	interferon alfa/ribavirin		peginterferon alfa/ribavirin		
	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, 16.9
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, 58.8	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 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
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/m^2 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 12**.

Table 12 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 13**.

Table 13 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– Paediatric population

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

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 (intra-subject 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_{12hr}. 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: 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). 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 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 14.** The pharmacokinetics of Ribavirin and interferon alfa-2b (dose-normalized) are similar in adults and children or adolescents.

Table 14 Mean (% CV) multiple-dose pharmacokinetic parameters for interferon alfa-2b and Ribavirin when administered to children or adolescents 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)
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_{0-24} (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

Capsule contents:
- Microcrystalline cellulose,
- Lactose monohydrate,
- Croscarmellose sodium,
- Povidone.

Capsule shell:
- Gelatin,
- Titanium dioxide (E171).

Capsule imprint:

Shellac,
Propylene glycol,
Ammonia solution, concentrated,
Yellow iron oxide (E172),
Indigotine (E132),
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 36 months
Blisters: 36 months

6.4 Special precautions for storage

Bottles: Do not store above 30°C.
Blisters: No special storage conditions.

6.5 Nature and contents of container

Ribavirin Mylan capsules are packaged in:

High-density polyethylene (HDPE) bottle, closed with a child resistant (CR) polypropylene (PP) screw cap.

Pack sizes of 84, 112, 140 and 168 capsules.

Blisters:
Cardboard box containing 56 or 168 hard capsules in PVC/Aclar – Aluminium foil blisters

Unit Dose Blisters:
Cardboard box containing 56x1, 84x1, 112x1, 140x1, 168x1 hard capsules in PVC/Aclar – Aluminium foil perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004
EU/1/10/634/005
EU/1/10/634/006
EU/1/10/634/007
EU/1/10/634/008
EU/1/10/634/009
EU/1/10/634/010
EU/1/10/634/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
United Kingdom

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road, Dublin 13
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, Section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

PSURs

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 200 mg ribavirin.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56x1 hard capsules
84x1 hard capsules
112x1 hard capsules
140x1 hard capsules
168x1 hard capsules56 hard capsules
84 hard capsules
112 hard capsules
140 hard capsules
168 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Bottles - Do not store above 30°C.
Blisters - No special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004
EU/1/10/634/005
EU/1/10/634/006
EU/1/10/634/007
EU/1/10/634/008
EU/1/10/634/009
EU/1/10/634/010
EU/1/10/634/011

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ribavirin Mylan hard capsules

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 200 mg ribavirin.

3. LIST OF EXCIPIENTS

Contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

84 hard capsules
112 hard capsules
140 hard capsules
168 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/634/001
EU/1/10/634/002
EU/1/10/634/003
EU/1/10/634/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON UNIT DOSE BLISTERS

PVC/Aclar® - Aluminium

1. NAME OF THE MEDICINAL PRODUCT

Ribavirin Mylan 200 mg hard capsules
Ribavirin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Generics [UK] Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ribavirin Mylan 200 mg hard capsules
ribavirin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Ribavirin Mylan is and what it is used for

Ribavirin Mylan contain the active substance ribavirin. Ribavirin Mylan stops the multiplication of many types of viruses, including hepatitis C virus. Ribavirin Mylan must not be used without interferon alfa-2b, i.e. Ribavirin Mylan must not be used alone.

Previously untreated patients:
The combination of Ribavirin Mylan with interferon alfa-2b is used to treat patients 3 years of age and older who have chronic hepatitis C (HCV) infection. For children and adolescents weighing less than 47 kg a solution formulation is available.

Previously treated adult patients:
The combination of Ribavirin Mylan with interferon alfa-2b is used to treat adult patients with chronic hepatitis C, who have previously responded to treatment with an alpha interferon alone, but whose condition has recurred.

There is no safety or efficacy information on the use of Ribavirin Mylan with pegylated or other forms of interferon (i.e., not alfa-2b).

