PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MODERIBA™

ribavirin tablets, AbbVie Standard
(200 mg, 400 mg and 600 mg)

Antiviral Agent

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[Pr]MODERIBA™

ribavirin

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	Lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

MODERIBA™ (ribavirin tablets) is indicated in combination with other agents for the treatment of chronic hepatitis C virus (HCV) infection in adults including patients with compensated cirrhosis.

Treatment with MODERIBA™ should be initiated and monitored by a physician experienced in the management of chronic hepatitis C (CHC).

Geriatrics (> 65 years of age):

In general, caution should be exercised when administering MODERIBA™ 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):

Safety and effectiveness of MODERIBA™ in children less than 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

MODERIBA™ (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 MODERIBA™.

MODERIBA™ is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.
- Women who are pregnant or in men whose female partners are pregnant because of the associated risk of birth defects and fetal death (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pregnant Women**).
- Patients with hemoglobinopathies (e.g., thalassemia or sickle-cell anemia).
- Patients taking didanosine 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.**
- **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 MODERIBA™ (see WARNINGS AND PRECAUTIONS, Hematologic).**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, MODERIBA™ 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 six months after completion of treatment in both female patients and in female partners of male patients who are taking MODERIBA™ (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).**

General

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

Cardiovascular

Although ribavirin has no direct cardiovascular effects, the anemia associated with ribavirin may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Therefore, MODERIBA™ should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before initiation of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status associated with anemia, MODERIBA™ therapy should be suspended or discontinued (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, **Dose Modifications).**

MODERIBA™ should not be used in patients with pre-existing severe, unstable or uncontrolled cardiac disease.

Hematologic

The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with MODERIBA™ occurs within 1 to 2 weeks of initiation of therapy. Because the initial acute 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 appropriate.

Caution should be exercised in initiating treatment in any patient with baseline risk of severe anemia (e.g., spherocytosis, history of gastrointestinal bleeding). MODERIBA™ should be used with extreme caution in patients with baseline hemoglobin < 100 g/L.

Deterioration of blood hemoglobin concentration during treatment may require MODERIBA™ dose adjustments (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment, Dose Modifications).**

Pancytopenia (marked decreases in red blood counts (RBC), neutrophils and platelets) and bone marrow suppression have been reported to occur within 3 to 7 weeks after the concomitant administration of ribavirin and azathioprine. This myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone (see **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. Safety and efficacy of ribavirin have not been established in patients with decompensated cirrhosis.

Renal

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

Sexual Function/Reproduction

Significant teratogenic and/or embryocidal potential have been demonstrated for ribavirin in all animal species in which adequate studies have been conducted, occurring at doses well below the recommended human dose. Malformations of the skull, palate, eye, jaw, limbs, skeleton, central nervous system and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the ribavirin dose. Survival of fetuses and offspring was reduced.

Ribavirin accumulates intracellularly and is cleared from the body very slowly. In animal studies, ribavirin produced changes in sperm at doses approximating the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. 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 six months after completion of therapy (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pregnant Women**).

Special Populations

Pregnant Women

Prior to initiation of treatment with ribavirin, the physician must comprehensively inform the patient of the teratogenic risk of MODERIBA™, the necessity of two forms of effective and continuous contraception, the possibility that contraceptive methods may fail and the possible consequences of pregnancy should it occur during treatment with ribavirin. For laboratory monitoring of pregnancy see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests** section.

Female Patients

MODERIBA™ must not be used by women who are pregnant (see **CONTRAINDICATIONS)**. Ribavirin may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. MODERIBA™ therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least six months (i.e., 15 half-lives for ribavirin clearance from the body) after treatment has concluded. If pregnancy does

occur during treatment or within six months from stopping treatment the patient must be advised of the significant teratogenic risk of MODERIBA™ to the fetus. Routine monthly pregnancy tests must be performed during this time (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pregnant Women** and **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Male Patients and their Female Partners

Extreme care must be taken to avoid pregnancy in partners of male patients taking MODERIBA™. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. It is unknown whether the ribavirin that is contained in sperm will exert its known teratogenic effects upon fertilisation of the ova. Male patients and their female partners of childbearing age must, therefore, be counselled to use two types of effective contraception simultaneously during treatment with MODERIBA™ and for six months after treatment has been concluded. A pregnancy test must be performed before therapy is started.

