PRODUCT MONOGRAPH

Pr IBAVYR™

Ribavirin Tablets, USP

200 mg, 400 mg, 600 mg

Antiviral Agent

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PrIBAVYR™

Ribavirin Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet ▪ 200 mg ▪ 400 mg ▪ 600 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

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

Geriatrics (> 65 years of age):
In general, caution should be exercised when administering IBAVYR in elderly patients, reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy (See WARNINGS AND PRECAUTIONS).

Pediatrics (< 18 years of age):
The safety and effectiveness of IBAVYR in pediatric patients have not been established (See WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

IBAVYR (ribavirin tablets) must be used in combination with other therapeutic agents for the treatment of CHC. The contraindications applicable to those agents are therefore also applicable to the combination ribavirin therapy. The Product Monograph(s) of other agent(s) used in combination with ribavirin should be consulted before starting treatment with IBAVYR.

IBAVYR is contraindicated in:

- Patients with known hypersensitivity to any of the components of the product. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- Women who are pregnant or men whose female partners are pregnant because of the associated risks of birth defects and fetal death. IBAVYR should be started only when a report of a negative pregnancy test has been obtained immediately prior to initiation of ribavirin therapy. Women of childbearing potential and their male partners must not receive IBAVYR therapy unless they are using effective contraception (two reliable forms, one for each partner) during treatment with IBAVYR and for the 6-month post-therapy period (see WARNINGS AND PRECAUTIONS, Special Populations).
- Patients with hemoglobinopathies (e.g., thalassemia or sickle-cell anemia).
- Coadministration of didanosine and ribavirin is contraindicated because exposures of the active metabolite of didanosine (dideoxyadenosine 5′-triphosphate) are increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving both didanosine and ribavirin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Ribavirin monotherapy is not effective for treatment of chronic hepatitis C infection.**
- **Product Monographs of co-administered agents should be consulted prior to initiating therapy with ribavirin.**
- **Hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with IBAVYR (**see WARNINGS AND PRECAUTIONS, Hematologic**).**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, IBAVYR is contraindicated in women who are pregnant, and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking IBAVYR (**see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**).**

General

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

Cardiovascular

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia 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 anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin (see WARNINGS AND PRECAUTIONS Hematologic).

Hematologic

Anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit 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 anemia (e.g., spherocytosis, history of gastrointestinal bleeding).

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 DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic

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 (see ACTION AND CLINICAL PHARMACOLOGY). Safety and efficacy of ribavirin have not been established in patients with decompensated cirrhosis.

Renal

IBAVYR should not be used in patients with a creatinine clearance < 50 mL/min (see WARNINGS AND PRECAUTIONS, Special Populations, Renal Impairment).

Sexual Function/Reproduction

In all animal species in which adequate studies have been conducted, significant teratogenic and/or embryocidal potential of ribavirin has been demonstrated at doses well below the recommended human dose. Increases in the dose of ribavirin correlated with increases in the incidence and severity of teratogenic effects. Reduced survival of fetuses and offspring were observed, as well as malformations of the skeleton, skull, limbs, palate, eye, jaw, and gastrointestinal tract.

Accumulation of ribavirin occurs intracellularly and clearance is slow. It is unknown whether there would be propagation of teratogenic effects upon fertilization of ova with sperm containing ribavirin. Because of the potential risk of teratogenicity, it is recommended that both male and female patients must practice effective contraception (at least 2 reliable forms, one for each partner) during ribavirin therapy and for 6 months after completion of therapy (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

Special Populations

Pregnant women: IBAVYR must not be used in women who are pregnant, or by men whose female partners are pregnant, due to the risk of birth defects and/or fetal death (see CONTRAINDICATIONS).

Females of childbearing potential and their male partners must be advised of the teratogenic/embryocidal risks and must be instructed to use two forms of effective and reliable contraception (one for each partner) during treatment and for 6 months after treatment has terminated. IBAVYR should be started only when a report of a negative pregnancy test has been obtained immediately prior to initiation of ribavirin therapy.

During therapy, routine monthly pregnancy tests must be performed and patients should be advised to tell their physician immediately if a pregnancy is detected. When used in combination with sofosbuvir, two (one for each partner) effective non-hormonal methods of contraception must be used, since there are no data on the effectiveness of systemic hormonal contraceptives in women taking sofosbuvir. In the event of a pregnancy during treatment or within 6 months post-therapy, the patient must be advised of the significant risks of teratogenic effects of ribavirin on the fetus (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).

Nursing women: 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 IBAVYR, based on the importance of the therapy to the mother.

Pediatrics (< 18 years of age): IBAVYR is not indicated in children as safety and effectiveness have not been established in this group of patients.

Geriatrics (> 65 years of age): In general, caution should be exercised when administering IBAVYR in elderly patients, reflecting the greater frequency of anemia, decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy in this population. The risk of toxic reactions to this drug may be greater in patients with impaired renal function.

Renal impairment: The pharmacokinetics of ribavirin following administration of the drug have not been studied in patients with renal impairment. 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 IBAVYR.

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

HCV Patients Post-Liver Transplant: The safety and efficacy of ribavirin + sofosbuvir combination therapy have not been established in post-liver transplant patients.

Monitoring and Laboratory Tests

It is recommended that standard hematological and biochemical laboratory tests be performed in all patients prior to initiating combination therapy with IBAVYR and periodically during therapy. Hematological tests should be performed at least at 2 weeks and 4 weeks after initiation of therapy, and biochemical tests should be performed at 4 weeks after initiation of therapy.

Pregnancy screening in women of childbearing potential must be performed. Monthly pregnancy testing must be performed during IBAVYR combination therapy, and for 6 months after discontinuation of therapy, both 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.

ADVERSE REACTIONS

Adverse Reaction Overview

Please also consult the Adverse Reactions section of the Product Monograph(s) of other agents used in combination with IBAVYR.

The most common adverse reaction (≥ 5%; Grade 2 and higher) for ribavirin + sofosbuvir combination therapy (12-24 weeks treatment) was fatigue. The most common adverse reactions (≥ 5%) for ribavirin + peginterferon alfa + sofosbuvir combination therapy were fatigue, anemia, neutropenia, insomnia, headache and nausea.

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

When ribavirin is used in combination with other agents, please refer to the appropriate Product Monograph(s) for a complete list of clinical trial adverse reactions.

Ribavirin in Combination with Sofosbuvir

The safety assessment of ribavirin combination therapy with sofosbuvir was based on pooled Phase 3 clinical trial data (both controlled and uncontrolled studies) including 650 subjects who received sofosbuvir + ribavirin for 12 weeks, 250 subjects who received sofosbuvir + ribavirin for 24 weeks, 327 subjects who received sofosbuvir + peginterferon alfa + ribavirin combination therapy for 12 weeks, 243 subjects who received peginterferon alfa + ribavirin for 24 weeks and 71 subjects who received placebo for 12 weeks.

The proportion of subjects who permanently discontinued treatment due to adverse events in these trials was 4% for subjects receiving placebo, 1% for subjects receiving ribavirin +

sofosbuvir for 12 weeks, <1% for subjects receiving ribavirin + sofosbuvir for 24 weeks, 11% for subjects receiving ribavirin + peginterferon alfa for 24 weeks and 2% for subjects receiving ribavirin + peginterferon alfa + sofosbuvir for 12 weeks.

Table 1 lists adverse reactions (Grade 2 and higher) observed in clinical trials including ribavirin combination therapy with sofosbuvir that occurred in greater than or equal to 3% of subjects in any of the treatment arms.

