Neuropathy, peripheral neuropathy
Rare:	Seizure (convulsion)*
Very rare:	Cerebrovascular haemorrhage*, cerebrovascular ischaemia*, encephalopathy*, polyneuropathy*
Not known:	Facial palsy, mononeuropathies
Eye disorders	

Common:	Visual disturbance, blurred vision, conjunctivitis, eye irritation, eye pain, abnormal vision, lacrimal gland disorder, dry eye
Rare:	Retinal haemorrhages*, retinopathies (including macular oedema)*, retinal artery occlusion*, retinal vein occlusion*, optic neuritis*, papilloedema*, loss of visual acuity or visual field*, retinal exudates
Ear and labyrinth disorders	
Common:	Vertigo, hearing impaired/loss, tinnitus, ear pain
Cardiac disorders	
Common:	Palpitation, tachycardia
Uncommon:	Myocardial infarction
Rare:	Cardiomyopathy, arrhythmia*
Very rare:	Cardiac ischaemia*
Not known:	Pericardial effusion*, pericarditis*
Vascular disorders	
Common:	Hypotension, hypertension, flushing
Rare:	Vasculitis
Very rare:	Peripheral ischaemia*
Respiratory, thoracic and mediastinal disorders	
Very common:	Dyspnoea, coughing
Common:	Epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain, nonproductive cough
Very rare:	Pulmonary infiltrates*, pneumonitis*, interstitial pneumonitis*
Gastrointestinal disorders	
Very common:	Diarrhoea, vomiting, nausea, abdominal pain
Common:	Ulcerative stomatitis, stomatitis, mouth ulceration, colitis, upper right quadrant pain, dyspepsia, gastroesophageal reflux*, glossitis, cheilitis, abdominal distension, gingival bleeding, gingivitis, loose stools, tooth disorder, constipation, flatulence
Uncommon:	Pancreatitis, oral pain
Rare:	Ischaemic colitis
Very rare:	Ulcerative colitis*
Not Known:	Periodontal disorder, dental disorder, tongue pigmentation
Hepatobiliary disorders	
Common:	Hepatomegaly, jaundice, hyperbilirubinemia*
Very rare:	Hepatotoxicity (including fatalities)*
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, pruritus, skin dry, rash
Common:	Psoriasis, aggravated psoriasis, eczema, photosensitivity reaction, maculopapular rash, erythematous rash, night sweats, hyperhidrosis, dermatitis, acne, furuncule, erythema, urticaria, skin disorder, bruise, sweating increased, abnormal hair texture, nail disorder*
Rare:	Cutaneous sarcoidosis
Very rare:	Stevens Johnson syndrome*, toxic epidermal necrolysis*, erythema multiforme*
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia, musculoskeletal pain
Common:	Arthritis, back pain, muscle spasms, pain in extremity
Uncommon:	Bone pain, muscle weakness
Rare:	Rhabdomyolysis*, myositis*

Renal and urinary disorders	
Common:	Micturition frequency, polyuria, urine abnormality
Rare:	Renal failure*, renal insufficiency*
Very rare:	Nephrotic syndrome*
Reproductive system and breast disorders	
Common:	Female: amenorrhea, menorrhagia, menstrual disorder, dysmenorrhea, breast pain, ovarian disorder, vaginal disorder. Male: impotence, prostatitis, erectile dysfunction Sexual dysfunction (not specified)*
General disorders and administration site conditions	
Very common:	Fatigue, rigors, pyrexia, influenza like illness, asthenia, irritability
Common:	Chest pain, chest discomfort, peripheral oedema, malaise, feeling abnormal, thirst
Uncommon:	Face oedema
Investigations	
Very common:	Weight decrease
Common:	Cardiac murmur

* Since ribavirin has always been prescribed with an alpha interferon product, and the listed adverse drug reactions included reflecting post-marketing experience do not allow precise quantification of frequency, the frequency reported above is from clinical trials using ribavirin in combination with interferon alfa-2b (pegylated or non-pegylated).

Description of selected adverse reactions
A reduction in haemoglobin concentrations by > 4 g/dL was observed in 30 % of patients treated with ribavirin and peginterferon alfa-2b and 37 % of patients treated with ribavirin and interferon alfa-2b. Haemoglobin levels dropped below 10 g/dL in up to 14 % of adult patients and 7 % of children and adolescents treated with ribavirin 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 ribavirin in combination with peginterferon alfa-2b (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]); WHO grade 3 leukopenia was also reported in 7 % of this treatment group.

An increase in uric acid and indirect bilirubin values associated with haemolysis was observed in some patients treated with ribavirin 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.

HCV/HIV co-infected patients
For HCV/HIV co-infected patients receiving ribavirin in combination with peginterferon alfa-2b, other adverse reactions (that were not reported in mono-infected patients) which have been reported in the studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

Mitochondrial toxicity
Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated-ribavirin for co-HCV infection (see section 4.4).