2. What you need to know before you take Ribavirin Mylan

Do not take Ribavirin Mylan:
If any of the following apply to you or the child you are caring for, **do not take** Ribavirin Mylan, and **tell your doctor** if you:

- are **allergic** (hypersensitive) to ribavirin or any of the other ingredients of this medicine (listed in section 6).
- are **pregnant or planning to become pregnant**. (see section "Pregnancy, breast-feeding and fertility")
- are **breast-feeding**.
- had a problem with your **heart** during the past 6 months.

- have severe medical conditions that leave you very weak.
- have severe **kidney** disease and/or are on haemodialysis.
- have a serious problem with your **liver** other than chronic hepatitis C.
- have any **blood disorders**, such as anaemia (low blood count), thalassemia, sickle-cell anaemia.
- have autoimmune hepatitis or any other problem with your **immune system**.
- are taking medicine that suppresses your immune system (that protects you against infection and some diseases).

Children and adolescents must not take combination therapy with Ribavirin Mylan and alpha interferon when there is existence or history of serious nervous or mental problems, such as severe depression, thoughts of suicide or attempted suicide.

Reminder: Please read the "Do not take" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment with this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before taking Ribavirin Mylan.

Seek medical help **immediately** if you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing or hives) while taking this treatment.

Children and adolescents weighing less than 47 kg:
The use of Ribavirin Mylan hard capsules is not recommended. An oral solution of ribavirin may be available for children 3 years of age and older and adolescents weighing less than 47 kg.

You should **tell your doctor** if you or the child you are caring for:
- are an adult who has or had a severe **nervous or mental disorder**, confusion, unconsciousness, or have had **thoughts of suicide** or **have attempted suicide, or have a history of substance abuse (e.g., alcohol or drugs)**.
- have ever had **depression** or develop symptoms associated with depression (e.g. feeling of sadness, dejection, etc.) while on treatment with this medicine (see section 4. "Possible side effects").
- are a woman of **childbearing** age (see section "Pregnancy, breast-feeding and fertility").
- are a **male** and your female partner is of childbearing age (see section "Pregnancy, breast-feeding and fertility").
- had a previous serious **heart** condition or have cardiac disease. are older than **65 years** or if you have problems with your **kidneys.**
- have or have had any **serious illness.**
- have **thyroid** problems.

During treatment with Ribavirin Mylan in combination therapy with an alfa interferon, **dental and gum disorders**, which may lead to loss of teeth, have been reported. In addition, **dry mouth** that could have a damaging effect on teeth and membranes of the mouth has been reported during long-term treatment with Ribavirin Mylan in combination therapy with an alpha interferon. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience **vomiting**. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

During treatment with Ribavirin Mylan in combination therapy with an alpha interferon, patients may experience **eye problems,** or loss of vision in rare instances. If you receive ribavirin in combination with an alpha interferon, you should have a baseline eye examination. Any patient complaining of decrease or loss of vision must have a prompt and complete eye examination. Patients with pre-existing eye disorders (e.g. diabetic or hypertensive retinopathy) should receive periodic eye exams during combination therapy with ribavirin and an alpha interferon. Combination therapy with

ribavirin and an alpha interferon should be discontinued in patients who develop new or worsening eye disorders.

Children and adolescents:
The use of Ribavirin Mylan is not recommended for use in patients under the age of 3 years. An oral solution of ribavirin is available for children 3 years of age and older and adolescents weighing less than 47 kg.