Table 1 - Treatment-Emergent Adverse Reactions (Grade 2 and Higher) Reported in at Least 3% of Subjects in Any Ribavirin Combination Treatment Arm[a,b]

	Placebo N= 71	**PEG+RBV 24 weeks N=243**	**SOF+RBV 12 weeks N=650**	**SOF+RBV 24 weeks N=250**	**PEG+RBV+SOF 12 weeks N=327**
Fatigue	4 (5.6%)	42 (17.3%)	49 (7.5%)	13 (5.2%)	39 (11.9%)
Anemia	0	14 (5.8%)	31 (4.8%)	7 (2.8%)	46 (14.1%)
Insomnia	1 (1.4%)	22 (9.1%)	19 (2.9%)	11 (4.4%)	20 (6.1%)
Headache	0	15 (6.2%)	22 (3.4%)	7 (2.8%)	26 (8.0%)
Neutropenia	0	23 (9.5%)	1 (0.2%)	0	40 (12.2%)
Nausea	0	10 (4.1%)	16 (2.5%)	4 (1.6%)	18 (5.5%)
Irritability	0	13 (5.3%)	10 (1.5%)	3 (1.2%)	12 (3.7%)
Pruritus	0	8 (3.3%)	7 (1.1%)	10 (4.0%)	8 (2.4%)
Dyspnea	0	3 (1.2%)	11 (1.7%)	5 (2.0%)	13 (4.0%)
Depression	0	17 (7.0%)	7 (1.1%)	2 (0.8%)	5 (1.5%)
Influenza like illness	0	11 (4.5%)	3 (0.5%)	2 (0.8%)	11 (3.4%)
Decreased appetite	1 (1.4%)	12 (4.9%)	7 (1.1%)	1 (0.4%)	5 (1.5%)
Thrombocytopenia	1 (1.4%)	19 (7.8%)	0	0	6 (1.8%)
Myalgia	0	9 (3.7%)	7 (1.1%)	2 (0.8%)	6 (1.8%)
Rash	1 (1.4%)	11 (4.5%)	3 (0.5%)	1 (0.4%)	7 (2.1%)
Asthenia	0	2 (0.8%)	3 (0.5%)	12 (4.8%)	3 (0.9%)

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

[a] Frequencies of adverse drug reactions are based on Grade 2 and higher treatment-emergent adverse events, considered related to study drug.

[b] Additionally, the following adverse drug reactions of low severity (Grade 1) occurred with SOF +RBV combination therapy: dry skin (5%), nasopharyngitis (4%).

Less Common Clinical Trial Adverse Reactions in Combination with Sofosbuvir (< 3%)

Treatment-emergent, related (to any active treatment) adverse drug reactions of at least moderate intensity (Grade 2 and higher) occurring in less than 3% of patients receiving ribavirin in combination with sofosbuvir are listed below by body system:

Table 2. Treatment-Emergent Adverse Drug Reactions (Grade 2 and Higher) Reported in < 3% of Subjects Receiving Ribavirin in Combination with Sofosbuvir

Body System	RBV + SOF	RBV + SOF + PEG
Blood and Lymphatic System Disorders	Lymphadenopathy, lymphopenia, neutropenia	Hemolytic anemia, leukopenia, thrombocytopenia
Cardiac Disorders	Palpitations	N/A
Ear And Labyrinth Disorders	Vertigo	N/A
Eye Disorders	Amaurosis Fugax, dry eye, eye irritation, visual impairment	Vision blurred
Gastrointestinal Disorders	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, anal inflammation, constipation, diarrhea, dry mouth, dyspepsia, epigastric discomfort, frequent bowel movements, gastritis, gastroesophageal reflux disease, nausea, stomatitis, tongue ulceration, toothache, vomiting	Abdominal pain, abdominal pain lower, abdominal pain upper, aphthous stomatitis, cheilitis, constipation, diarrhea, dyspepsia, gastroesophageal reflux disease, glossitis, vomiting
General Disorders and Administration Site Conditions	Asthenia, chest pain, chills, feeling abnormal, feeling cold, influenza like illness, irritability, malaise, nodule, oedema peripheral, pain, pyrexia, xerosis	Asthenia, chest discomfort, chills, feeling abnormal, injection site rash, injection site reaction, pain, pyrexia, spinal pain
Hepatobiliary Disorders	Hyperbilirubinaemia	Hyperbilirubinaemia
Immune System Disorders	Sarcoidosis	Cryoglobulinaemia
Infections and Infestations	Bronchitis, fungal infection, kidney infection, nasopharyngitis, oral herpes, upper respiratory tract infection, urinary tract infection, varicella	Folliculitis, gastroenteritis viral, infected skin ulcer, skin bacterial infection, urinary tract infection
Injury, Poisoning and Procedural Complications	Excoriation, sunburn, wound	N/A
Investigations	Blood glucose increased, eosinophil count increased, hemoglobin abnormal, hemoglobin decreased, heart rate increased, thyroid function test abnormal, weight decreased	Blood creatinine increased, blood uric acid increased, hemoglobin abnormal, hemoglobin decreased, neutrophil count decreased, platelet count decreased, transaminases increased, weight decreased
Metabolism and Nutrition Disorders	Decreased appetite, hyperglycemia, hypokalemia, increased appetite	Decreased appetite, hyperglycemia, hyponatremia
Musculoskeletal And Connective Tissue Disorders	Arthralgia, flank pain, muscle spasms, muscle twitching, myalgia, pain in extremity	Arthralgia, back pain, muscle spasms, muscular weakness, myalgia

Body System	RBV + SOF	RBV + SOF + PEG
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	Basal cell carcinoma	N/A
Nervous System Disorders	Amnesia, burning sensation, disturbance in attention, dizziness, dysgeusia, lethargy, memory impairment, migraine, nerve root compression, neuropathy peripheral, paresis, restless legs syndrome	Ageusia, amnesia, disturbance in attention, dizziness, dizziness postural, dysgeusia, loss of consciousness, mental impairment, migraine, sinus headache, tremor
Psychiatric Disorders	Abnormal dreams, aggression, agitation, anxiety, apathy, confusional state, depressed mood, depression, hallucination, libido decreased, libido increased, mood altered, mood swings, nightmare, sleep disorder, suicidal ideation, suicide attempt, thinking abnormal	Affect lability, agitation, anxiety, confusional state, depression, distractibility, libido decreased, mood swings, restlessness, tachyphrenia
Renal and Urinary Disorders	Renal failure	N/A
Reproductive System and Breast Disorders	N/A	Pelvic pain
Respiratory, Thoracic and Mediastinal Disorders	Cough, dyspnea, dyspnoea at rest, dyspnea exertional, nasal dryness, oropharyngeal pain	Cough, nasal dryness
Skin And Subcutaneous Tissue Disorders	Alopecia, asteatosis, dermatitis, dry skin, eczema, erythema, hyperhidrosis, night sweats, onychoclasis, photosensitivity reaction, pruritus, pruritus generalised, psoriasis, rash, rash generalised, rash macular, rash maculo-papular, rash papular, skin fissures	Dermatitis, pruritus, psoriasis, rash, rash generalised, rash maculo-papular, urticarial
Vascular Disorders	Hematoma, hot flush	Hot flush, hypertension

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

Special Populations

For information on the safety profile of ribavirin and sofosbuvir in HIV-1 co-infected patients and patients awaiting liver transplantation, consult the Product Monograph for sofosbuvir.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Table 3 lists the frequency of treatment-emergent laboratory abnormalities (Grades 3-4) observed in clinical trials including ribavirin combination therapy with sofosbuvir that occurred in at least 2% of subjects in any of the treatment arms.

Table 3 – Laboratory Abnormalities (Grades 3-4) Reported in ≥ 2% of Subjects in Any Ribavirin Combination Treatment Arm

Laboratory Abnormality Parameters	Placebo 12 weeks N= 71	PEG+RBV[b] 24 weeks N=243	SOF+RBV[a] 12 weeks N=650	SOF+RBV[a] 24 weeks N=250	SOF+PEG+RBV[a] 12 weeks N=327
Hemoglobin[c] (< 9 g/dL or change from baseline ≥ 4.5 g/dL)	0	10%	9%	11%	27%
Neutrophils (< 0.75 x10^9/L)	1%	15%	< 1%	0	20%
Platelets (< 50 x10^9/L)	3%	7%	< 1%	1%	< 1%
Lymphocytes (< 0.5 x10^3/μL)	0	11%	1%	2%	5%
White blood cells (< 1.5 x10^3/μL)	0	5%	< 1%	0	6%
ALT (> 5 x ULN)	9%	4%	< 1%	1%	2%
AST (> 5 x ULN)	14%	2%	< 1%	0	3%
Lipase (> 3 x ULN)	1%	2%	2%	2%	< 1%
Serum glucose (> 250 mg/dL)	6%	2%	2%	1%	2%
Total bilirubin (> 2.5 x ULN)	0	1%	3%	3%	0

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

[a] Subjects received weight-based ribavirin (1000 mg per day if weighing < 75 kg or 1200 mg per day if weighing ≥ 75 kg).

