AUSTRALIAN PRODUCT INFORMATION – IBAVYR® (RIBAVIRIN) TABLETS 200 MG

1. NAME OF THE MEDICINE

Ribavirin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IBAVYR (ribavirin) 200 mg tablet contains 200 mg ribavirin.

Ribavirin is a nucleoside analogue with antiviral activity.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablets.

IBAVYR (ribavirin) 200 mg tablet is a white, capsule-shaped, coated tablet, debossed with “200” on one side and nothing on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBAVYR (ribavirin tablets) is indicated in combination with other oral agents for the treatment of chronic hepatitis C (CHC) in adults.

4.2 Dose and method of administration

Dose

Ribavirin monotherapy is not effective and IBAVYR must only be used in combination with other oral agents for the treatment of CHC.

Treatment with IBAVYR should be initiated and monitored by a physician experienced in the management of CHC.

The recommended dose and treatment duration should be individualised to the patient depending on body weight, baseline disease characteristics (e.g., genotype), response to therapy, and underlying conditions.

The recommended dose and treatment duration for combination therapy with sofosbuvir are shown in Table 1. When IBAVYR is used in combination treatment with any other oral agent, refer to the appropriate Product Information for dosage information.

Table 1: Recommended Dose/Treatment Duration for IBAVYR in Combination Therapy with Sofosbuvir

HCV Genotype	Treatment Duration	IBAVYR Dose (daily)[1]	Sofosbuvir Dose (daily)
Patients with genotype 2 CHC	12 weeks	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	400 mg
Patients with genotype 3 CHC	16 weeks[2]		

Patients with CHC awaiting liver transplantation	Until liver transplantation[3]		

1. Administered orally in two divided doses with food.
2. Consideration should be given to potentially extending the duration of therapy beyond 16 weeks and up to 24 weeks guided by an assessment of the potential benefits and risks for the individual patient (these factors may include cirrhosis status and treatment history).
3. Ribavirin in combination with sofosbuvir was administered for up to 24 weeks to 28 patients with hepatocellular carcinoma awaiting liver transplantation to prevent post-transplant HCV reinfection. The duration of administration of sofosbuvir + ribavirin in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

Dose Modifications

If a patient has a serious adverse effect or develops laboratory abnormalities potentially related to ribavirin, the dose should be modified or discontinued, as appropriate, until the adverse effects abate or decrease in severity.

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

Table 2: IBAVYR Dosage Modification Guidelines for Treatment Emergent Anaemia

Laboratory Values	Reduce Only IBAVYR Dose to 600 mg/day[1] if:	Discontinue[2] IBAVYR if:
Haemoglobin in patients with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Haemoglobin in patients with history of stable cardiac disease	> 2 g/dL decrease in haemoglobin during any 4 week period treatment	< 12 g/dL despite 4 weeks at reduced dose

1. Administered orally in two divided doses with food.
2. Once IBAVYR has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart IBAVYR at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that IBAVYR be increased to its original assigned dose (1000 mg to 1200 mg daily).

When IBAVYR is used in combination treatment with any other oral agent, refer to the appropriate Product Information for dose reduction information.

Discontinuation of Dosing

If the other oral agents used in combination with IBAVYR are permanently discontinued, IBAVYR should not be continued as monotherapy.

Missed Dose

The missed doses should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to call their healthcare provider if they have questions.

Renal impairment

IBAVYR should not be used in patients with creatinine clearance < 50 mL/min.

Method of Administration

IBAVYR is administered orally in two daily divided doses with food.

4.3 Contraindications

IBAVYR is used in combination with other therapeutic agents; the contraindications applicable to those agents are therefore applicable to the combination therapy. Refer to their respective Product Information for a list of their contraindications.

IBAVYR is also contraindicated in:

- Women who are pregnant [see Section 4.6 Fertility, pregnancy and lactation, Use in pregnancy].

- Men whose partners are pregnant [see Section 4.6 Fertility, pregnancy and lactation, Use in pregnancy].
- Patients with hemoglobinopathies (e.g., thalassemia major or sickle-cell anaemia).
- In combination with didanosine. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials [see Section 4.5 Interactions with other medicines and other forms of interactions].
- Patients with hypersensitivity to ribavirin or to any of the excipients listed in Section 6.1 List of excipients.
- A history of severe pre-existing cardiac, including unstable or uncontrolled cardiac disease, in the previous six months.

4.4 Special warnings and precautions for use

The Product Information of other oral agent(s) used in combination should be consulted before starting treatment with IBAVYR.