Laboratory values for HCV/HIV co-infected patients
Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving ribavirin in combination with

peginterferon alfa-2b when compared to patients receiving ribavirin in combination with interferon alfa-2b. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/mm^3 was observed in 4 % (8/194) of patients and decrease in platelets below 50,000/mm^3 was observed in 4 % (8/194) of patients receiving ribavirin in combination with peginterferon alfa-2b. Anaemia (haemoglobin < 9.4 g/dL) was reported in 12 % (23/194) of patients treated with ribavirin in combination with peginterferon alfa-2b.

CD4 lymphocytes decrease
Treatment with ribavirin in combination with peginterferon alfa-2b was associated with decreases in absolute $CD4^+$ cell counts within the first 4 weeks without a reduction in $CD4^+$ cell percentage. The decrease in $CD4^+$ cell counts was reversible upon dose reduction or cessation of therapy. The use of ribavirin in combination with peginterferon alfa-2b had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N = 25) are available in co-infected patients with $CD4^+$ cell counts < 200/µL (see section 4.4).
Please refer to the corresponding SmPC of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with ribavirin in combination with other medicinal products.

Paediatric population
In combination with peginterferon alfa-2b
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of peginterferon alfa-2b and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with pegylated interferon alfa-2b and ribavirin, growth inhibition was observed that resulted in reduced height in some patients (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and in height percentiles were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3rd percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still 3 percentiles and 7 percentiles, respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3rd percentile). Ninety four of 107 children enrolled in the 5 year long-term follow up trial. The effects on growth were less in those children treated for 24 weeks than those treated for 48 weeks. From pre-treatment to end of long-term follow-up among children treated for 24 or 48 weeks, height-for-age percentiles decreased 1.3 and 9.0 percentiles, respectively. Twenty-four percent of children (11/46) treated for 24 weeks and 40 % of children (19/48) treated for 48 weeks had a > 15 percentile height for age decrease from pre-treatment to the end of 5 year long-term follow-up compared to pre-treatment baseline percentiles. Eleven percent of children (5/46) treated for 24 weeks and 13 % of children (6/48) treated for 48 weeks were observed to have a decrease from pre-treatment baseline > 30 height-for-age percentiles to the end of the 5 year long-term follow-up. For weight, pre-treatment to end of long-term follow-up, weight-for-age percentiles decreased 1.3 and 5.5 percentiles among children treated for 24 weeks or 48 weeks, respectively. For BMI, pre-treatment to end of long-term follow-up, BMI-for-age percentiles decreased 1.8 and 7.5 percentiles among children treated for 24 weeks or 48 weeks, respectively. Decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children. The decline of height, weight and BMI Z scores observed during the treatment phase in comparison to a normative population did not fully recover at the end of long-term follow-up period for children treated with 48 weeks of therapy (see section 4.4).

In the treatment phase of this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection

site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

In combination with interferon alfa-2b
In clinical trials of 118 children and adolescents 3 to 16 years of age treated with combination therapy of interferon alfa-2b and ribavirin, 6 % discontinued therapy due to adverse events. In general, the adverse event profile in the limited children and adolescent population studied was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition, as decrease in height percentile (mean percentile decrease of 9 percentile) and weight percentile (mean percentile decrease of 13 percentile) were observed during treatment. Within the 5 years follow-up post-treatment period, the children had a mean height of 44th percentile, which was below the median of the normative population and less than their mean baseline height (48th percentile). Twenty (21 %) of 97 children had a > 15 percentile decrease in height percentile, of whom 10 of the 20 children had a > 30 percentile decrease in their height percentile from the start of treatment to the end of long-term follow-up (up to 5 years). Final adult height was available for 14 of those children and demonstrated that 12 continued to show height deficits > 15 percentiles, 10 to 12 years after the end of treatment. During combination therapy for up to 48 weeks with interferon alfa-2b and ribavirin, growth inhibition was observed that resulted in reduced final adult height in some patients. In particular, decrease in mean height percentile from baseline to the end of the long-term follow-up was most prominent in prepubertal age children (see section 4.4).

Furthermore, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs. 1 %) during treatment and during the 6 month follow-up after treatment. As in adult patients, children and adolescents also experienced other psychiatric adverse reactions (e.g., depression, emotional lability, and somnolence) (see section 4.4). In addition, injection site disorders, pyrexia, anorexia, vomiting and emotional lability occurred more frequently in children and adolescents compared to adult patients. Dose modifications were required in 30 % of patients, most commonly for anaemia and neutropenia.