[b] Subjects received 800 mg ribavirin per day regardless of weight.

[c] Grade 4 hemoglobin abnormality (< 7 g/dL) occurred in 1 subject in the SOF+PEG+RBV treatment arm.

Post-Market Adverse Reactions

The post-marketing adverse reactions for combination therapies including ribavirin + sofosbuvir are not yet available.

The following adverse reactions have been identified and reported during post-approval use of peginterferon alfa-2a + ribavirin combination therapy. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders: Pure red cell aplasia

Ear and Labyrinth disorders: Hearing impairment, hearing loss

Eye disorders: Serous retinal detachment

Immune disorders: Liver and renal graft rejection

Metabolism and Nutrition disorders: Dehydration

Skin and Subcutaneous Tissue disorders: Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN)

For complete safety information of ribavirin in combination with other agents, please refer to the appropriate Product Monograph(s).

DRUG INTERACTIONS

Overview

The drug interactions applicable to agents used in combination with ribavirin also apply to IBAVYR combination therapy. Refer to the appropriate Product Monograph(s) 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 minimal potential for P450 enzyme-based interactions.

Co-administration of ribavirin with an antacid containing magnesium, aluminum and methicone reduced the bioavailability of ribavirin (AUC_{tf} decreased 14%). This change is not considered to be of clinical relevance.

No pharmacokinetic interactions between interferon-alfa products and ribavirin have been observed in HCV clinical trials in which the two agents were used in combination therapy and there is no evidence of any interaction of ribavirin with sofosbuvir.

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

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.

Drug-Drug Interactions

Table 4 - Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Ribavirin and Didanosine	CT	The antiretroviral effect of didanosine (ddI) was potentiated by ribavirin *in vitro* and in animals by an increase in the formation of the active triphosphate anabolite (ddATP). Concomitant ribavirin did not significantly affect plasma pharmacokinetics of ddI in patients with HIV (note that intracellular ddATP was not measured). When ddI is co-administered with ribavirin, exposure to ddI or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased.	Co-administration of ddI and ribavirin is contraindicated. There have been reports of fatal hepatic failure, pancreatitis, peripheral neuropathy, and symptomatic hyperlactatemia/ lactic acidosis.
Ribavirin and Lamivudine, Stavudine, Zidovudine	T CT	Ribavirin inhibits phosphorylation of zidovudine and stavudine *in vitro*. In a 12 week pharmacokinetic substudy in 47 HCV/HIV co-infected patients to determine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors, no evidence of drug interaction was seen.	Plasma HIV RNA levels should be closely monitored in patients treated concomitantly with ribavirin and any of these nucleoside reverse transcriptase inhibitors (NRTIs). The use of ribavirin concomitantly with NRTIs must be reviewed if an increase in HIV RNA levels is observed. Concomitant administration of ribavirin and NRTIs did not appear to affect plasma exposure of ribavirin.
Myelosuppressive agents (e.g. azathioprine, zidovudine)	C	By having an inhibitory effect on inosine monophosphate dehydrogenase (IMPDH), ribavirin may interfere with azathioprine metabolism. This can potentially lead to an accumulation of 6 methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients on azathioprine therapy.	On an individual patient basis where the benefit of concomitant therapy with ribavirin and azathioprine outweighs the potential risk, hematologic monitoring should be performed to identify signs of myelotoxicity; if detected, treatment with these drugs should be discontinued.

C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

The presence of food in the gastrointestinal tract appears to increase the bioavailability of ribavirin. IBAVYR should be taken with food (see ACTION AND CLINICAL PHARMACOLOGY).

Drug-Alcohol Interactions

No data is available on interaction with alcohol. However, patients should be advised not to drink alcohol, as alcohol exacerbates liver disease and reduces the efficacy of CHC treatment.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

The recommended dose and treatment durations of IBAVYR should be individualized to the patient depending on body weight, baseline disease characteristics (e.g., genotype), response to therapy and underlying conditions. Depending on the agent(s) it is combined with, the usual IBAVYR dose varies between 800 mg and 1200 mg daily (and up to 1400 mg in certain situations). For information on dosage and treatment duration of ribavirin in combination with other agents in patients with CHC, please refer to the appropriate Product Monograph(s). The recommended dose and treatment duration for combination therapy with sofosbuvir are shown in Table 5 .

Table 5 - Recommended Dose/Treatment Duration[1] for IBAVYR Combination Therapy with Sofosbuvir[2]

HCV Genotype	Treatment Duration	IBAVYR Dose (daily)[3]	Sofosbuvir Dose (daily)	Peginterferon alfa Dose
Patients with genotype 1 or 4-CHC	12 weeks	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg	400 mg	Refer to peginterferon alfa PM
Patients with genotype 2 CHC	12 weeks			NA
Patients with genotype 3 CHC	24 weeks			

NA: Not applicable; PM: Product Monograph

1 Treatment duration is fixed and is not guided by subjects' HCV RNA levels (i.e., no response guided therapy).

2 Depending on the HCV genotype , IBAVYR can be used in combination with sofosbuvir alone (dual therapy) or with sofosbuvir and peginterferon alfa (triple therapy).

3 The daily dose of ribavirin is administered orally in two divided doses with food.

IBAVYR in combination with sofosbuvir for 24 weeks can be considered as a therapeutic option for treatment naïve and non-cirrhotic treatment experienced CHC patients with genotype 1 infection who are ineligible to receive an interferon-based regimen. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

For information on dosage and administration of IBAVYR in combination with sofosbuvir in HIV-1 co-infected patients and patients awaiting liver transplantation, consult the Product Monograph for sofosbuvir.

Dose Modification

If a patient has a serious adverse reaction potentially related to ribavirin, the dose should be modified or discontinued, if appropriate, until the adverse reaction abates or decreases in severity. Table 6 provides guidelines for dose modifications and discontinuation of IBAVYR based on the patient's hemoglobin concentration and cardiac status.

Table 6 - Dose Modification Guideline for Management of Treatment Emergent Anemia

Laboratory Values	Reduce IBAVYR dose to 600 mg daily[1] if:	Discontinue[2] IBAVYR if :
Hemoglobin in subjects with no cardiac disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in subjects with history of stable cardiac disease	≥ 2 g/dL decrease in hemoglobin during any 4 week treatment period	< 12 g/dL despite 4 weeks at reduced dose

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

When IBAVYR is used in combination treatment with other agent(s), refer to the appropriate Product Monograph(s) for additional dose reduction information.

Discontinuation of Dosing

If the other agents used in combination with IBAVYR are permanently discontinued, IBAVYR should also be discontinued.

Pediatrics (< 18 Years of Age)

IBAVYR is not indicated for use in pediatric patients < 18 years of age.

Geriatrics (> 65 years of age)

Caution should be exercised when administering IBAVYR to elderly patients. This is due to the greater frequency of anemia, the greater frequency of decreased hepatic, renal and cardiac function, and the greater frequency of concomitant disease and other drug therapy in the geriatric population.

Renal Impairment

Clearance of ribavirin is substantially reduced in patients with serum creatinine > 177 µmol/L or creatinine clearance < 50 mL/min. Patients with creatinine clearance < 50 mL/min should not be treated with ribavirin. Hemodialysis has negligible effects on the plasma concentration of ribavirin.

Hepatic Insufficiency

Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls. Safety and efficacy of ribavirin have not been established in patients with decompensated cirrhosis.

Missed Dose

A missed dose should be taken as soon as possible during the same day. However, if it is almost time for the following dose (i.e. less than 6 hours before the next scheduled dose), the missed dose should be skipped and the next dose should be taken at the regular scheduled time. Two doses should not be taken at the same time.