Cardiovascular

Fatal and nonfatal myocardial infarctions have been reported in patients with anaemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anaemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

Hematologic

Anaemia

The primary toxicity of ribavirin is haemolytic anaemia, which was commonly observed in clinical trials with other therapies and is the most common reason for dose modification of ribavirin in CHC patients [see Section 4.2 Dose and method of administration]. Anaemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in haemoglobin may be significant, it is advised that haemoglobin or haematocrit be obtained pre-treatment and at week 2 and week 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate. Caution should be exercised in initiating treatment in any patient with baseline risk of severe anaemia (e.g., spherocytosis, history of gastrointestinal bleeding)

Bone Marrow Suppression

Concomitant administration of ribavirin and azathioprine has been reported to produce myelotoxicity (pancytopenia and bone marrow suppression) within 3 to 7 weeks of concomitant therapy. This was reversible within 4 to 6 weeks after withdrawal of either drug and did not recur after the reintroduction of either drug alone [see Section 4.5 Interactions with other medicines and other forms of interactions].

Treatment-experienced Patients with genotype 1, 4, 5 and 6 HCV Infection

The safety and efficacy of IBAVYR combination therapy has not been studied in a Phase 3 study in treatment-experienced patients with genotype 1, 4, 5 and 6 HCV infection. Thus, the optimal treatment duration in this population has not been established.

The clinical data to support the use of IBAVYR combination therapy in patients with genotype 5 and 6 HCV infection is very limited.

Interferon-free therapy for genotype 1, 4, 5 and 6 HCV Infection

Interferon-free regimens for patients with genotype 1, 4, 5 and 6 HCV infection with SOVALDI have not been fully investigated in Phase 3 studies. The optimal regimen and treatment duration have not been established. Such regimens should only be used for patients that are intolerant to or ineligible for interferon therapy, and are in urgent need of treatment.

HCV/HBV (Hepatitis B Virus) Coinfected Patients

The safety and efficacy of IBAVYR combination therapy have not been established in patients co-infected with Hepatitis B Virus (HBV).

HCV/HIV Coinfected Patients

There is limited data on the safety and efficacy of IBAVYR combination therapy in HCV/HIV co-infected patients with untreated HIV.

Post-Liver Transplant Patients

The safety and efficacy of IBAVYR combination therapy has not been established in post-liver transplant patients.

Acute Hypersensitivity

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

Race

A pharmacokinetic study in 42 subjects demonstrated there is no clinically significant difference in ribavirin pharmacokinetics among Black (n=14), Hispanic (n=13) and Caucasian (n=15) subjects.

Gender

No clinically significant differences in the pharmacokinetics of ribavirin were observed between male and female subjects. Ribavirin pharmacokinetics, when corrected for weight, are similar in male and female patients.

Use in Hepatic Impairment

Safety and efficacy of ribavirin have not been established in patients with decompensated cirrhosis.

The effect of hepatic impairment on the pharmacokinetics of ribavirin has not been evaluated. The clinical trials of ribavirin were restricted to patients with Child-Pugh class A disease.

Use in Renal Impairment

The pharmacokinetics of ribavirin have not been studied in patients with renal impairment and there are limited data from clinical trials on the administration of ribavirin in patients with creatinine clearance <50 mL/min. Therefore, patients with creatinine clearance <50 mL/min should not be treated with ribavirin.

Effects on Laboratory Tests

It is recommended that standard haematological and biochemical laboratory tests be performed in all patients prior to initiating combination therapy with IBAVYR and periodically during therapy. Haematological tests should be performed at least at 2 weeks and 4 weeks and biochemical tests should be performed at 4 weeks after initiation of therapy. Additional testing should be performed periodically during therapy. In the clinical studies, the CBC (including haemoglobin level and white blood cell and platelet counts) and chemistries (including liver function tests and uric acid) were measured at 1, 2, 4, 6, and 8 weeks, and then every 4 to 6 weeks or more frequently if abnormalities were found. Thyroid stimulating hormone (TSH) was measured every 12 weeks.

Pregnancy screening in women of childbearing potential must be performed. Monthly pregnancy testing should be performed during combination therapy and for 6 months after discontinuation of therapy in female patients and the female partners of male patients.

Patients who have pre-existing cardiac abnormalities should have electrocardiograms administered before treatment with IBAVYR and should be monitored during therapy

Use in the elderly

Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. IBAYVR should not be administered to patients with creatinine clearance < 50 mL/min.

Paediatric use

Safety and effectiveness in paediatric patients have not been established. Therefore, use in children under the age of 18 is not recommended.

4.5 Interactions with other medicines and other forms of interaction

The drug interactions applicable to agents used in combination with ribavirin also apply to IBAVYR combination therapy. Refer to the appropriate Product Information for a detailed list of their drug interactions.

Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicology studies that ribavirin induces liver enzymes. Therefore, ribavirin has a minimal potential for P450 enzyme-based interactions.