Reminder: Please read the "Warnings and precautions" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Other medicines and Ribavirin Mylan

Tell your doctor or pharmacist if you or the child you are caring for are taking, have recently taken or might take any other medicines and/or:
-
- are receiving azathioprine in combination with ribavirin and pegylated alpha interferons and, therefore may be at an increased risk of developing severe blood disorders.
- are infected with both **Human Immunodeficiency Virus** (HIV-positive) and **Hepatitis C Virus** (HCV) and are being treated with an anti-HIV medicinal product(s) – [nucleoside reverse transcriptase inhibitor (**NRTI**), and/or highly active anti-retroviral therapy (**HAART**)]:
  - Taking Ribavirin Mylan in combination with an alpha interferon and an anti-HIV medicinal product(s) may increase the risk of lactic acidosis, liver failure, and blood abnormalities development (reduction in number of red blood cells which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).
  - With **zidovudine** or **stavudine**, it is not certain if Ribavirin Mylan will change the way these medicines work. Therefore, your blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your Ribavirin Mylan treatment needs to be changed. Additionally, patients receiving **zidovudine** with **ribavirin** in combination **with alpha interferons** could be at increased risk of developing anaemia (low number of red blood cells). Therefore the use of zidovudine and ribavirin in combination with alpha interferons is not recommended.
  - Due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis, the use of **ribavirin and didanosine** is not recommended and the use of **ribavirin and stavudine** should be avoided.
  - Co-infected patients with advanced liver disease receiving (HAART) may be at increased risk of worsening liver function. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset.

Reminder: Please read the "Other medicines" section of the Package Leaflet for interferon alfa-2b before you begin combination treatment.

Ribavirin Mylan with food and drink
Ribavirin Mylan must be taken with food. See section 3

Pregnancy, breast-feeding and fertility

Pregnancy
If you are **pregnant** you must not take Ribavirin Mylan. Ribavirin Mylan can be very damaging to your unborn baby (embryo).

Both female and male patients must take **special precautions** in their sexual activity if there is any possibility for pregnancy to occur:

- **Girl** or **woman** of childbearing age:

You must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. This should be discussed with your doctor.

- **Men**
  Do not have sex with a pregnant woman unless you **use a condom**. This will lessen the possibility for ribavirin to be left in the woman's body.
  If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. You or your female partner must use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This should be discussed with your doctor (see "Do not take Ribavirin Mylan").

Breast-feeding
If you are a woman who is **breast-feeding**, you must not take Ribavirin Mylan. Discontinue breast-feeding before starting to take Ribavirin Mylan.

Driving and using machines
Ribavirin Mylan does not affect your ability to drive or use machines; however, interferon alfa-2b may affect your ability to drive or use machines. Therefore, do not drive or use machines if you become tired, sleepy, or confused from this treatment.

Ribavirin Mylan contains lactose
Each Ribavirin Mylan hard capsule contains a small amount of **lactose**. If you have been told by your doctor that you have **an intolerance to some sugars**, discuss with your doctor before taking this medicinal product.

3. How to take Ribavirin Mylan

General information about taking Ribavirin Mylan
If the child you are caring for is **under the age of 3 years**, do not administer.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
Do not take more than the recommended dosage and take the medicine for as long as prescribed.
Your doctor has determined the correct dose of Ribavirin Mylan based on how much you or the child you are caring for weighs.

Standard blood tests will be taken to check your blood, kidney and liver function.
- Blood tests will be done regularly to help your doctor to know if this treatment is working.
- Depending upon the results of these tests, your doctor may change/adjust the number of hard capsules you or the child you are caring for take, prescribe a different pack size of Ribavirin Mylan, and/or change the length of time to take this treatment.
- If you have or develop severe kidney or liver problems, this treatment will be stopped.

The recommended dose, according to how much the patient weighs, is shown in the table below:
1. Look for the line that shows how much the adult or child/adolescent weighs.
   Reminder: If the child is under the age of 3 years, do not administer.
2. Read across on the same line to see how many hard capsules to take.
   Reminder: If your doctor's instructions are different from the amounts in the below table, follow your doctor's instructions.
3. If you have any questions about the dose, ask your doctor.