Administration

IBAVYR is administered orally in two divided doses with food.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

No cases of overdose with ribavirin have been reported in clinical trials. Hypocalcemia and hypomagnesemia 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

IBAVYR (ribavirin) is a nucleoside analogue with antiviral activity. Ribavirin has shown both *in vitro* and *in vivo* activity against a wide range of RNA and DNA viruses, including the hepatitis C virus. The mechanism of action by which ribavirin contributes to its antiviral efficacy is not fully understood. It likely involves the direct inhibition of HCV replication, the inhibition of inosine monophosphate dehydrogenase, the induction of mutagenesis, and immunomodulation.

Pharmacodynamics

The oral form of ribavirin is used in combination with other agents for the treatment of CHC. Ribavirin alone has limited effect on HCV RNA levels and on improving hepatic histology, as demonstrated in randomized placebo controlled trials in patients with confirmed CHC. Evaluation of ribavirin in combination with sofosbuvir in replicon cells showed no antagonistic effect in reducing HCV-RNA levels.

Pharmacokinetics

Absorption: Orally administered ribavirin is absorbed rapidly, reaching maximal plasma concentrations between 1 and 2 hours. Table 7 presents a summary of ribavirin pharmacokinetic parameters after single and multiple dosing of 600 mg under fasted conditions.

Table 7 - Summary of Ribavirin Pharmacokinetic Parameters After Single and Multiple Dose of 600 mg in Healthy Subjects (n=12) Under Fasted Conditions

Parameter	Single Dose	Multiple Dose
T_{max}, hours	1.7 (46)*	3 (60)
C_{max}, ng/mL	782 (37)	3,680 (85)
AUC_{tf} ng hr/mL	13,400 (48)	228,000 (25)

T_{max}: time from drug administration to maximum concentration
C_{max}: maximum concentration
AUC_{tf}: area under the curve of time from drug administration to final time point
Values in parentheses represent the mean coefficient of variation (% CV).
*N = 11

Ribavirin accumulates extensively in plasma; the ratio of multiple-dose to single-dose AUC at 12 hours (AUC_{12h}) is 6. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL. Upon discontinuation of dosing, the mean half-life was 298 hours, which probably reflects slow elimination from nonplasma compartments.

Absorption of ribavirin is extensive with about 10% to 15% of a radiolabelled dose excreted in the feces. However, the absolute bioavailability ranges between 33% to 52%, likely due to high first-pass metabolism. Ribavirin is absorbed from the gastrointestinal tract via an active sodium dependent nucleoside transport process. Since this process is saturable, less than proportional increases in C_{max} were observed for doses above 800 mg. However, the exposure as measured by $AUC_{0\text{-}192h}$ was proportional up to at least a 1200 mg dose.

Bioavailability of ribavirin is increased by co-administration with a high-fat meal. In the pivotal clinical trials, patients were instructed to take ribavirin with food.

Distribution: Ribavirin partitions rapidly and extensively into all cells, with a very large steady-state volume of distribution of approximately 850 L following intravenous dosing. Oral ribavirin is distributed systemically following intestinal absorption facilitated by the sodium independent *es* nucleoside transporter present on virtually all cell types; this may account for the extensive

volume of distribution. As a result ribavirin accumulates in erythrocytes, ova and spermatozoa. Ribavirin sequesters extensively in erythrocytes; the concentration of ribavirin and its nucleotides in red blood cells was approximately nine-fold greater than that in plasma. Ribavirin does not bind to plasma proteins.

Metabolism: The metabolism of ribavirin has been well characterized and follows two main pathways: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. About one-third of absorbed ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of 14C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose. The cytochrome P450 enzyme system is not involved in the metabolism of ribavirin.

Excretion: The major routes of ribavirin elimination in humans and animals are through metabolism and renal excretion. Following intravenous dosing, the total body clearance was approximately 20 L/h to 25 L/h, with approximately 30% accounted for by renal clearance. In humans, the radioactivity of a 600 mg oral dose showed that around 61% of the dose was eliminated in the urine within 336 hours, of which 17% was unchanged ribavirin.

Due to extensive distribution, the terminal half-life of a single oral or intravenous dose is around 120 to 170 hours. Following multiple doses, the half-life is prolonged to 270 to 300 hours. Extensive accumulation of ribavirin is observed after multiple dosing such that the AUC at steady-state was six fold higher than that of a single dose.

Special Populations and Conditions

Pediatrics (< 18 Years of Age): The safety and effectiveness of ribavirin in pediatric patients have not been established.

Geriatrics (> 65 years of age): Specific pharmacokinetic evaluations for elderly patients have not been performed. A population pharmacokinetic study showed that renal function and not age is the determining factor in the pharmacokinetics of ribavirin.

Hepatic Insufficiency: Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction are similar to those of normal controls.

Renal Insufficiency: The pharmacokinetics of single-dose ribavirin were altered in patients with renal dysfunction; AUC_{tf} and C_{max} increased in these patients compared to control subjects whose creatinine clearance was > 90 mL/min. The oral clearance of ribavirin is substantially reduced in patients with serum creatinine > 177 μmol/L or creatinine clearance < 50 mL/min. IBAVYR should not be administered to patients with a creatinine clearance < 50 mL/min due to insufficient data on the safety and efficacy of ribavirin in these patients. Hemodialysis has negligible effects on the plasma concentration of ribavirin.

STORAGE AND STABILITY

IBAVYR must be stored between 15ºC and 30ºC. Keep bottle tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

IBAVYR (ribavirin) 200 mg tablet is a white, capsule-shaped, coated tablet, debossed with "200" on one side and with no markings on the other side. Available in bottles of 100.

IBAVYR (ribavirin) 400 mg tablet is a light pink, capsule-shaped, coated tablet, debossed with "400" on one side and scored on the other side. Available in bottles of 100.

IBAVYR (ribavirin) 600 mg tablet is a white, capsule-shaped, coated tablet, debossed with "600" on one side and with no markings on the other side. Available in bottles of 100.

Composition

Medicinal ingredient: ribavirin

Non-medicinal ingredients (alphabetically): Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Red Iron Oxide (400 mg tablet), Sodium Croscarmellose, Talc (200 mg, 600 mg tablet), Titanium Dioxide, Yellow Iron Oxide (400 mg tablet).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

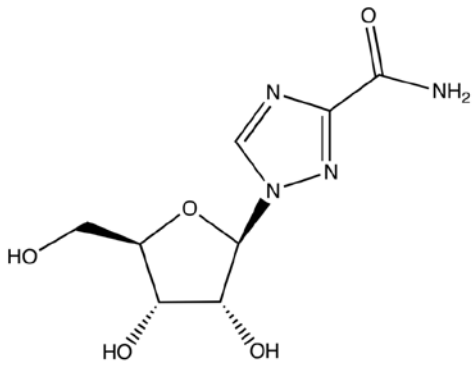
Proper name: Ribavirin

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

Structural formula:



Physicochemical properties: Ribavirin is freely soluble in water and slightly soluble in anhydrous ethanol and insoluble in ether and chloroform. The pH of 2.0% w/v aqueous solution of ribavirin is between 4.0 and 6.5. Ribavirin melts between 167°C and 171°C. The specific rotation is between -33º and -37º.

CLINICAL TRIALS

For information on clinical studies with various agents used in combination with ribavirin, consult the respective Product Monograph(s) of the other products.