Due to the long half-life of ribavirin (approximately 120–170 h) any potential drug interactions may persist for up to 2 months (5 half-lives for ribavirin) following the end of treatment.

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

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Lamivudine, stavudine, and zidovudine

In vitro data indicate ribavirin reduces phosphorylation of lamivudine, stavudine, and zidovudine. However, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppression) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were co-administered as part of a multi-drug regimen to HCV/HIV co-infected patients.

Didanosine

Co-administration of IBAVYR and didanosine is contraindicated. Ribavirin potentiates the phosphorylation of didanosine via inhibition of inosine 5-monophosphate dehydrogenase (IMPD) enzyme. As a result, the concentrations of didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) are increased when didanosine is co-administered with ribavirin. There have been reports of fatal hepatic failure, pancreatitis, peripheral neuropathy, and symptomatic hyperlactatemia/lactic acidosis in clinical trials.

Azathioprine

The use of ribavirin to treat chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. IMDH is involved in one of the metabolic pathways of azathioprine. Co-administration of this drug with ribavirin may possibly lead to an accumulation of the 6-methylthioinosine monophosphate (6-MTITP) metabolite. This metabolite has been associated with myelotoxicity (neutropenia, thrombocytopenia, and anaemia) in patients treated with azathioprine anaemia.

Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary [see Section 4.4 Special warnings and precautions for use].

Drug-Food Interactions

The presence of food in the gastrointestinal tract appears to increase the bioavailability of ribavirin. IBAVYR tablets should be taken with food [see Section 5.2 Pharmacokinetic properties].

4.6 Fertility, pregnancy and lactation

Effects on fertility

In a fertility study in rats, ribavirin showed a marginal reduction in sperm counts at the dose of 100 mg/kg/day with no effect on fertility. Upon cessation of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (approximately 0.1 to 0.8 times the maximum recommended daily human dose of ribavirin) administered for 3 to 6 months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenic cycles.

Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive IBAYVR unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilised for 6 months post therapy (i.e., 15 half-lives of clearance for ribavirin).

Use in pregnancy

Pregnancy: Category X

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate 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 drug dose.

Survival of foetuses and offspring was reduced.

In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended daily human dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (approximately 0.01 times the maximum recommended daily human dose of ribavirin).

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin is contained in sperm, and if so, will exert a potential teratogenic effect upon fertilization of the ova. However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

IBAVYR should not be used by pregnant women or by men whose female partners are pregnant. Female patients of childbearing potential and male patients with female partners of childbearing potential should not receive IBAVYR unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months post therapy [see Section 4.3 Contraindications].

Use in lactation

It is not known whether ribavirin is excreted in human milk. Because many drugs are excreted in human milk and to avoid any potential for serious adverse reactions in nursing infants from ribavirin, a decision should be made either to discontinue nursing or therapy with IBAYVR, based on the importance of the therapy to the mother.

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue, disturbance in attention, dizziness and blurred vision have been reported during treatment with ribavirin in combination with other agents. Patients who develop these symptoms should be cautioned to avoid driving or operating machinery.

4.8 Adverse effects (Undesirable effects)

When ribavirin is used in combination with other oral agents, please refer to the appropriate Product Information for a complete list of adverse drug effects.

Adverse Events from Clinical Trials

Assessment of adverse reactions associated with ribavirin and sofosbuvir combination therapy is based on pooled data from 650 patients who received sofosbuvir and ribavirin combination therapy for 12 weeks, 98 patients who received sofosbuvir and ribavirin combination therapy for 16 weeks, 250 patients who received sofosbuvir and ribavirin for 24 weeks, and 71 patients who received placebo for 12 weeks.

The proportion of patients who permanently discontinued treatment due to adverse events was 4% for patients receiving placebo, 1% for patients receiving sofosbuvir + ribavirin for 12 weeks, and <1% for patients receiving sofosbuvir + ribavirin for 24 weeks.

The following adverse reactions listed below by body system organ class have been identified with sofosbuvir and ribavirin therapy (Table 3). Frequencies are defined as follows: very common ≥ 10%, common ≥ 1% and < 10%, or uncommon > 0.1% and ≤ 1%.

The most common adverse events (≥ 20%) for sofosbuvir + ribavirin combination therapy were fatigue and headache.