Ribavirin Mylan for oral use - dose based on body weight		
If the **adult** weighs	Usual daily Ribavirin	Number of 200 mg capsules

(kg)	Mylan dose	
< 65	800 mg	2 capsules in the morning and 2 capsules in the evening
65 – 80	1,000 mg	2 capsules in the morning and 3 capsules in the evening
81 - 105	1,200 mg	3 capsules in the morning and 3 capsules in the evening
> 105	1,400 mg	3 capsules in the morning and 4 capsules in the evening
If the **child/adolescent** weighs (kg)	Usual daily Ribavirin Mylan dose	Number of 200 mg capsules
47 – 49	600 mg	1 capsule in the morning and 2 capsules in the evening
50 – 65	800 mg	2 capsules in the morning and 2 capsules in the evening
> 65	see adult dose and corresponding number of hard capsules	

Take your prescribed dose by mouth with water and during your meal. Do not chew the hard capsules. For children or adolescents who cannot swallow a hard capsule, an oral solution of ribavirin is available.

Reminder: Ribavirin Mylan is only to be used in combination with interferon alfa-2b for hepatitis C virus infection. For complete information be sure to read the "How to take" section of the Package Leaflet for interferon alfa-2b.

Interferon medicine that is used in combination with Ribavirin Mylan may cause unusual tiredness; if you are injecting this medicine yourself or giving it to a child, use it at bedtime.

If you take more Ribavirin Mylan than you should
Tell your doctor or pharmacist as soon as possible.

If you forget to take Ribavirin Mylan
If you are self-administering treatment, or if you are the caregiver of a child taking Ribavirin Mylan in combination with interferon alfa-2b, take/administer the missed dose as soon as possible during the same day. If an entire day has gone by, check with your doctor. Do not take a double dose to make up for a forgotten dose.

If you have any questions on the use of this medicine, ask your doctor or pharmacists.

4. Possible side effects

Please read the "Possible side effects" section of the Package Leaflet for interferon alfa-2b.

Like all medicines, this medicine used in combination with an alpha interferon product can cause side effects, although not everybody gets them. Although not all of these unwanted effects may occur, they may need medical attention if they do occur.

Psychiatric and Central Nervous System:
Some people get depressed when taking Ribavirin in combination treatment with an interferon, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

Children and adolescents are particularly prone to develop depression when being treated with ribavirin and interferon alpha. Immediately contact the doctor or seek emergency treatment if they

display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

Growth and development (children and adolescents):
During the one year of treatment with Ribavirin in combination with interferon alfa-2b, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-12 years after completing treatment.

Contact your doctor immediately if you notice any of the following side effects occuring during combination treatment with an alpha interferon product:

- chest pain or persistent cough; changes in the way your heart beats, fainting,
- confusion, feeling depressed; suicidal thoughts or aggressive behaviour, attempt suicide, thoughts about threatening the life of others,
- feelings of numbness or tingling,
- trouble sleeping, thinking or concentrating,
- severe stomach pain; black or tar-like stools; blood in stool or urine, lower back or side pain,
- painful or difficult urination,
- severe bleeding from your nose,
- fever or chills beginning after a few weeks of treatment,
- problems with your eyesight or hearing**,**
- severe skin rash or redness.

The following side effects have been reported with the combination of Ribavirin Mylan and an alpha interferon product **in adults**:

Very common: may affect more than 1 in 10 people

- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness), decrease in neutrophils (that make you more susceptible to different infections).
- difficulty concentrating, feeling anxious or nervous, mood swings, feeling depressed or irritable, tired feeling, trouble falling asleep or staying asleep,
- cough, dry mouth, pharyngitis (sore throat),
- diarrhoea, dizziness, fever, flu-like symptoms, headache, nausea, shaking chills, virus infection, vomiting, weakness,
- loss of appetite, loss of weight, stomach pain,
- dry skin, irritation, pain or redness at the site of injection, hair loss, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Common: may affect up to 1 in 10 people