Clinical Trials in Combination Therapy Containing Sofosbuvir

The efficacy of ribavirin in combination therapy with sofosbuvir was evaluated in five phase 3 trials in a total of 1724 HCV mono-infected subjects with genotypes 1 to 6 CHC, one Phase 3 trial in 223 HIV-1 co-infected subjects with genotype 1, 2 or 3 CHC and one Phase 2 trial in 61 subjects with genotype 1 through 6 HCV infection and hepatocellular carcinoma (HCC) meeting the Milan criteria awaiting liver transplantation. One of the five trials was conducted in treatment-naïve subjects with genotypes 1, 4, 5 or 6 CHC in combination with peginterferon alfa 2a and sofosbuvir and the other four trials were conducted in subjects with genotype 2 or 3 CHC in combination only with sofosbuvir, including: one in treatment-naïve adults (FISSION), one in interferon intolerant, ineligible, or unwilling adults (POSITRON), one in adults who did not achieve sustained virologic response (SVR) with prior interferon-based treatment (FUSION), and one in all subjects irrespective of prior treatment history or ability to take interferon (VALENCE). The trial in HIV-1 co-infected subjects was conducted in combination with sofosbuvir in treatment-naïve subjects with genotype 1 CHC and all subjects with genotype 2 or 3 CHC irrespective of prior treatment history or ability to take interferon (PHOTON-1). Subjects in these trials had compensated liver disease including cirrhosis. Ribavirin dose was weight-based (1000-1200 mg daily administered in two divided doses), and treatment duration was fixed and not guided by subjects' HCV RNA levels (no response guided algorithm). SVR was the primary endpoint to determine the HCV cure rate for all trials which was defined as HCV RNA less than 25 IU per mL at 12 weeks after the end of treatment.

Clinical trials in subjects with Genotypes 1, 4, 5 or 6

For information on clinical studies in patients with Genotypes 1, 4, 5, or 6 CHC who were treated with ribavirin, sofosbuvir and peginterferon, consult the Product Monograph for sofosbuvir.

Clinical trials in subjects with Genotypes 2 or 3 CHC

Treatment Naïve Adults – FISSION Study

Study demographics and trial design

FISSION was a randomized, open-label, active-controlled trial that evaluated 12 weeks of treatment with sofosbuvir and ribavirin compared to 24 weeks of treatment with peginterferon alfa 2a and ribavirin in treatment-naïve subjects with genotype 2 and 3 HCV. The ribavirin doses used in the ribavirin + sofosbuvir and in the ribavirin + peginterferon arms were 1000-1200 mg per day (weight-based) and 800 mg per day (regardless of weight), respectively. Subjects were randomized 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). Subjects with genotype 2 or 3 HCV were enrolled in an approximately 1:3 ratio.

Table 8 - Study Treatment and Demographic Characteristics of Adult Subjects in the FISSION Study

Dosage, Route of Administration and Duration	Demographics		
	Total	**Treatment Arm**	**Comparator Arm**
SOF 400 mg p.o. + RBV 1000-1200 mg p.o. daily; 12 weeks (Treatment Arm) PEG 180 µg/week + RBV 800 mg/day; 24 weeks (Comparator Arm)	**N = 499**	**N = 256**	**N = 243**
	Gender: n (%) Male 327 (66%) Female 172 (34%)	**Gender: n (%)** Male 171 (67%) Female 85 (33%)	**Gender: n (%)** Male 156 (64%) Female 87 (36%)
	Age: median (range) 50 (19–77)	**Age: median (range)** 50 (20–72)	**Age: median (range)** 50 (19–77)
	Race: n (%) White – 435 (87) Black – 17 (3) Asian – 29 (6) Other – 18 (4)	**Race: n (%)** White – 223 (87) Black – 12 (5) Asian – 14 (6) Other – 7 (3)	**Race: n (%)** White – 212 (87) Black – 5 (2) Asian – 15 (6) Other – 11 (5)
	Body Mass Index: mean (range) 28 kg/m^2 (17-52 kg/m^2)	**Body Mass Index: mean (range)** 28 kg/m^2 (17-51 kg/m^2)	**Body Mass Index: mean (range)** 28 kg/m^2 (19-52 kg/m^2)
	Baseline HCV RNA Category: n (%) ≥ 6 $\log_{10}$ IU/mL – 285 (57)	**Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 148 (58)	**Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 137 (56)
	Cirrhosis: n (%) Yes – 100 (20%)	**Cirrhosis: n (%)** Yes – 50 (20%)	**Cirrhosis: n (%)** Yes – 50 (20%)
	HCV Genotype: n (%) Genotype 1 – 3 (1) Genotype 2 – 137 (27) Genotype 3 – 359 (72)	**HCV Genotype: n (%)** Genotype 1 – 3 (1) Genotype 2 – 70 (27) Genotype 3 – 183 (72)	**HCV Genotype: n (%)** Genotype 1 – 0 Genotype 2 – 67 (28) Genotype 3 – 176 (72)

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

Study results

Table 9 presents the response rates for the treatment groups of sofosbuvir + ribavirin and peginterferon alfa + ribavirin.

Table 9 - Virologic Outcome in the FISSION Study

	SOF + RBV 12 weeks (N=256[a])	**PEG + RBV 24 weeks** (N=243[a])
Overall SVR	67% (171/256)	67% (162/243)
Genotype 2	95% (69/73)	78% (52/67)
Genotype 3	56% (102/183)	63% (110/176)
< LLOQ[b] at treatment week 12	99% (245/247)	92% (207/224)
Outcome for subjects without SVR		
On-treatment virologic failure	<1% (1/256)	7% (18/243)
Relapse[c]	30% (76/252)	21% (46/217)
Other[d]	3% (8/256)	7% (17/243)
Death[e]	<1% (1/256)	0/243
Discontinued study treatment due to adverse event (AE)	1% (3/256)	11% (26/243)
Discontinued study treatment for other reasons	3% (17/256)	12% (28/243)

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

[a] Including three subjects with recombinant genotype 2/1 HCV infection..
[b] Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).
[c] The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.
[d] Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).
[e] Treatment emergent death.

The difference in the overall SVR rates between the 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) subjects achieved SVR in the sofosbuvir + ribavirin treatment group compared to 40% (2/5) in the peginterferon alfa + ribavirin treatment group.

Response rates for subjects with cirrhosis at baseline are presented in Table 10 by genotype.

Table 10 - SVR Rates by Cirrhosis and Genotype in the FISSION Study

	Genotype 2		**Genotype 3**	
Cirrhosis	**SOF+ RBV 12 weeks** (N=73)	**PEG + RBV 24 weeks** (N=67)	**SOF + RBV 12 weeks** (N=183)	**PEG + RBV 24 weeks** (N=176)
No	97% (59/61)	81% (44/54)	61% (89/145)	71% (99/139)
Yes	83% (10/12)	62% (8/13)	34% (13/38)	30% (11/37)

SOF: sofosbuvir; RBV: ribavirin; PEG: peginterferon alfa

Interferon Intolerant, Ineligible or Unwilling Adults – POSITRON Study

Study demographics and trial design

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

Table 11 - Study Treatment and Demographic Characteristics of Adult Subjects in the POSITRON Study

Dosage, Route of Administration and Duration	Demographics		
	Total	**Treatment Arm**	**Comparator Arm**
Sofosbuvir 400 mg p.o. + RBV 1000-1200 mg p.o. daily; 12 weeks (Treatment Arm) Placebo; 12 weeks (Comparator Arm)	**N = 278**	**N = 207**	**N = 71**
	Gender: n (%) Male 151 (54%) Female 127 (46%)	**Gender: n (%)** Male 117 (57%) Female 90 (44%)	**Gender: n (%)** Male 34 (48%) Female 37 (52%)
	Age: median (range) 54 (21–75)	**Age: median (range)** 53 (21–75)	**Age: median (range)** 54 (28–67)
	Race: n (%) White – 254 (91) Black – 13 (5) Asian – 8 (3) Other – 3 (1)	**Race: n (%)** White – 188 (91) Black – 9 (4) Asian – 7 (3) Other – 3 (1)	**Race: n (%)** White – 66 (93) Black – 4 (6) Asian – 1 (1) Other – 0
	Body Mass Index: mean (range) 28 kg/m^2 (18-53 kg/m^2)	**Body Mass Index: mean (range)** 28 kg/m^2 (18-53 kg/m^2)	**Body Mass Index: mean (range)** 28 kg/m^2 (20-43 kg/m^2)
	Baseline HCV RNA Category: n (%) ≥ 6 $\log_{10}$ IU/mL – 194 (70)	**Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 140 (68)	**Baseline HCV RNA Category: n (%)** ≥ 6 $\log_{10}$ IU/mL – 54 (76)
	Cirrhosis: n (%) Yes – 44 (16%)	**Cirrhosis: n (%)** Yes – 31 (15%)	**Cirrhosis: n (%)** Yes – 13 (18%)
	HCV Genotype: n (%) Genotype 2 – 143 (51) Genotype 3 – 135 (49)	**HCV Genotype: n (%)** Genotype 2 – 109 (53) Genotype 3 – 98 (47)	**HCV Genotype: n (%)** Genotype 2 – 34 (48) Genotype 3 – 37 (52)
	Interferon Classification: n (%) Ineligible – 121 (44) Intolerant – 25 (9) Unwilling – 132 (47)	**Interferon Classification: n (%)** Ineligible – 88 (43) Intolerant – 17 (8) Unwilling – 102 (49)	**Interferon Classification: n (%)** Ineligible – 33 (47) Intolerant – 8 (11) Unwilling – 30 (42)
	Prior HCV Treatment: n (%) No – 226 (81)	**Prior HCV Treatment: n (%)** No – 170 (82)	**Prior HCV Treatment: n (%)** No – 56 (79)

Study Results

Table 12 presents the response rates for the treatment groups of sofosbuvir + ribavirin and placebo.