Tabulated list of adverse reactions in paediatric population

Reported adverse reactions listed in **Table 6** are based on experience from the two multicentre children and adolescents clinical trials using ribavirin with interferon alfa-2b or peginterferon alfa-2b. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 6	Adverse reactions very commonly, commonly and uncommonly reported during clinical trials in children and adolescents with ribavirin in combination with interferon alfa-2b or peginterferon alfa-2b
System Organ Class	**Adverse Reactions**
Infections and infestations	
Very common:	Viral infection, pharyngitis
Common:	Fungal infection, bacterial infection, pulmonary infection, nasopharyngitis, pharyngitis streptococcal, otitis media, sinusitis, tooth abscess, influenza, oral herpes, herpes simplex, urinary tract infection, vaginitis, gastroenteritis
Uncommon:	Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common:	Neoplasm unspecified
Blood and lymphatic system disorders	
Very common:	Anaemia, neutropenia
Common:	Thrombocytopenia, lymphadenopathy
Endocrine disorders	
Very common:	Hypothyroidism
Common:	Hyperthyroidism, virilism
Metabolism and nutrition disorders	
Very common:	Anorexia, increased appetite, decreased appetite
Common:	Hypertriglyceridemia, hyperuricemia
Psychiatric disorders	
Very common:	Depression, insomnia, emotional lability
Common:	Suicidal ideation, aggression, confusion, affect lability, behaviour disorder, agitation, somnambulism, anxiety, mood altered, restlessness, nervousness, sleep disorder, abnormal dreaming, apathy
Uncommon:	Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare
Nervous system disorders	
Very common:	Headache, dizziness
Common:	Hyperkinesia, tremor, dysphonia, paresthaesia, hypoaesthesia, hyperaesthesia, concentration impaired, somnolence, disturbance in attention, poor quality of sleep
Uncommon:	Neuralgia, lethargy, psychomotor hyperactivity
Eye disorders	
Common:	Conjunctivitis, eye pain, abnormal vision, lacrimal gland disorder
Uncommon:	Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia
Ear and labyrinth disorders	
Common:	Vertigo
Cardiac disorders	
Common:	Tachycardia, palpitations
Vascular disorders	
Common:	Pallor, flushing
Uncommon:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Common:	Dyspnoea, tachypnea, epistaxis, coughing, nasal congestion, nasal irritation, rhinorrhoea, sneezing, pharyngolaryngeal pain
Uncommon:	Wheezing, nasal discomfort
Gastrointestinal disorders	
Very common:	Abdominal pain, abdominal pain upper, vomiting , diarrhoea, nausea
Common:	Mouth ulceration, stomatitis ulcerative, stomatitis, aphthous stomatitis, dyspepsia, cheilosis, glossitis, gastroesophageal reflux,

	rectal disorder, gastrointestinal disorder, constipation, loose stools, toothache, tooth disorder, stomach discomfort, oral pain
Uncommon:	Gingivitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal
Uncommon:	Hepatomegaly
Skin and subcutaneous tissue disorders	
Very common:	Alopecia, rash
Common:	Pruritus, photosensitivity reaction, maculopapular rash, eczema, hyperhidrosis, acne, skin disorder, nail disorder, skin discolouration, dry skin, erythema, bruise
Uncommon:	Pigmentation disorder, dermatitis atopic, skin exfoliation
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, myalgia, musculoskeletal pain
Common:	Pain in extremity, back pain, muscle contracture
Renal and urinary disorders	
Common:	Enuresis, micturition disorder, urinary incontinence, proteinuria
Reproductive system and breast disorders	
Common:	Female: amenorrhea, menorrhagia, menstrual disorder, vaginal disorder, Male: testicular pain
Uncommon:	Female: dysmenorrhoea
General disorders and administration site conditions	
Very common:	Fatigue, rigors, pyrexia, influenza-like illness, asthenia, malaise, irritability
Common:	Chest pain, oedema, pain, feeling cold
Uncommon:	Chest discomfort, facial pain
Investigations	
Very common:	Growth rate decrease (height and/or weight decrease for age)
Common:	Blood thyroid stimulating hormone increased, thyroglobulin increased
Uncommon:	Anti-thyroid antibody positive
Injury, poisoning and procedural complications	
Common:	Skin laceration
Uncommon:	Contusion

Most of the changes in laboratory values in the ribavirin/peginterferon alfa-2b clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with ribavirin used in combination with peginterferon alfa-2b in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical trials with ribavirin used in combination with peginterferon alfa-2b or interferon alfa-2b, the maximum overdose reported was a total dose of 10 g of ribavirin (50 x 200 mg film-coated tablets) and 39 MIU of interferon alfa-2b (13 subcutaneous injections of 3 MIU 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 reaction from the overdose was noted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, antivirals for treatment of HCV infections, ATC code: J05AP01.

Mechanism of action

Ribavirin is a synthetic nucleoside analogue which has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin in combination with other medicinal products exerts its effects against HCV is unknown. 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.