- decrease in blood clotting cells called platelets that may result in easy bruising and spontaneous bleeding, decrease in certain white blood cells called lymphocytes that help fight infection, decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms) excess of sugar or uric acid (as in gout) in the blood, low calcium level in the blood, severe anaemia,
  fungal or bacterial infections, crying, agitation, amnesia, memory impaired, nervousness, abnormal behaviour, aggressive behaviour, anger, feeling confused, lack of interest, mental disorder, mood changes, unusual dreams, wanting to harm yourself, feeling sleepy, trouble sleeping, lack of interest in sex or inability to perform, vertigo (spinning feeling),
- blurred or abnormal vision, eye irritation or pain or infection, dry or teary eyes, changes in your hearing or voice, ringing in ears, ear infection, earache, cold sores (herpes simplex), change in taste, taste loss, bleeding gums or sores in mouth, burning sensation on tongue, sore tongue, inflamed gums, tooth problem, migraine, respiratory infections, sinusitis, nose bleed, nonproductive cough, rapid or difficult breathing, stuffy or runny nose, thirst, tooth disorder,

- cardiac murmur (abnormal heart beat sounds), chest pain or discomfort, feeling faint, feeling unwell, flushing, increased sweating, heat intolerance and excessive sweating, low or high blood pressure, palpitations (pounding heart beat), rapid heart rate.
- bloating, constipation, indigestion intestinal gas (flatus), increased appetite, irritated colon, irritation of prostate gland, jaundice (yellow skin), loose stools, pain on the right side around your ribs, enlarged liver, stomach upset, frequent need to urinate, passing more urine than usual, urinary tract infection, abnormal urine,
- difficult, irregular, or no menstrual period, abnormally heavy and prolonged menstrual periods, painful menstruation, disorder of ovary or vagina, breast pain, erectile problem,
- abnormal hair texture, acne, arthritis, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), hives, increased or decreased sensitivity to touch, nail disorder, muscle spasms, numbness or tingling feeling, limb pain, pain at the site of injection, pain in joints, shaky hands, psoriasis, puffy or swollen hands and ankles, sensitivity to sunlight, rash with raised spotted lesions, , redness of skin or skin disorder, swollen face, swollen glands (swollen lymph nodes), tense muscles, tumour (unspecified), unsteady when walking, water impairment.

Uncommon: may affect up to 1 in 100 people
- hearing or seeing images that are not present,
- heart attack, panic attack,
- hypersensitivity reaction to the medication,
- inflammation of pancreas, pain in bone, diabetes mellitus,
- muscle weakness.

Rare: may affect up to 1 in 1,000 people
- seizure (convulsions),
- pneumonia,
- rheumatoid arthritis, kidney problems,
- dark or bloody stools, intense abdominal pain,
- sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands),
- vasculitis.

Very rare: may affect up to 1 in 10,000 people
- suicide.
- stroke (cerebrovascular events).

Not known: frequency cannot be estimated from the available data
- thoughts about threatening the life of others,
- mania (excessive or unreasonable enthusiasm),
- pericarditis (inflammation of the lining of the heart), pericardial effusion [a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself.
- change in colour of the tongue.

Additional side effects in children and adolescents

The following side effects have been reported with the combination of Ribavirin Mylan and interferon alfa-2b product **in children and adolescents:**

Very common: may affect more than 1 in 10 people
- decreases in the number of red blood cells (that may cause fatigue, shortness of breath, dizziness) decrease in neutrophils (that make you more susceptible to different infections),

- decrease in thyroid gland activity (which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms),
- feeling depressed or irritable, feeling sick to stomach, feeling unwell, mood swings, tired feeling, trouble falling asleep or staying asleep, virus infection, weakness,
- diarrhoea, dizziness, fever, flu-like symptoms, headache, loss of or increase in appetite, loss of weight, decrease in the rate of growth (height and weight), pain on right side of ribs, pharyngitis (sore throat), shaking chills, stomach pain, vomiting,
- dry skin, hair loss, irritation, pain or redness at the site of injection, itching, muscle pain, muscle aches, pain in joints and muscles, rash.