Table 12 - Virologic Outcome in the POSITRON Study

	SOF + RBV 12 weeks (N=207)	**Placebo 12 weeks** (N=71)
Overall SVR	78% (161/207)	0/71
Genotype 2	93% (101/109)	0/34
Genotype 3	61% (60/98)	0/37
< LLOQ[a] at treatment week 12	100% (202/202)	0/68
Outcome for subjects without SVR		
On-treatment virologic failure	0/207	97% (69/71)
Relapse[b]	20% (42/205)	0/0
Other[c]	2% (4/207)	3% (2/71)
Death[d]	0/207	0/71
Discontinued study treatment due to adverse event (AE)	2% (4/207)	4% (3/71)
Discontinued study treatment for other reasons	<1% (2/207)	0% (0/71)

SOF: sofosbuvir; RBV: ribavirin

[a] Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).

[b] The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.

[c] Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

[d] Treatment emergent death.

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

Table 13 presents the subgroup analysis by genotype for cirrhosis and interferon classification.

Table 13 - SVR Rates for Selected Subgroups by Genotype in the POSITRON Study

	SOF + RBV 12 weeks	
	Genotype 2 (N=109)	**Genotype 3** (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)

SOF: sofosbuvir; RBV: ribavirin

Previously Treated Adults – FUSION Study

Study demographics and trial design

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

Table 14 - Study Treatment and Demographic Characteristics of Adult Subjects in the FUSION Study

Dosage, Route of Administration and Duration	Demographics		
	Total	**Treatment Arm 1**	**Treatment Arm 2**
SOF 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; 12 weeks (Treatment Arm 1) SOF 400 mg p.o. + RBV 1000 or 1200 mg p.o. daily; 16 weeks (Treatment Arm 2)	**N = 201**	**N = 103**	**N = 98**
	Gender: n (%) Male 140 (70%) Female 61 (30%)	**Gender: n (%)** Male 73 (71%) Female 30 (29%)	**Gender: n (%)** Male 67 (68%) Female 31 (31%)
	Age: median (range) 56 (24–70)	**Age: median (range)** 56 (30–69)	**Age: median (range)** 55 (24–70)
	Race: n (%) White – 174 (87) Black – 6 (3) Asian – 12 (6) Other – 9 (4) Missing – 1 (0.5)	**Race: n (%)** White – 88 (85) Black – 5 (5) Asian – 7 (7) Other – 3 (3) Missing – 0	**Race: n (%)** White – 86 (88) Black – 1 (1) Asian – 5 (5) Other – 6 (6) Missing – 1 (1)
	Body Mass Index: mean (range) 29 kg/m^2 (19-44 kg/m^2)	**Body Mass Index: mean (range)** 28 kg/m^2 (19-43 kg/m^2)	**Body Mass Index: mean (range)** 29 kg/m^2 (20-44 kg/m^2)
	Baseline HCV RNA Category: n (%) $\geq$ 6 $\log_{10}$ IU/mL – 146 (73)	**Baseline HCV RNA Category: n (%)** $\geq$ 6 $\log_{10}$ IU/mL – 77 (75)	**Baseline HCV RNA Category: n (%)** $\geq$ 6 $\log_{10}$ IU/mL – 69 (70)
	Cirrhosis: n (%) Yes – 68 (34%)	**Cirrhosis: n (%)** Yes – 36 (35%)	**Cirrhosis: n (%)** Yes – 32 (33%)
	HCV Genotype: n (%) Genotype 1 – 6 (3) Genotype 2 – 68 (34) Genotype 3 – 127 (63)	**HCV Genotype: n (%)** Genotype 1 – 3 (3) Genotype 2 – 36 (33) Genotype 3 – 64 (62)	**HCV Genotype: n (%)** Genotype 1 – 3 (3) Genotype 2 – 32 (33) Genotype 3 – 63 (64)
	Response to Prior HCV Treatment: n (%) Relapser – 151 (75)	**Response to Prior HCV Treatment: n (%)** Relapser – 78 (76)	**Response to Prior HCV Treatment: n (%)** Relapser – 73 (75)

SOF: sofosbuvir; RBV: ribavirin

Study Results

Table 15 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks and 16 weeks.

Table 15 - Virologic Outcome in the FUSION Study

	SOF + RBV 12 weeks (N=103)[a]	**SOF + RBV 16 weeks** (N=98)[a]
Overall SVR	50% (51/103)	71% (70/98)
Genotype 2	82% (32/39)	89% (31/35)
Genotype 3	30% (19/64)	62% (39/63)
< LLOQ[b] at treatment week 12	100% (103/103)	100% (98/98)
< LLOQ[b] at treatment week 16	Not Applicable	100% (98/98)
Outcome for subjects without SVR		
On-treatment virologic failure	0/103	0/98
Relapse[c]	48% (49/103)	29% (28/98)
Other[d]	3% (3/103)	0/98
Death[e]	0/103	0/98
Discontinued study treatment due to adverse event (AE)	1% (1/103)	0/98
Discontinued study treatment for other reasons	0/103	0/103

SOF: sofosbuvir; RBV: ribavirin

[a] Including six subjects with recombinant genotype 2/1 HCV infection

[b] Number of subjects reporting HCV RNA < LLOQ (Lower Limit of Quantitation) detected + the number of subjects with HCV RNA < LLOQ TND (target not detected).

[c] The denominator for relapse is the number of subjects with HCV RNA < LLOQ at their last on-treatment assessment.

[d] Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

[e] Treatment emergent death.

Table 16 presents the subgroup analysis by genotype for cirrhosis and response to prior HCV treatment.

Table 16 - SVR Rates for Selected Subgroups by Genotype in the FUSION Study

	Genotype 2		**Genotype 3**	
	SOF + RBV 12 weeks (N=39)	**SOF + RBV 16 weeks** (N=35)	**SOF + RBV 12 weeks** (N=64)	**SOF + RBV 16 weeks** (N=63)
Cirrhosis				
No	90% (26/29)	92% (24/26)	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	86% (25/29)	89% (24/27)	31% (15/49)	65% (30/46)
Nonresponder	70% (7/10)	88% (7/8)	27% (4/15)	53% (9/17)

SOF: sofosbuvir; RBV: ribavirin

Treatment-Naïve and Previously Treated Adults – VALENCE

Study demographics and trial design

The VALENCE trial evaluated ribavirin in combination with sofosbuvir for the treatment of genotype 2 or 3 HCV infection in treatment-naïve subjects or subjects who did not achieve SVR with prior interferon-based treatment, including subjects with compensated cirrhosis. The original trial design was a 4 to 1 randomization to sofosbuvir + ribavirin for 12 weeks or placebo. Based on emerging data, this trial was unblinded and all genotype 2 HCV-infected subjects continued the original planned treatment and received sofosbuvir + ribavirin for 12 weeks, and duration of treatment with sofosbuvir + ribavirin in genotype 3 HCV-infected subjects was extended to 24 weeks. Eleven genotype 3 subjects had already completed sofosbuvir + ribavirin for 12 weeks at the time of the amendment.