Table 3: Treatment-Emergent Adverse Drug Reactions (Grade 2 and Higher) Reported in at ≥ 15% of Patients in Any Treatment Arm[a,b]

	Placebo 12 weeks	**Sofosbuvir +RBV**	**Sofosbuvir +RBV**
	N=71	N=650	N=250
Fatigue	24%	38%	30%

	Placebo 12 weeks	Sofosbuvir +RBV	Sofosbuvir +RBV
	N=71	N=650	N=250
Headache	20%	24%	30%
Nausea	18%	22%	13%
Insomnia	4%	15%	16%
Pruritus	8%	11%	27%
Anaemia	0%	10%	6%
Asthenia	3%	6%	21%
Rash	8%	8%	9%
Decreased Appetite	10%	6%	6%
Chills	1%	2%	2%
Influenza Like Illness	3%	3%	6%
Pyrexia	0%	4%	4%
Diarrhoea	6%	9%	12%
Neutropenia	0%	<1%	<1%
Myalgia	0%	6%	9%
Irritability	1%	10%	10%

a. Patients received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing ≥75 kg)
b. Patients received 800 mg ribavirin per day regardless of weight.

With the exception of anaemia and neutropenia, the majority of events presented in Table 3 occurred at severity of grade 1 in sofosbuvir-containing regimens.

Less Common Adverse Reactions reported in Clinical trials (<1%): The following ADRs occurred in <1% of patients receiving ribavirin in a combination regimen in any one trial. These events have been included because of their seriousness or assessment of potential causal relationship.

Psychiatric Disorders: severe depression (particularly in patients with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

Other special population(s)

HIV/HCV co-infection

The safety profile of ribavirin and sofosbuvir in HCV/HIV co-infected patients was similar to that observed in mono-infected HCV patients treated with of ribavirin and sofosbuvir in Phase 3 clinical studies.

Patients awaiting liver transplantation

The safety profile of ribavirin and sofosbuvir in HCV infected patients prior to liver transplantation was similar to that observed in patients treated with ribavirin and sofosbuvir in Phase 3 clinical studies.

Post-Market Adverse Drug Effects

For complete safety information of ribavirin in combination with other oral agents, please refer to the appropriate Product Information.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

No cases of overdose with ribavirin have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered greater than the recommended dosage of

ribavirin. In most of these cases, ribavirin was administered intravenously at dosages up to and in some cases exceeding four times the recommended maximum oral daily dose.

For information on the management of overdose, contact the Poison Information Centre at 131126 (Australia) or 0800 764 766 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for treatment of HCV infections, ATC code: J05AP01

Mechanism of action

Ribavirin is an antiviral drug. The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. It has shown direct antiviral activity in tissue culture against numerous viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits hepatitis C virus (HCV) polymerase in a biochemical reaction.

Antiviral Activity in vitro

The antiviral activity of ribavirin was investigated in the stable HCV cell culture model system (HCV replicon). Ribavirin inhibited autonomous HCV RNA replication with a 50% effective concentration (EC50) value of 11-21 mcM. Evaluation of sofosbuvir in combination with ribavirin showed no antagonistic effect in reducing HCV-RNA levels in replicon cells.

Clinical Trials

Ribavirin monotherapy is not effective and IBAVYR must only be used in combination with other oral agents for the treatment of CHC.

The clinical trials which evaluated the efficacy of ribavirin in combination therapy with sofosbuvir are summarised below. For more information on the clinical trials conducted on ribavirin in combination with sofosbuvir and/or other agents, please consult the respective Product Information.

Clinical Trials of Ribavirin in Combination with Sofosbuvir

The efficacy of ribavirin in combination with sofosbuvir was evaluated in five phase 3 trials in patients with genotypes 1 to 6 chronic hepatitis C (CHC). One study was conducted in treatment-naïve patients with genotype 1, 4, 5 or 6 CHC and the other four trials were conducted in patients with genotype 2 or 3 CHC including one trial in treatment-naïve patients, one in interferon intolerant, ineligible or unwilling patients and one in patients previously treated with an interferon-based regimen and one in all patients irrespective of prior treatment history or ability to take interferon. Patients in these trials had compensated liver disease including cirrhosis. The ribavirin dose was weight-based 1000-1200 mg daily administered in two divided doses. Sofosbuvir was administered at a dose of 400 mg once daily. Treatment duration was fixed in each trial and was not guided by patients' HCV RNA levels (no response guided algorithm).

Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL. Sustained virologic response (SVR) was the primary endpoint to determine the HCV cure rate for all trials which was defined as HCV RNA less than LLOQ at 12 weeks after the end of treatment (SVR 12).

Treatment Naïve Adults — FISSION (Study 1231)

FISSION was a randomised, open-label, active-controlled trial that evaluated 12 weeks of treatment with ribavirin and sofosbuvir compared to 24 weeks of treatment with ribavirin and peginterferon alfa 2a in treatment-naïve patients with genotype 2 and 3 HCV. The ribavirin doses used in the sofosbuvir + ribavirin and peginterferon alfa 2a + ribavirin arms were weight-based 1000-1200 mg per day and 800 mg per day regardless of weight, respectively. Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence vs absence), HCV genotype (2 vs 3) and baseline HCV RNA level (< 6 $\log_{10}$ IU/mL vs ≥ 6 $\log_{10}$ IU/mL). Patients with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Treated patients (N=499) had a median age of 50 years (range: 19 to 77); 66% of the patients were male; 87% were White, 3% were Black; 14% were Hispanic or Latino, 29% were Asian; mean body mass index was 28 kg/m^2 (range: 17 to 52 kg/m^2); 57% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 20% had cirrhosis; 72% had HCV genotype 3.9% were on opiate replacement therapy. Table 4 presents the response rates from this study.