Clinical efficacy and safety

Ribavirin in combination with Direct Antiviral Agent (DAA):
Please refer to the SmPC of the corresponding DAA for a full description of the clinical data with such combination.
Only the description of the use of ribavirin from the original development with (peg)interferon alfa-2b is detailed in the current SmPC:

Bitherapy with peginterferon alfa-2b or interferon alfa-2b:
The use of ribavirin in combination treatment with peginterferon alfa-2b or interferon alfa-2b was evaluated in a number of clinical trials. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction assay (PCR) (> 30 IU/mL), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

Naïve patients
Three trials examined the use of interferon in naïve patients, two with ribavirin + interferon alfa-2b (C95-132 and I95-143) and one with ribavirin + peginterferon alfa-2b (C/I98-580). In all cases the treatment was for one year with a follow-up of six months. The sustained response at the end of follow-up was significantly increased by the addition of ribavirin to interferon alfa-2b (41 % vs 16 %, $p < 0.001$).

In clinical trials C95-132 and I95-143, ribavirin + interferon alfa-2b combination therapy proved to be significantly more effective than interferon alfa-2b monotherapy (a doubling in sustained response). Combination therapy also decreased the relapse rate. This was true for all HCV genotypes, particularly Genotype 1, in which the relapse rate was reduced by 30 % compared with interferon alfa-2b monotherapy.

In clinical trial C/I98-580, 1,530 naïve patients were treated for one year with one of the following combination regimens:
- Ribavirin (800 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week) (n = 511).
- Ribavirin (1,000/1,200 mg/day) + peginterferon alfa-2b (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) (n = 514).
- Ribavirin (1,000/1,200 mg/day) + interferon alfa-2b (3 MIU three times a week) (n = 505).

In this trial, the combination of ribavirin and peginterferon alfa-2b (1.5 micrograms/kg/week) was significantly more effective than the combination of ribavirin and interferon alfa-2b, particularly in

patients infected with Genotype 1. Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with peginterferon alfa-2b or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

Table 7 Sustained response rates with ribavirin + peginterferon alfa-2b (by ribavirin dose [mg/kg], genotype and viral load)

HCV Genotype	Ribavirin dose (mg/kg)	P 1.5/R	P 0.5/R	I/R
All Genotypes	**All**	**54 %**	**47 %**	**47 %**
	≤ 10.6	50 %	41 %	27 %
	> 10.6	61 %	48 %	47 %
Genotype 1	**All**	**42 %**	**34 %**	**33 %**
	≤ 10.6	38 %	25 %	20 %
	> 10.6	48 %	34 %	34 %
Genotype 1 ≤ 600,000 IU/mL	All	73 %	51 %	45 %
	≤ 10.6	74 %	25 %	33 %
	> 10.6	71 %	52 %	45 %
Genotype 1 > 600,000 IU/mL	All	30 %	27 %	29 %
	≤ 10.6	27 %	25 %	17 %
	> 10.6	37 %	27 %	29 %
Genotype 2/3	**All**	**82 %**	**80 %**	**79 %**
	≤ 10.6	79 %	73 %	50 %
	> 10.6	88 %	80 %	80 %

P1.5/R Ribavirin (800 mg) + peginterferon alfa-2b (1.5 micrograms/kg)
P0.5/R Ribavirin (1,000/1,200 mg) + peginterferon alfa-2b (1.5 to 0.5 microgram/kg)
I/R Ribavirin (1,000/1,200 mg) + interferon alfa-2b (3 MIU)

In a separate trial, 224 patients with genotype 2 or 3 received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

Table 8	Virologic Response at End of Treatment, Sustained Virologic Response and Relapse by HCV Genotype and Viral Load*		
	Ribavirin 800-1,400 mg/day plus peginterferon alfa-2b 1.5 µ/kg once weekly		
	End of Treatment Response	Sustained Virologic Response	Relapse
All Subjects	**94 % (211/224)**	**81 % (182/224)**	**12 % (27/224)**
HCV 2	**100 % (42/42)**	**93 % (39/42)**	**7 % (3/42)**
≤ 600.000 IU/mL	**100 % (20/20)**	**95 % (19/20)**	**5 % (1/20)**
> 600.000 IU/mL	**100 % (22/22)**	**91 % (20/22)**	**9 % (2/22)**
HCV 3	**93 % (169/182)**	**79 % (143/182)**	**14 % (24/166)**
≤ 600.000 IU/mL	**93 % (92/99)**	**86 % (85/99)**	**8 % (7/91)**
> 600.000 IU/mL	**93 % (77/83)**	**70 % (58/83)**	**23 % (17/75)**

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the followup week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/mL) received peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n = 49) and prospectively confirmed (n = 48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two peginterferon alfa-2b/ribavirin regimens [peginterferon alfa-2b 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate* and Sustained Virologic Response (SVR)			
Treatment group	% (number) of patients		
	peginterferon alfa-2b 1.5 µg/kg + ribavirin	peginterferon alfa-2b 1 µg/kg + ribavirin	peginterferon alfa-2a 180 µg + ribavirin
Undetectable HCV-RNA at treatment week 12	40 (407/1,019)	36 (366/1,016)	45 (466/1,035)
End of treatment response*	53 (542/1,019)	49 (500/1,016)	64 (667/1,035)
Relapse*	24 (123/523)	20 (95/475)	32 (193/612)
SVR*	40 (406/1,019)	38 (386/1,016)	41 (423/1,035)
SVR in patients with undetectable HCV-RNA at treatment week 12	81 (328/407)	83 (303/366)	74 (344/466)

*HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/mL
Lack of early virologic response by treatment week 12 (detectable HCV-RNA with a < 2 log10 reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with peginterferon alfa-2b (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to peginterferon alfa-2b 1 µg/kg dose. At the peginterferon alfa-2b 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/mL and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

Predictability of sustained virological response in naïve patients
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA. Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

Table 10 Predictive Value of In-Treatment Virologic Response while on peginterferon alfa-2b 1.5 µg/kg/ribavirin 800-1,400 mg Combination Therapy						
	Negative			**Positive**		
	No response at treatment week	No sustained response	Predictive value	Response at treatment week	Sustained response	Predictive value
Genotype 1*						
By Week 4* **(n = 950)**						
HCV-RNA negative	834	539	**65 %** (539/834)	116	107	**92 %** (107/116)
HCV-RNA negative or ≥ 1 log decrease in viral load	220	210	**95 %** (210/220)	730	392	**54 %** (392/730)
By Week 12* **(n = 915)**						
HCV-RNA negative	508	433	**85 %** (433/508)	407	328	**81 %** (328/407)
HCV-RNA negative or ≥ 2 log decrease in viral load	206	205	**N/A**†	709	402	**57%** (402/709)
Genotype 2, 3**						
By Week 12 **(n = 215)**						
HCV-RNA negative or ≥ 2 log decrease in viral load	2	1	**50 %** (1/2)	213	177	**83 %** (177/213)

*Genotype 1 receive 48 weeks treatment
**Genotype 2, 3 receive 24 weeks treatment
***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.
† These criteria were used in the protocol: If week 12 HCV-RNA is positive and < 2 $\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ 2 $\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table 11**. Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either ribavirin (800 mg/day) plus peginterferon alfa-2b (1.5 µg/kg/week) or ribavirin (800 mg/day) plus interferon alfa-2b (3 MIU TIW) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either ribavirin (800-1,200 mg/day based on weight) plus peginterferon alfa-2b (100 or 150 µg/week based on weight) or ribavirin (800-1,200 mg/day based on weight) plus interferon alfa-2b (3 MIU TIW). The duration of therapy was 48 weeks with a follow-up period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/mL (Amplicor) who were treated for 24 weeks with a 6 month follow-up period.

Table 11 Sustained virological response based on genotype after ribavirin in combination with peginterferon alfa-2b in HCV/HIV co-infected patients

	Study 1[1]			**Study 2**[2]		
	ribavirin (800 mg/day) + peginterferon alfa-2b (1.5 µg/kg/ week)	ribavirin (800 mg/day) + interferon alfa-2b (3 MIU TIW)	p value[a]	ribavirin (800-1,200 mg/day)[d] + peginterferon alfa-2b (100 or 150[c] µg/week)	ribavirin (800-1,200 mg/day)[d] + interferon ß alfa-2b (3 MIU TIW)	p value[b]
All	27 % (56/205)	20 % (41/205)	0.047	44 % (23/52)	21 % (9/43)	0.017
Genotype 1, 4	17 % (21/125)	6 % (8/129)	0.006	38 % (12/32)	7 % (2/27)	0.007
Genotype 2, 3	44 % (35/80)	43 % (33/76)	0.88	53 % (10/19)	47 % (7/15)	0.730

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week peginterferon alfa-2b and subjects ≥ 75 kg received 150 µg/week peginterferon alfa-2b .
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.
[1] Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

Histological response
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with ribavirin in combination with peginterferon alfa-2b. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

Previously treated patients
- Retreatment of prior treatment failures (relapse and non-responder patients) with peginterferon alfa-2b in combination with ribavirin:
In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with peginterferon alfa-2b, 1.5 microgram/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at Treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table 12**).