Table 17 - Study Treatment and Demographic Characteristics of Adult Subjects in VALENCE

Demographics*			
Genotype 2 SOF + RBV 12 Weeks**	**Genotype 3 SOF + RBV** 24 Weeks**	**SOF Placebo + RBV Placebo**	**Total**
N = 73	**N = 250**	**N = 85**	**N = 419**
Gender: n (%) Male - 40 (55) Female - 33 (45)	**Gender: n (%)** Male - 155 (62) Female - 95 (38)	**Gender: n (%)** Male - 49 (58) Female - 36 (#42)	**Gender: n (%)** Male - 250 (60) Female - 169 (40)
Age: median (range) 60 (28–74)	**Age: median (range)** 50 (19–69)	**Age: median (range)** 51 (19–72)	**Age: median (range)** 51 (19–74)
Race: n (%) White – 65 (89) Black – 5 (7) Asian – 1 (1) Not permitted – 2 (3)	**Race: n (%)** White – 236 (94) Black – 0 Asian – 9 (4) Not permitted – 5 (2)	**Race: n (%)** White – 81 (95) Black – 1 (1) Asian – 3 (4) Not permitted – 0	**Race: n (%)** White – 393 (94) Black – 6 (1) Asian – 13 (3) Not permitted – 7 (2)
Body Mass Index: mean (range) 26 kg/m^2 (20-35 kg/m^2)	**Body Mass Index: mean (range)** 25 kg/m^2 (17-41 kg/m^2)	**Body Mass Index: mean (range)** 25 kg/m^2 (18-40 kg/m^2)	**Body Mass Index: mean (range)** 25 kg/m^2 (17-44 kg/m^2)
Baseline HCV RNA: median (range) 6.7 log_{10} IU/mL (4.6-7.6)	**Baseline HCV RNA: median (range)** 6.5 log_{10} IU/mL (3.5-7.6)	**Baseline HCV RNA: median (range)** 6.7 log_{10} IU/mL (4.6-7.4)	**Baseline HCV RNA: median (range)** 6.6 log_{10} IU/mL (3.5-7.6)
Cirrhosis: n (%) Yes – 10 (14)	**Cirrhosis: n (%)** Yes – 58 (23)	**Cirrhosis: n (%)** Yes – 18 (21)	**Cirrhosis: n (%)** Yes – 88 (21)
Prior HCV Treatment Experience And Interferon Classification: n (%) *Experienced - 41 (56)* IFN Intolerant - 3 (7) Non-Response - 10 (24) Relapse/Breakthrough - 28 (68) *Naïve - 32 (44)* IFN-eligible - 27 (84) IFN-ineligible - 5 (16)	**Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 145 (58)* IFN Intolerant - 10 (7) Non-Response - 41 (28) Relapse/Breakthrough - 94 (65) *Naïve - 105 (42)* IFN-eligible - 94 (90) IFN-ineligible - 11 (10)	**Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 50 (59)* IFN Intolerant - 0 Non-Response - 18 (36) Relapse/Breakthrough - 32 (64) *Naïve - 35 (41)* IFN-eligible - 30 (86) IFN-ineligible - 5 (14)	**Prior HCV Treatment Experience And Interferon Classification: n (%)** *Experienced - 245 (58)* IFN Intolerant - 13 (5) Non-Response - 73 (30) Relapse/Breakthrough - 159 (65) *Naïve - 174 (42)* IFN-eligible - 153 (88) IFN-ineligible - 21 (12)

SOF: sofosbuvir; RBV: ribavirin

*Demographics for GT3 patients receiving 12 weeks (N=11) were similar.

**Dosage: SOF 400 mg p.o. daily, RBV 1000 or 1200 mg p.o daily.

Table 18 presents the response rates for the treatment groups of sofosbuvir + ribavirin for 12 weeks (Genotype 2) and 24 weeks (Genotype 3). Eleven genotype 3 subjects who received sofosbuvir + ribavirin for 12 weeks had an overall SVR12 rate of 27.3%. Placebo subjects (N=85) are not included in the table as none achieved SVR12.

Table 18 - Virologic Outcome in Study VALENCE

	Genotype 2 SOF + RBV 12 weeks	**Genotype 3 SOF + RBV 24 weeks**
	N=73	N=250[a]
Overall SVR	93% (68/73)	84% (210/250)
Outcome for subjects without SVR		
On-treatment virologic failure	0% (0/73)	<1% (1/250)
Relapse[b]	7% (5/73)	14% (34/249)
Treatment-naïve	3% (1/32)	5% (5/105)
Treatment-experienced	10% (4/41)	20% (29/144)
Other[c]	0% (0/73)	2% (5/250)
Death[d]	0/73	0/250
Discontinued study treatment due to adverse event (AE)	0/73	<1% (1/250)
Discontinued study treatment for other reasons	0/73	1% (3/250)

SOF: sofosbuvir; RBV: ribavirin

a. Eleven genotype 3 subjects who received SOF + RBV for 12 weeks were not included.
b. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on treatment assessment.
c. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria (e.g., lost to follow up).
d. Treatment emergent death.

Table 19 presents the subgroup analysis by genotype for cirrhosis and prior HCV treatment experience.

Table 19 - SVR Rates for Selected Subgroup by Genotype in Study VALENCE

	Genotype 2 SOF + RBV 12 weeks	Genotype 3 SOF + RBV 24 weeks
	N=73	N=250
Treatment-naïve	97% (31/32)	93% (98/105)
Non-cirrhotic	97% (29/30)	93% (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)

SOF: sofosbuvir; RBV: ribavirin

Clinical Trials in Special Populations

For information on clinical trials conducted in HIV-1 co-infected patients and patients awaiting liver transplantation, consult the Product Monograph for sofosbuvir.

Comparative Bioavailability Studies

A single dose, randomized, 2-arm, parallel-group comparative bioavailability study was performed in normal healthy male volunteers (n=80) under fasting conditions using IBAVYR (ribavirin) 600 mg tablets (PENDOPHARM, Division of Pharmascience Inc.) versus the 3 x 200 mg Ribasphere® (Kadmon Pharmaceuticals, LLC) ribavirin tablets. The pharmacokinetic data calculated for the two product formulations are shown in Table 20:

Table 20 - Summary of the Comparative Bioavailability Data

Ribavirin (1 x 600 mg tablet* versus 3 x 200 mg tablets†, fasted) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng·h/mL)	10382.7 10600.20 (20.3)	9574.4 9902.90 (26.5)	108.4	99.2 -118.6
C_{MAX} (ng/mL)	713.0 749.30 (32.6)	662.4 702.50 (33.3)	107.6	95.3 – 121.6
T_{MAX}§ (h)	1.50 (0.83 – 3.50)	1.50 (0.53 – 2.50)		

* IBAVYR, PENDOPHARM, Division of Pharmascience Inc., Canada
† Ribasphere®, Kadmon Pharmaceuticals, LLC, USA.
§ Expressed as the median (range)
Accurate AUC_I and $T_{1/2}$ could not be derived for ribavirin in this study

DETAILED PHARMACOLOGY

Ribavirin, a synthetic nucleoside analog, has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic when used in combination with other agents is not fully understood, although it is likely to involve both direct antiviral and immunomodulatory activities (see ACTION AND CLINICAL PHARMACOLOGY).

TOXICOLOGY

Acute Toxicity

The quantitative lethal potency of ribavirin single dose was assessed in mice, rats and dogs. In all cases, comparatively high single doses were required to produce lethal toxic changes for both oral or intraperitoneal (i.p.) administration routes. The oral LD50 in mice and rats was > 10,000 mg/kg and *ca.* 5000 mg/kg, respectively. The median lethal i.p. dose in mice and rats is lower, 1300 and 1700 mg/kg, respectively. The oral LD50 in dogs was > 480 mg/kg.