Table 4: Response Rates in Study FISSION

	Sofosbuvir + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	N=253[a]	N=243[a]
Overall SVR	67% (170/253)	67% (162/243)
Genotype 2	97% (68/70)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
Outcome for patients without SVR		
On-treatment virologic failure	<1% (1/253)	7% (18/243)
Relapse[b]	30% (74/249)	21% (46/217)
Other[c]	3% (8/253)	7% (17/243)

a. Three patients were excluded from efficacy analysis because they were classified as genotype 1 by NS5B sequencing assay.
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

The difference in the overall SVR rates between sofosbuvir + ribavirin and peginterferon alfa + ribavirin treatment groups was 0.3% (95% confidence interval:
-7.5% to 8.0%) and the study met the predefined noninferiority criterion. Among the small number of Black/African Americans enrolled in the trial, 75% (9/12) of patients achieved SVR in the sofosbuvir + ribavirin treatment group compared to 40% (2/5) in the peginterferon alfa + ribavirin treatment group.

Response rates for patients with cirrhosis at baseline are presented in Table 5 by genotype.

Table 5: SVR Rates by Cirrhosis and Genotype in Study FISSION

	Genotype 2		Genotype 3	
	Sofosbuvir + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks	SOVALDI + RBV 12 weeks	Peg-IFN alfa + RBV 24 weeks
	(N=70)	(N=67)	(N=183)	(N=176)
Cirrhosis				
No	98% (58/59)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	91% (10/11)	62% (8/13)	34% (13/38)	30% (11/37)

Interferon Intolerant, Ineligible or Unwilling Adults — POSITRON (Study 107)

POSITRON was a randomised, double-blinded, placebo-controlled trial that evaluated 12 weeks of treatment with ribavirin and sofosbuvir (N =207) compared to placebo (N =71) in patients who are interferon intolerant, ineligible or unwilling. Patients were randomised in 3:1 ratio and stratified by cirrhosis (presence vs absence).

Treated patients (N=278) had a median age of 54 years (range: 21 to 75); 54% of the patients were male; 91% were White, 5% were Black; 11% were Hispanic or Latino, 8% were Asian; mean body mass index was 28 kg/m^2 (range: 18 to 53 kg/m^2); 70% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 16% had cirrhosis; 49% had HCV genotype 3. 8% were on opiate replacement therapy. The proportions of patients who were interferon intolerant, ineligible, or unwilling were 9%, 44%, and 47%, respectively. Most patients had no prior HCV treatment (81.3%). Table 6 presents the response rates for the treatment groups of sofosbuvir + ribavirin and placebo.

Table 6: Response Rates in Study POSITRON

	Sofosbuvir + RBV 12 weeks	Placebo 12 weeks
	N=207	N=71
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37

Outcome for patients without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse[a]	20% (42/205)	0/0
Other[b]	2% (4/207)	3% (2/71)

a. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
b. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

The SVR12 rate in the sofosbuvir + ribavirin treatment group was statistically significant when compared to placebo ($p < 0.001$).

Table 7 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 7: SVR Rates for Selected Subgroups by Genotype in POSITRON

	Sofosbuvir + RBV 12 weeks	
	Genotype 2	**Genotype 3**
	N=109	N=98
Cirrhosis		
No	92% (85/92)	68% (57/84)
Yes	94% (16/17)	21% (3/14)
Interferon Classification		
Ineligible	88% (36/41)	70% (33/47)
Intolerant	100% (9/9)	50% (4/8)
Unwilling	95% (56/59)	53% (23/43)

Previously Treated Adults — FUSION (Study 108)

FUSION was a randomised, double-blinded trial that evaluated 12 or 16 weeks of treatment with ribavirin and sofosbuvir in patients who did not achieve SVR with prior interferon-based treatment (relapsers and nonresponders). Patients were randomised in a 1:1 ratio and stratified by cirrhosis (presence vs absence) and HCV genotype (2 vs 3).

Treated patients (N=201) had a median age of 56 years (range: 24 to 70); 70% of the patients were male; 87% were White; 3% were Black; 9% were Hispanic or Latino, 12% were Asian; mean body mass index was 29 kg/m^2 (range: 19 to 44 kg/m^2); 73% had baseline HCV RNA levels greater than 6 $\log_{10}$ IU per mL; 34% had cirrhosis; 63% had HCV genotype 3; 75% were prior relapsers. 3% were on opiate replacement therapy. Table 8 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 16 weeks.