Table 12	Rates of Response to retreatment in prior treatment failures				
	Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement				
	interferon alpha/ribavirin		peginterferon alpha/ribavirin		Overall Population*
	Response week 12 % (n/N)	SVR % (n/N) 99 % CI	Response week 12 % (n/N)	SVR % (n/N) 99 % CI	SVR % (n/N) 99 % CI
Overall	38.6 (549/1,423)	59.4 (326/549) 54.0, 64.8	31.5 (272/863)	50.4 (137/272) 42.6, 58.2	21.7 (497/2,293) 19.5, 23.9
Prior Response					
Relapse	67.7 (203/300)	59.6 (121/203) 50.7, 68.5	58.1 (200/344)	52.5 (105/200) 43.4, 61.6	37.7 (243/645) 32.8, 42.6
Genotype 1/4	59.7 (129/216)	51.2 (66/129) 39.8, 62.5	48.6 (122/251)	44.3 (54/122) 32.7, 55.8	28.6 (134/468) 23.3, 34.0
Genotype 2/3	88.9 (72/81)	73.6 (53/72) (60.2, 87.0)	83.7 (77/92)	64.9 (50/77) 50.9, 78.9	61.3 (106/173) 51.7, 70.8
NR	28.6 (258/903)	57.0 (147/258) 49.0, 64.9	12.4 (59/476)	44.1 (26/59) 27.4, 60.7	13.6 (188/1,385) 11.2, 15.9
Genotype 1/4	23.0 (182/790)	51.6 (94/182) 42.1, 61.2	9.9 (44/446)	38.6 (17/44) 19.7, 57.5	9.9 (123/1,242) 7.7, 12.1
Genotype 2/3	67.9 (74/109)	70.3 (52/74) 56.6, 84.0	53.6 (15/28)	60.0 (9/15) 27.4, 92.6	46.0 (63/137) 35.0, 57.0
Genotype					
1	30.2 (343/1,135)	51.3 (176/343) 44.4, 58.3	23.0 (162/704)	42.6 (69/162) 32.6, 52.6	14.6 (270/1,846) 12.5, 16.7
2/3	77.1 (185/240)	73.0 (135/185) 64.6, 81.4	75.6 (96/127)	63.5 (61/96) 50.9, 76.2	55.3 (203/367) 48.6, 62.0
4	42.5 (17/40)	70.6 (12/17) 42.1, 99.1	44.4 (12/27)	50.0 (6/12) 12.8, 87.2	28.4 (19/67) 14.2, 42.5
METAVIR Fibrosis score					
F2	46.0 (193/420)	66.8 (129/193) 58.1, 75.6	33.6 (78/232)	57.7 (45/78) 43.3, 72.1	29.2 (191/653) 24.7, 33.8
F3	38.0 (163/429)	62.6 (102/163) 52.8, 72.3	32.4 (78/241)	51.3 (40/78) 36.7, 65.9	21.9 (147/672) 17.8, 26.0
F4	33.6 (192/572)	49.5 (95/192) 40.2, 58.	29.7 (116/390)	44.8 (52/116) 32.9, 56.7	16.5 (159/966) 13.4, 19.5
Baseline Viral Load					
HVL (>600,000 IU/mL)	32.4 (280/864)	56.1 (157/280) 48.4, 63.7	26.5 (152/573)	41.4 (63/152) 31.2, 51.7	16.6 (239/1,441) 14.1, 19.1
LVL (≤ 600,000 IU/mL)	48.3 (269/557)	62.8 (169/269) 55.2, 70.4	41.0 (118/288)	61.0 (72/118) 49.5, 72.6	30.2 (256/848) 26.1, 34.2

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment. Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory
*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/mL). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with non-pegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to non-pegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Retreatment of relapse patients with ribavirin and interferon alfa-2b combination treatment
Two trials examined the use of ribavirin and interferon alfa-2b combination treatment in relapse patients (C95-144 and I95-145); 345 chronic hepatitis patients who had relapsed after previous interferon treatment were treated for six months with a six month follow-up. Combination therapy with ribavirin and interferon alfa-2b resulted in a sustained virological response that was ten-fold higher than that with interferon alfa-2b alone (49 % vs 5 %, $p < 0.0001$). This benefit was maintained irrespective of standard predictors of response to interferon alfa-2b such as virus level, HCV genotype and histological staging.

Long-term efficacy data - Adults
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. Twelve out of 492 sustained responders and only 3 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: 98-100 %) for patients receiving pegylated interferon alfa-2b (with or without ribavirin). SVR after treatment of chronic HCV with interferon alfa-2b (pegylated and non-pegylated, with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

Paediatric population

Clinical efficacy and safety

Ribavirin in combination with peginterferon alfa-2b
Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus pegylated interferon alfa-2b 60 µg/m2 once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and

the potential for undesirable effects, the benefit/risk of the combination of ribavirin and pegylated interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).

The study results are summarized in **Table 13**.

Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects n = 107		
	24 weeks	**48 weeks**
All Genotypes	26/27 (96 %)	44/80 (55 %)
Genotype 1	-	38/72 (53 %)
Genotype 2	14/15 (93 %)	-
Genotype 3[c]	12/12 (100 %)	2/3 (67 %)
Genotype 4	-	4/5 (80 %)

[a]: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment, lower limit of detection = 125 IU/mL.
[b]: n = number of responders/number of subjects with given genotype, and assigned treatment duration.
[c]: Patients with genotype 3 low viral load (< 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/mL) were to receive 48 weeks of treatment.