Common: may affect up to 1 in 10 people

- decrease in blood clotting cells called platelets (that may result in easy bruising and spontaneous bleeding),
- excess of triglycerides in the blood, excess of uric acid (as in gout) in the blood, increase in thyroid gland activity (which may cause nervousness, heat intolerance and excessive sweating, weight loss, palpitation, tremors),
- agitation, anger, aggressive behaviour, behaviour disorder, difficulty concentrating, emotional instability, fainting, feeling anxious or nervous, feeling cold, feeling confused, feeling of restlessness, feeling sleepy, lack of interest or attention, mood changes, pain, poor quality sleep, sleepwalking, suicide attempt, trouble sleeping, unusual dreams, wanting to harm yourself,
- bacterial infections, common cold, fungal infections, abnormal vision, dry or teary eyes, ear infection, eye irritation or pain or infection, change in taste, changes in your voice, cold sores, coughing, inflamed gums, nose bleed, nose irritation, oral pain, pharyngitis (sore throat), rapid breathing, respiratory infections, scaling lips and clefts in the corner of the mouth, shortness of breath, sinusitis, sneezing, sores in mouth, sore tongue, stuffy or runny nose, throat pain, toothache, tooth abscess, tooth disorder, vertigo (spinning feeling), weakness
- chest pain, flushing, palpitations (pounding heart beat), rapid heart rate,
- abnormal liver function,
- acid reflux, back pain, bedwetting, constipation, gastroesophageal or rectal disorder, incontinence, increased appetite, inflammation of the membrane of the stomach and intestine, stomach upset, loose stools,
- urination disorders, urinary tract infection,
- difficult, irregular or no menstrual period, abnormally heavy and prolonged menstrual periods, disorder of vagina, inflammation of the vagina, testis pain, development of male body traits,
- acne, bruising, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), increased or decreased sensitivity to touch, increased sweating, increase in muscle movement, tense muscle, irritation or itching at the site of injection, limb pain, nail disorder, numbness or tingling feeling, pale skin, rash with raised spotted lesions, shaky hands, redness of skin or skin disorder, skin discolouration, skin sensitive to sunlight, skin wound, swelling due to a build-up of excess water, swollen glands (swollen lymph nodes), tremor, tumour (unspecified).

Uncommon: may affect up to 1 in 100 people

- abnormal behaviour, emotional disorder, fear, nightmare,
- bleeding of the mucous membrane that lines the inner surface of the eyelids, blurred vision, drowsiness, intolerance to light, itchy eyes, facial pain, inflamed gums,
- chest discomfort, difficult breathing, lung infection, nasal discomfort, pneumonia, wheezing,
- low blood pressure,
- enlarged liver,
- painful menstruation,
- itchy anal area (pinworms or ascarids), blistering rash (shingles), decreased sensitivity to touch, muscle twitching, pain in skin, paleness, peeling of skin, redness, swelling.

The attempt to harm yourself has also been reported in adults, children, and adolescents.

Ribavirin Mylan in combination with an alpha interferon product may also cause:
- aplastic anaemia, pure red cell aplasia (a condition where the body stopped or reduced the production of red blood cells); this causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy,
- delusions,
- upper and lower respiratory tract infection,
- inflammation of the pancreas,
- severe rashes which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes (erythema multiforme, Stevens Johnson syndrome), toxic epidermal necrolysis (blistering and peeling of the top layer of skin),

The following other side effects have also been reported with the combination of Ribavirin Mylan and an alpha interferon product:
- abnormal thoughts, hearing or seeing images that are not present, altered mental status, disorientation,
- angioedema (swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing),
- Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord),
- bronchoconstriction and anaphylaxis (a severe, whole-body allergic reaction), constant cough,
- eye problems including damage to the retina, obstruction of the retinal artery, inflammation of the optic nerve, swelling of the eye and cotton wool spots (white deposits on the retina),
- enlarged abdominal area, heartburn, trouble having bowel movement or painful bowel movement,
- acute hypersensitivity reactions including urticaria (hives), bruises, intense pain in a limb, leg or thigh pain, loss of range of motion, stiffness, sarcoidosis, (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands).