Table 8: Response Rates in Study FUSION

	Sofosbuvir+ RBV 12 weeks	**Sofosbuvir + RBV 16 weeks**
	N= 100[a]	N=95[a]
Overall SVR	50% (50/100)	73% (69/95)
Genotype 2	86% (31/36)	94% (30/32)
Genotype 3	30% (19/64)	62% (39/63)
Outcome for patients without SVR		
On-treatment virologic failure	0/100	0/95
Relapse[b]	47% (47/100)	27% (26/95)
Other[c]	3% (3/100)	0/95

a. Six patients were excluded from efficacy analysis because they were classified as HCV genotype 1 by NS5B sequencing assay.
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 9 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 9: SVR Rates for Selected Subgroups by Genotype in Study FUSION

	Genotype 2		Genotype 3	
	Sofosbuvir + RBV 12 weeks	**Sofosbuvir + RBV 16 weeks**	**Sofosbuvir + RBV 12 weeks**	**Sofosbuvir + RBV 16 weeks**
	N=36	N=32	N=64	N=63
Cirrhosis				
No	96% (25/26)	100% (23/23)	37% (14/38)	63% (25/40)
Yes	60% (6/10)	78% (7/9)	19% (5/26)	61% (14/23)
Response to prior HCV treatment				
Relapser	92% (24/26)	96% (23/24)	31% (15/49)	65% (30/46)
Nonresponder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

Treatment-naïve and previously treated adults - VALENCE (Study 133)

The VALENCE trial evaluated sofosbuvir in combination with weight-based ribavirin for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior interferon-based treatment, including patients with compensated cirrhosis. The study was designed as a direct comparison of sofosbuvir and ribavirin *versus* placebo for 12 weeks. However, based on emerging data, the study was unblinded and all HCV genotype 2 patients continued to receive sofosbuvir and ribavirin for 12 weeks, whilst treatment for HCV genotype 3 patients was extended to 24 weeks. Eleven HCV genotype 3 patients had already completed treatment with sofosbuvir and ribavirin for 12 weeks at the time of the amendment.

Treated patients (n = 419) had a median age of 51 years (range: 19 to 74); 60% of the patients were male; median body mass index was 25 kg/ m^2 (range: 17 to 44 kg/m^2); the mean baseline HCV RNA level was 6.4 $\log_{10}$ IU/mL; 21% had cirrhosis; 78% had HCV genotype 3; 65% were prior relapsers. Table 7 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 24 weeks.

Placebo recipients are not included in the tables since none achieved SVR12.

Table 10: Response rates in Study VALENCE[a]

	Genotype 2 Sofosbuvir + RBV 12 weeks (n = 73)	**Genotype 3 Sofosbuvir + RBV 24 weeks (n = 250)**
Overall SVR12	93% (68/73)	84% (210/250)
Outcome for subjects without SVR12		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse[b]	7% (5/73)	14% (34/249)
Other[c]	0% (0/73)	2% (34/249)

a. Placebo patients (n=85) were not included as none achieved SVR12. Eleven genotype 3 patients who received sofosbuvir + ribavirin for 12 weeks were not included
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 11 presents the subgroup analysis by genotype for cirrhosis and exposure prior to HCV treatment.

Table 11: SVR12 rates for selected subgroups by genotype in study VALENCE

	Genotype 2 sofosbuvir +RBV 12 weeks (n = 73)	**Genotype 3 sofosbuvir +RBV 24 weeks (n = 250)**

Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	94% (86/92)
Cirrhotic	100% (2/2)	92% (12/13)
Treatment-experienced	90% (37/41)	77% (112/145)
Non-cirrhotic	91% (30/33)	85% (85/100)
Cirrhotic	88% (7/8)	60% (27/45)

SVR12 to SVR24 concordance

The concordance between SVR12 and SVR24 (SVR 24 weeks after the end of the treatment) following treatment with sofosbuvir in combination with ribavirin or ribavirin and pegylated interferon demonstrates a positive predictive value of 99% and a negative predictive value of 99%.

Clinical efficacy and safety in special populations

HCV/HIV co-infected patients – PHOTON-1 (Study 123)

Sofosbuvir was studied in an open-label clinical study evaluating the safety and efficacy of 12 or 24 weeks of treatment with sofosbuvir and ribavirin in patients with genotype 1, 2 or 3 chronic hepatitis C co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were naïve to prior treatment. Patients received 400 mg sofosbuvir and weight-based ribavirin (1,000 mg for patients weighing <75 kg or 1,200 mg for patients weighing ≥75 kg) daily for 12 or 24 weeks based on genotype and prior treatment history. Patients were either not on antiretroviral therapy with a CD4+ cell count >500 cells/mm^3 or had virologically suppressed HIV-1 with a CD4+ cell count >200 cells/mm^3. Efficacy data 12 weeks post treatment are available for 210 patients (Table 12).