Long-term Toxicity

Long-term studies in the mouse and rat (18 to 24 months; dose 20 to 75, and 10 to 40 mg/kg/day, respectively, approximately 0.1 to 0.4 times the maximum daily human dose of ribavirin) have demonstrated a relationship between chronic ribavirin exposure and an increased incidence of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats. Preclinical toxicology data showed anemia, reticulocytosis, and lymphoid atrophy in rats and dogs following repeat-dose oral administration. In general, the anemia and lymphoid effects are reversed within 6 weeks following the cessation of ribavirin administration.

Mutagenicity

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *in vitro* Cell Transformation assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) 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.

Carcinogenicity

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg. The estimated human equivalent of this dose is 25 mg/kg based on body surface area adjustment for a 60 kg adult, i.e. *ca.* 1.9 times the maximum recommended human daily dose. Ribavirin was non-carcinogenic

when administered for 2 years to rats at doses up to 40 mg/kg. The estimated human equivalent for this dose is 5.71 mg/kg based on body surface area adjustment for a 60 kg adult.

Reproduction and Teratology

Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose 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 fetuses and offspring was reduced.

Studies in mice evaluated the time course and reversibility of ribavirin-induced testicular degeneration administered for 3 or 6 months at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1-0.8 times the maximum human 24-hour dose of ribavirin). Abnormalities in sperm occurred. However, upon cessation of treatment, total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

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PART III: CONSUMER INFORMATION

PrIBAVYR™
Ribavirin Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when IBAVYR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about IBAVYR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

IBAVYR must be used in combination with other agents for the treatment of adults with chronic hepatitis C (CHC).

Also read the leaflet(s) of the other medication(s) prescribed by your doctor for the treatment of chronic hepatitis C for further information before you use this medication.

What it does:

IBAVYR (also known as ribavirin) is an antiviral medication used in combination with other medications to treat chronic (lasting) hepatitis C in adults. IBAVYR is not used by itself to treat hepatitis C. IBAVYR used with other medicines may cure chronic hepatitis C infection in the majority of patients. Cure usually means the HCV virus is cleared from your blood (remains at an undetectable level) when measured 3 months after finishing all treatment.

When it should not be used:

Do not take IBAVYR if:

- **you are pregnant or planning to become pregnant, if you are male and have a female partner who is pregnant or is planning to become pregnant** (see *WARNINGS AND PRECAUTIONS*)
- you have hemoglobinopathies (blood disorders) such as thalassemia or sickle cell anemia
- you are allergic to ribavirin or any of the non-medicinal ingredients in IBAVYR (see *What the non-medicinal ingredients are*)
- you are taking didanosine

There may be other instances when IBAVYR combination therapy should not be used, depending on the information available for the other medications it is combined with. Talk to your healthcare provider for more information. Read the consumer information documents for the other medications that will be used with IBAVYR.

What the medicinal ingredient is:

Ribavirin

What the non-medicinal ingredients are:

Colloidal Silicon Dioxide, Crospovidone, Hypromellose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Red Iron Oxide (400 mg tablet), Sodium Croscarmellose, Talc (200 mg, 600 mg tablet), Titanium Dioxide, Yellow Iron Oxide (400 mg tablet).

What dosage forms it comes in:

IBAVYR is available in unscored, white tablets containing 200 mg of ribavirin, scored, light pink tablets containing 400 mg of ribavirin, and unscored, white tablets containing 600 mg of ribavirin.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **You must not take IBAVYR alone to treat hepatitis C infection.**
- **IBAVYR use is associated with hemolytic anemia (loss of red blood cells) which can worsen any heart problems you have and may lead to heart attack or death. If you have heart diseases you should not take IBAVYR.**
- **IBAVYR may cause birth defects or death of your unborn baby. Do not take IBAVYR if you are pregnant. Male partners must not take IBAVYR if their female partners are pregnant. Females and female partners of males taking IBAVYR, must avoid pregnancy during IBAVYR therapy and for 6 months after stopping IBAVYR.**

Pregnancy:

Therapy with IBAVYR must not be started until a negative pregnancy test has been confirmed immediately before starting treatment. IBAVYR may cause birth defects and/or death of an unborn child. Extreme care must be taken to avoid pregnancy during therapy with IBAVYR and for 6 months after completion of treatment in both female and male patients. Two forms of effective birth control (one for each partner) must be used during this time and for 6 months after stopping therapy. During this time, you must also have monthly pregnancy tests that show you are not pregnant. If pregnancy occurs, report the pregnancy to your doctor right away.

BEFORE you use IBAVYR, talk to your doctor or pharmacist if:

- you are taking any other medicines, vitamins or herbal supplements, including those not prescribed by your doctor.
- you are allergic to any component of the medication
- you have unstable or advanced liver disease
- you have high blood pressure or a history of heart disease or previous heart attack
- you have kidney problems
  you have blood disorders such as anemia
- you have been infected with hepatitis B virus and/or human immunodeficiency virus (HIV - the virus that causes AIDS)

- you have a history of liver, kidney, or other organ transplant
- you are pregnant, planning to become pregnant, breastfeeding or planning to breastfeed. You and your doctor will decide whether you should breastfeed while taking IBAVYR.
- you have a history of any bleeding (e.g. nosebleeds)

This information will help your doctor and you decide what extra care may need to be taken while you are on a combination therapy containing IBAVYR. If you have any concerns about your health condition or about taking this medication, talk to your doctor.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Some medicines can cause serious side effects if taken while you are taking IBAVYR. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

Drugs that may interact with IBAVYR include, but are not limited to: azathioprine, didanosine, lamivudine, stavudine and zidovudine.

When ribavirin is taken with azathioprine, pancytopenia (marked decreases in red and white blood cells and platelets) and bone marrow (tissue inside bones that makes blood cells) suppression have been seen. These effects were reversible when the treatments were stopped.

PROPER USE OF THIS MEDICATION

While taking your combination therapy, you will need to see your doctor regularly for medical examinations and/or blood tests (e.g., pregnancy, blood counts/hemoglobin, liver function, heart function/ECG) to make sure your treatment is working and to check for side effects.

Usual adult dose:

IBAVYR is not effective when used alone to treat hepatitis C. Your doctor will tell you what other medicines you must take with IBAVYR.

IBAVYR tablet should be taken each day in two doses (morning and evening) and should be taken with food. Your healthcare provider will determine the correct dose based on your body weight, disease characteristics and your treatment regimen. Take IBAVYR exactly as prescribed by your doctor.

Your doctor will tell you how long you need to take IBAVYR. Over time, your doctor might change your dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of IBAVYR, take it as soon as you remember, and then take the next dose at your usual time. If it is almost time for the next dose (i.e. less than 6 hours before the next dose), wait and take the next dose at your usual time. Do not take two doses at the same time to make up for a missed dose.

To get the most benefit from this medicine, it is important to take your combination therapy exactly as your healthcare providers tell you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Before starting your combination therapy, you should talk with your doctor about the possible side effects of treatment. Talk to your doctor or pharmacist if you are worried about side effects or find them very bothersome. There may be a way to relieve your symptoms.

Side effects associated with combination treatments (ribavirin and other medications):

When IBAVYR is taken in combination with sofosbuvir or with sofosbuvir and peginterferon, the most common side effects include:

- tiredness
- low red blood cells (anemia)
- headache
- difficulty sleeping
- nausea
- low white blood cells
- irritability
- itching (pruritus)
- shortness of breath (dyspnea)
- influenza like illness
- weakness (asthenia)

Combination therapy with other agents can cause some serious side effects. Talk to your doctor about all other possible side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptoms/Effect*	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very common	**Low red blood cell count** (anemia) with symptoms such as weakness, fatigue, shortness of breath, pale skin, dizziness		✓	
	Low white blood cell count (neutropenia) with a symptom such as increased infection, when used with azathioprine		✓	
	Low blood platelet count (thrombocytopenia) With symptoms such as bruising or increased tendency to bleed, when used with azathioprine		✓	

*These side effects are commonly associated with peginterferon alfa and ribavirin therapy.

This is not a complete list of side effects. For any unexpected effects while taking IBAVYR, contact your doctor or pharmacist.

HOW TO STORE IT

IBAVYR must be kept between 15°C and 30°C. Keep the bottle tightly closed.

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, PENDOPHARM, Division of Pharmascience Inc., at: 1-888-550-6060.

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