Ribavirin Mylan in combination with interferon alfa-2b may also cause:
- dark, cloudy or abnormally coloured urine,
- difficulty breathing, changes in the way your heart beats, chest pain, pain down left arm, jaw pain,
- loss of consciousness,
- loss of use, drooping or loss of power of facial muscles, loss of feeling sensation,
- loss of vision.

You or your caregiver should call your doctor immediately if you have any of these symptoms.

For HCV/HIV co-infected patients receiving Ribavirin Mylan in combination with peginterferon alfa-2b, there is an increased risk of lactic acidosis, liver failure and blood abnormalities (reduction in red or white blood cells that fight infection, and blood clotting cells called platelets).

The following additional side effects have occurred in HCV/HIV co-infected patients receiving Ribavirin in combination with peginterferon alfa-2b: oral thrush, changes in the amount and distribution of body fat, reduction in the amount of white blood cells, decreased appetite, increase in gamma-glutamyltransferase (an enzyme produced by the liver, associated with early liver cell damage), back pain, increase amounts of amylase (an enzyme present in the blood) and lactic acid, hepatitis, increased lipase (the enzyme necessary for the absorption and digestion of nutrients in the intestines) and limb pain.

Reporting of side effects
If you get any of the side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V*. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ribavirin Mylan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle or blister after EXP. The expiry date refers to the last date of that month.

Do not store the bottles above 30°C.

There are no special storage conditions for capsules packed in blisters.

Do not use this medicine if you notice any change in the appearance of the capsules.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ribavirin Mylan contains

- The active substance is ribavirin. Each hard capsule contains 200 mg ribavirin.
- The other ingredients are croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, povidone. The capsule shell contains gelatine and titanium dioxide (E171). The capsule shell imprint contains shellac, propylene glycol, strong ammonia solution, colouring agents (E172, E132, E171).

What Ribavirin Mylan looks like and contents of the pack

The Ribavirin Mylan hard capsule is a white, opaque, hard capsule imprinted with green ink.

The Ribavirin Mylan hard capsule is available in different pack sizes:

High-density polyethylene (HDPE) bottle, closed with a child-resistant (CR) polypropylene (PP) screw cap. Pack sizes of 84, 112, 140 and 168 capsules.

Blisters:
Cardboard box containing 56 or 168 hard capsules in PVC/Aclar – Aluminium foil blisters

Unit Dose Blisters:
Cardboard box containing 56x1, 84x1, 112x1, 140x1, 168x1 hard capsules in PVC/Aclar – Aluminium foil perforated unit dose blisters

Not all pack sizes may be marketed.

Your physician will prescribe the pack size which is best for you.

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This Leaflet was Last Approved In.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Annex IV
Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSURs for Ribavirin containing medicinal products, the scientific conclusions are as follows:

This PSUSA covers a yearly period with a Data lock point up to 24 July 2013.

The MAH submitted an evaluation of a signal on tongue hyperpigmentation, as requested in the previous PSUR of Ribavirin. The number of cases of tongue pigmentation reported to date with ribavirin and/or peginterferon alfa 2b, even though some of them are insufficiently documented, is significant. In literature case reports, a positive dechallenge (with slowly resolution of symptoms) was generally reported after stopping antiviral therapy which is in favour of drug causality. This evaluation led to the conclusion that bitherapy with ribavirin and peginterferon can induce tongue pigmentation. PRAC therefore recommends the inclusion of this adverse reaction in section 4.8 of the SmPC of the oral formulations of ribavirin containing products. The package leaflet should be updated accordingly.

Furthermore, it was noted that the following adverse drug reactions should be included across the product information of all the ribavirin containing products: tinnitus, hypotension, vasculitis and cerebrovascular ischaemia. As such PRAC recommended that these adverse drug reactions be added to the product information of those products that do not contain them.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisations

On the basis of the scientific conclusions for Ribavirin containing medicinal products the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing the active substance Ribavirin is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.