There is limited data on the safety and efficacy of sofosbuvir in HCV/HIV co-infected patients with untreated HIV.

Table 12: Response rates in study PHOTON-1[a]

	HCV genotype 1	**HCV genotype 2**	**HCV genotype 3**
	Sofosbuvir + RBV 24 weeks TN (n = 114)	**Sofosbuvir + RBV 12 weeks TN (n = 26)**	**Sofosbuvir + RBV 24 weeks TE (n = 13)**
Overall SVR12	76% (87/114)	88% (23/26)	92% (12/13)
Outcome for subjects without SVR12			
On-treatment virologic failure	1% (1/114)	4% (1/26)	0/13
Relapse[b]	22% (25/113)	0/25	8% (1/13)
Other[c]	1% (1/114)	8% (2/26)	0/13

TN= Treatment-naïve, TE =Treatment-experienced

a. Patients with genotype 2 CHC treated with sofosbuvir + RBV for 24 weeks (n=15) and patients with genotype 3 CHC treated with sofosbuvir + RBV for 12 weeks (n=42) are not included in the table
b. The denominator for relapse is the number of patients with HCV RNA <LLOQ at their last on-treatment assessment.
c. Other includes patients who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow-up).

Table 13 presents the subgroup analysis by genotype for cirrhosis.

Table 13: SVR12 rates for selected subgroups by genotype in study PHOTON-1

	HCV genotype 2		**HCV genotype 3**	
	Sofosbuvir +RBV 12 weeks TN (n = 26)	**Sofosbuvir +RBV 24 weeks TE (n = 15)**	**Sofosbuvir +RBV 12 weeks TN (n = 42)**	**Sofosbuvir +RBV 24 weeks TE (n = 13)**
Overall	88% (23/26)	93% (14/15)	67% (28/42)	92% (12/13)

No cirrhosis	88% (22/25)	92% (12/13)	67% (24/36)	100% (8/8)
Cirrhosis	100% (1/1)	100% (2/2)	67% (4/6)	80% (4/5)

TN = treatment-naïve; TE = treatment-experienced.

Patients Awaiting Liver Transplantation

Sofosbuvir was studied in HCV-infected patients prior to undergoing liver transplantation in an open-label clinical trial evaluating the safety and efficacy of sofosbuvir and ribavirin administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the trial was post-transplant virologic response (pTVR) (HCV RNA < lower limit of quantification [LLOQ] at 12 weeks post-transplant). HCV-infected patients, regardless of genotype, with hepatocellular carcinoma (HCC) meeting the MILAN criteria received 400 mg sofosbuvir and 1000-1200 mg ribavirin daily for a maximum of 24 weeks or until the time of liver transplantation, whichever occurred first. An interim analysis was conducted on 61 patients who received sofosbuvir and ribavirin; 45 had genotype 1; 44 patients had a baseline CPT score less than 7. Of these 61 patients, 44 patients underwent liver transplantation following up to 48 weeks of treatment with sofosbuvir and ribavirin; 41 had HCV RNA < LLOQ at the time of transplantation, one of whom received an HCV-infected liver. The viral response rates of the 41 patients transplanted with HCV RNA<LLOQ are described in Table 14.

Table 14: Virologic Response Post-Transplant in Patients with HCV RNA < LLOQ at the Time of Liver Transplantation

	Week 12 post-transplant (pTVR)[b]
Virologic response in evaluable patients [a],[c]	23/37 (62%)

a. Evaluable patients are defined as those who have reached the specified time point at the time of the interim analysis.
b. pTVR: post transplant virologic response (HCV RNA < LLOQ at 12 weeks post-procedure).
c. HCV RNA < LLOQ (less than 25 IU per mL)

5.2 Pharmacokinetic properties

Absorption

Multiple dose ribavirin pharmacokinetic data are available for HCV patients who received ribavirin in combination with peginterferon alfa-2a. Following administration of 1200 mg/day with food for 12 weeks mean±SD (n=39; body weight > 75 kg) $AUC_{0\text{-}12hr}$ was 25,361±7110 ng·hr/mL and C_{max} was 2748±818 ng/mL.

The average time to reach C_{max} was 2 hours. Trough ribavirin plasma concentrations following 12 weeks of dosing with food were 1662±545 ng/mL in HCV infected patients who received 800 mg/day (n=89), and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; body weight > 75 kg).