Ribavirin in combination with interferon alfa-2b
Children and adolescents 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were enrolled in two multicentre trials and received ribavirin 15 mg/kg per day plus interferon alfa-2b 3 MIU/m^2 3 times a week for 1 year followed by 6 months follow-up after treatment. A total of 118 patients were enrolled: 57 % male, 80 % Caucasian, and 78 % genotype 1, 64 % ≤ 12 years of age. The population enrolled mainly consisted in children with mild to moderate hepatitis C. In the two multicentre trials, sustained virological response rates in children and adolescents were similar to those in adults. Due to the lack of data in these two multicentre trials for children with severe progression of the disease, and the potential for undesirable effects, the benefit/risk of the combination of ribavirin and interferon alfa-2b needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8).The study results are summarized in **Table 14**.

Table 14 Sustained virological response in previously untreated children and adolescents	
	Ribavirin 15 mg/kg/day + interferon alfa-2b 3 MIU/m^2 3 times a week
Overall Response[a] (n = 118)	54 (46 %)*
Genotype 1 (n = 92)	33 (36 %)*
Genotype 2/3/4 (n = 26)	21 (81 %)*

* Number (%) of patients
a. Defined as HCV-RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.

Long-term efficacy data

Ribavirin in combination with peginterferon alfa-2b
A five-year long-term, observational, follow-up study enrolled 94 paediatric chronic hepatitis C patients after treatment in a multicentre trial. Of these, sixty-three were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment with 24 or 48 weeks of peginterferon alfa-2b and ribavirin treatment. At the end of 5 years, 85 % (80/94) of all enrolled subjects and 86 % (54/63) of sustained responders completed the study. No paediatric subjects with SVR relapsed during the 5 years of follow-up.

Ribavirin in combination with interferon alfa-2b

A five-year long-term, observational, follow-up study enrolled 97 paediatric chronic hepatitis C patients after treatment in two previously mentioned multicentre trials. Seventy percent (68/97) of all enrolled subjects completed this study of which 75 % (42/56) were sustained responders. The purpose of the study was to annually evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes for patients who were sustained responders 24 weeks post-treatment of the 48-week interferon alfa-2b and ribavirin treatment. All but one of the paediatric subjects remained sustained virologic responders during long-term follow-up after completion of treatment with interferon alfa-2b plus ribavirin. The Kaplan-Meier estimate for continued sustained response over 5 years is 98 % [95 % CI: 95 %, 100 %] for paediatric patients treated with interferon alfa-2b and ribavirin. Additionally, 98 % (51/52) with normal ALT levels at follow-up week 24 maintained normal ALT levels at their last visit.

SVR after treatment of chronic HCV with non-pegylated interferon alfa-2b with ribavirin results in long-term clearance of the virus providing resolution of the hepatic infection and clinical 'cure' from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma)

5.2 Pharmacokinetic properties

In a single dose, crossover study of ribavirin in healthy adult subjects, the film-coated tablet and oral solution formulations were found to be bioequivalent.

Absorption
Ribavirin is absorbed rapidly following oral administration of a single dose (mean T_{max} = 1.5 hours), followed by rapid distribution and prolonged elimination phases (single dose half-lives of absorption, distribution and elimination are 0.05, 3.73 and 79 hours, respectively). Absorption is extensive with approximately 10 % of a radiolabelled dose excreted in the faeces. However, absolute bioavailability is approximately 45 %-65 %, which appears to be due to first pass metabolism. There is a linear relationship between dose and AUC_{tf} following single doses of 200-1,200 mg ribavirin. Volume of distribution is approximately 5,000 l. Ribavirin does not bind to plasma proteins.

Distribution
Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood:plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes.

Biotransformation
Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway; 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxyacid metabolite. Both ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are also excreted renally.

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses (intrasubject variability of approximately 30 % for both AUC and C_{max}), which may be due to extensive first pass metabolism and transfer within and beyond the blood compartment.

Elimination

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12h}. Following oral dosing with 600 mg BID, steady-state was reached by approximately four weeks, with mean steady state plasma concentrations approximately 2,200 ng/mL. Upon discontinuation of dosing the half-life was approximately 298 hours, which probably reflects slow elimination from non-plasma compartments.

Transfer into seminal fluid
Seminal transfer of ribavirin has been studied. Ribavirin concentration in seminal fluid is approximately two-fold higher compared to serum. However, ribavirin systemic exposure of a female partner after sexual intercourse with a treated patient has been estimated and remains extremely limited compared to therapeutic plasma concentration of ribavirin.

Food effect
The bioavailability of a single oral dose of ribavirin was increased by co-administration of a high fat meal (AUC_{tf} and C_{max} both increased by 70 %). It is possible that the increased bioavailability in this study was due to delayed transit of ribavirin or modified pH. The clinical relevance of results from this single dose study is unknown. In the pivotal clinical efficacy trial, patients were instructed to take ribavirin with food to achieve the maximal plasma concentration of ribavirin.