Distribution

Ribavirin partitions into all cells rapidly and extensively. It has a very large steady-state volume of distribution after intravenous dosing. This distribution is facilitated by the sodium independent equilibrative sensitive (es) nucleoside transporter that is present on virtually all cell types and may account for the extensive distribution. Ribavirin sequesters in erythrocytes extensively with a ratio of 60:1 between whole blood and plasma concentrations. Ribavirin does not bind to plasma proteins.

Metabolism

Ribavirin has two pathways of metabolism: (1) a reversible phosphorylation pathway (to mono-, di-, and triphosphate metabolites); and (2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxamide. Ribavirin is not a substrate and does not inhibit any cytochrome P450 (CYP) enzymes. There is minimal potential for P450 enzyme-based drug interactions.

Excretion

The contribution of renal and hepatic pathways to ribavirin elimination after administration of ribavirin is not known; however, it is thought that the principal route of elimination for both ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites is renal (accounting for about 5 – 15% of single dose elimination), with the majority of the dose eliminated as metabolites rather than as parent compound.

Due to extensive distribution, the terminal half-life of a single oral dose is around 120 to 170 hours and the total apparent clearance is around 26 L/h. There was extensive accumulation of ribavirin after multiple dosing (twice daily) such that the C_{max} at steady state was four-fold higher than that of a single dose. The terminal elimination phase was elongated following multiple dosing with a mean $t_{1/2}$ in the range 274– 298 h. Ribavirin

was detectable until 4 weeks following cessation of dose administration. These results reflect the slow elimination of ribavirin from tissue compartments.

Effect of Food

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. Patients are advised to take ribavirin with food [see Section 4.2 Dose and method of administration].

Age, Gender and Ethnicity

Specific pharmacokinetic evaluations for ribavirin in the elderly have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. Ribavirin should not be administered to patients with creatinine clearance < 50 mL/min [see Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration].

No clinically significant differences in ribavirin pharmacokinetics were observed between male and females subjects when corrected for weight. In a pharmacokinetic study in 42 subjects there were no clinically significant differences observed in ribavirin pharmacokinetics between Black, Hispanic or Caucasian subjects.

Patients with Impaired Renal Function

The pharmacokinetics of ribavirin following administration of ribavirin have not been studied in patients with renal impairment and there are limited data from clinical trials on administration of ribavirin in patients with creatinine clearance < 50 mL/min. Therefore, patients with creatinine clearance < 50 mL/min should not be treated with ribavirin [see Section 4.4 Special warnings and precautions for use and Section 4.2 Dose and method of administration].

Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin following administration of ribavirin has not been evaluated.

5.3 Preclinical safety data

Carcinogenicity

In a p53 (+/-) mouse carcinogenicity study up to the maximum tolerated dose of 100 mg/kg/day, ribavirin was not oncogenic. Ribavirin was also not oncogenic in a rat 2 year carcinogenicity study at doses up to the maximum tolerated dose of 60 mg/kg/day. On a body surface area basis, these doses are approximately 0.5 and 0.6 times the maximum recommended daily human dose of ribavirin, respectively. Potential carcinogenic risk to humans cannot be excluded.

Genotoxicity

Ribavirin demonstrated mutagenic activity in the *in vitro* mouse lymphoma assay. No clastogenic activity was observed in an *in vivo* mouse micronucleus assay at doses up to 2000 mg/kg. However, results from studies published in the literature show clastogenic activity in the *in vivo* mouse micronucleus assay at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each IBAVYR (ribavirin) 200 mg tablet contains povidone, croscarmellose sodium, microcrystalline cellulose, crospovidone, silicon dioxide, magnesium stearate, Opadry White 03F180000 PI (109444).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Keep bottle tightly closed. Protect from light.

6.5 Nature and contents of container

200 mg: HDPE bottles with child resistant closure of 28 tablets or HDPE bottles of 100 tablets.

Not all pack sizes may be available.

6.6 Special precautions for disposal

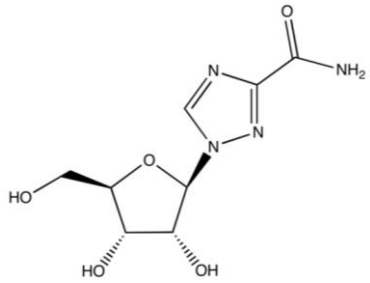
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Ribavirin is a white to off-white crystalline powder which is freely soluble in water and slightly soluble in anhydrous ethanol.

Chemical name:	1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
Molecular formula:	$C_8H_{12}N_4O_5$
Molecular mass:	244.21 g/mol

Chemical structure



CAS number

36791-04-5

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

26 February 2015

10. DATE OF REVISION

01 March 2022

Summary Table of Changes

Section Changed	Summary of New Information
2, 3, 6.1, 6.5	Removal of 400mg and 600mg strengths

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