Renal function
Based on published data, single-dose ribavirin pharmacokinetics were altered (increased AUC_{tf} and C_{max}) in patients with renal dysfunction compared with control subjects (creatinine clearance > 90 mL/minute). The mean AUC_{tf} was threefold greater in subjects with creatinine clearance between 10 and 30 mL/min compared with control subjects. In subjects with creatinine clearance between 30 and 50 mL/min, AUC_{tf} was twofold greater compared with control subjects. This appears to be due to reduction of apparent clearance in these patients. Ribavirin concentrations are essentially unchanged by haemodialysis.

Hepatic function
Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls.

Elderly patients (≥ 65 years of age)
Specific pharmacokinetic evaluations for elderly subjects have not been performed. However, in a population pharmacokinetic study, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor.

Population pharmacokinetic analysis
Population pharmacokinetic analysis was performed using sparsely sampled serum concentration values from four controlled clinical trials. The clearance model developed showed that body weight, gender, age, and serum creatinine were the main covariates. For males, clearance was approximately 20 % higher than for females. Clearance increased as a function of body weight and was reduced at ages greater than 40 years. Effects of these covariates on ribavirin clearance appear to be of limited clinical significance due to the substantial residual variability not accounted for by the model.

Paediatric population

Ribavirin in combination with peginterferon alfa-2b
Multiple-dose pharmacokinetic properties for ribavirin and peginterferon alfa-2b in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of peginterferon alfa-2b at 60 µg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 µg/kg/week. The pharmacokinetics of ribavirin (dose-normalized) in this trial were similar to those reported in a prior study of ribavirin in combination with interferon alfa-2b in children and adolescent patients and in adult patients.

Ribavirin in combination with interferon alfa-2b
Multiple-dose pharmacokinetic properties for ribavirin and interferon alfa-2b in children and adolescents with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 15**. The

pharmacokinetics of ribavirin and interferon alfa-2b (dose-normalized) is similar in adults and children or adolescents.

Table 15 Mean (% CV) multiple-dose pharmacokinetic parameters for interferon alfa-2b and ribavirin when administered to paediatric patients with chronic hepatitis C

Parameter	**Ribavirin** 15 mg/kg/day as 2 divided doses (n = 17)	**Interferon alfa-2b** 3 MIU/m^2 3 times a week (n = 54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3,275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	Not done

*AUC_{12} (ng*hr/mL) for ribavirin; $AUC_{0\text{-}24}$ (IU*hr/mL) for interferon alfa-2b

5.3 Preclinical safety data

Ribavirin
Ribavirin is embryotoxic or teratogenic, or both, at doses well below the recommended human dose in all animal species in which studies have been conducted. 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 dose. Survival of foetuses and offspring was reduced.

In a juvenile rat toxicity study, pups dosed from postnatal day 7 to 63 with 10, 25 and 50 mg/kg of ribavirin demonstrated a dose-related decrease in overall growth, which was subsequently manifested as slight decreases in body weight, crown-rump length and bone length. At the end of the recovery period, tibial and femoral changes were minimal although generally statistically significant compared to controls in males at all dose levels and in females dosed with the two highest doses compared to controls. No histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioural or reproductive development. Plasma concentrations achieved in rat pups were below human plasma concentrations at the therapeutic dose.

Erythrocytes are a primary target of toxicity for ribavirin in animal studies. Anaemia occurs shortly after initiation of dosing, but is rapidly reversible upon cessation of treatment.

In 3- and 6-month studies in mice to investigate ribavirin-induced testicular and sperm effects, abnormalities in sperm, occurred at doses of 15 mg/kg and above. These doses in animals produce systemic exposures well below those achieved in humans at therapeutic doses. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles (see section 4.6).

Genotoxicity studies have demonstrated that ribavirin does exert some genotoxic activity. Ribavirin was active in the Balb/3T3 *in vitro* transformation Assay. Genotoxic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Conventional carcinogenicity rodent studies 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 suggest that a carcinogenic potential of ribavirin in humans is unlikely.

Ribavirin plus interferon
When used in combination with peginterferon alfa-2b or interferon alfa-2b, ribavirin did not cause any effects not previously seen with either active substance alone. The major treatment-related change was

a reversible mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Pregelatinised maize starch
Colloidal anhydrous silicia
Talc
Magnesium stearate
Hypromellose
Macrogol 6000
Titanium dioxide
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Shelf life after first opening: 8 weeks.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[Product name] film-coated tablets are packaged in tablet containers consisting of high density polyethylene (HDPE) with a polypropylen (PP) screw cap.

200 mg
Pack sizes of 84, 112 and 168 film-coated tablets in tablet container**.**

400 mg
Pack size of 56 film-coated tablets in tablet container**.**

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Str. 3

89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

Ribavirine ratiopharm 200 mg, filmomhulde tabletten RVG 108116
Ribavirine ratiopharm 400 mg, filmomhulde tabletten RVG 108119

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Datum van laatste hernieuwing: 6 juli 2016

10. DATE OF REVISION OF THE TEXT

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