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 adverse reactions in nursing infants from MODERIBA™, a decision must be made whether to discontinue nursing or discontinue treatment with MODERIBA™, taking into account the importance of the therapy to the mother.

Pediatrics (< 18 years of age)

Safety and effectiveness of MODERIBA™ in children less than 18 years of age have not been established. Therefore, MODERIBA™ is not recommended for use in children and adolescents under the age of 18 years.

Geriatrics (> 65 years of age)

Caution should be exercised when administering MODERIBA™ 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.

HIV or HBV Co-infection

The safety and efficacy of MODERIBA™ combination therapy has not been established in patients co-infected with HIV or hepatitis B virus infection.

Post-Liver Transplant

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

Monitoring and Laboratory Tests

Standard hematologic tests and blood chemistries (complete blood count [CBC] and differential, platelet count, electrolytes, glucose, serum creatinine, liver function tests, uric acid) must be conducted in all patients prior to initiating therapy and as clinically appropriate during treatment.

Pregnancy screening in women of childbearing potential must be performed. Monthly pregnancy testing must be performed during MODERIBA™ 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 MODERIBA™ and should be monitored during therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The Adverse Reactions section(s) of the Product Monograph(s) of agents used in combination with MODERIBA™ should also be consulted.

For detailed information on the adverse reactions reported in patients treated with MODERIBA™ (ribavirin) in combination with HOLKIRA™ PAK, consult the HOLKIRA™ PAK Product Monograph.

In subjects receiving MODERIBA™ in combination with HOLKIRA™ PAK, the most commonly reported adverse reactions considered related to study drug by site investigator (greater than 10% of subjects) were fatigue, headache, nausea, pruritus and insomnia. The proportion of subjects who permanently discontinued treatment due to related adverse events was 0.8% (17/2,044). 0.5% (11/2,044) of subjects interrupted treatment due to related adverse events. 3.5% (72/2,044) of subjects had ribavirin dose reductions due to related adverse events.

The safety profile of MODERIBA™ and HOLKIRA™ PAK in subjects with cirrhosis was similar to that of subjects without cirrhosis.

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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 HOLKIRA™ PAK

Table 1 lists adverse drug reactions (Grades 2 to 4) observed in ≥ 3% of patients in the Phase 3 trials.

The majority of adverse events in the Phase 3 clinical trials were of grade 1 severity. The safety profile of HOLKIRA™ PAK with ribavirin was consistent with the known safety profile of ribavirin. The daily dose of MODERIBA™ used in these Phase 3 clinical trials was 1000 mg, for patients weighing less than 75 kg, and 1200 mg, for patients weighing more than or equal to 75 kg, administered orally in two divided doses.

Table 1. Side-by-Side Tabulation of Adverse Reactions (Grade 2 – 4) Rates in ≥ 3% of Subjects in Phase 3 Trials*

	SAPPHIRE I and II		PEARL II, III and IV		TURQUOISE II (subjects with cirrhosis)
Adverse Reaction	**HOLKIRA™ PAK + RBV 12 Weeks N = 770 n (%)**	**Placebo 12 Weeks N = 255 n (%)**	**HOLKIRA ™ PAK + RBV 12 Weeks N = 401 n (%)**	**HOLKIRA ™ PAK 12 Weeks N = 509 n (%)**	**HOLKIRA ™ PAK + RBV 12 or 24 Weeks N = 380 n (%)**
Fatigue	29 (3.8)	4 (1.6)	26 (6.5)	22 (4.3)	15 (3.9)
Nausea	26 (3.4)	2 (0.8)	2 (0.5)	2 (0.4)	8 (2.1)
Asthenia	22 (2.9)	3 (1.2)	6 (1.5)	1 (0.2)	12 (3.2)
Headache	35 (4.5)	6 (2.3)	10 (2.5)	12 (2.4)	12 (3.2)

* Frequencies of adverse events are based on treatment-emergent adverse events considered at least possibly related to study drug by site investigators.

Less Common Clinical Trial Adverse Drug Reactions (<3%)

Treatment emergent adverse events (Grades 2 to 4) considered at least possibly related to study drug by site investigators which occurred in less than 3% of subjects in Phase 3 trials are listed below by system organ class (**Table 2**).

Table 2. Adverse Events (Grade 2 – 4) in < 3% of Subjects in Phase 3 Trials

Body System	Adverse Events
Blood and lymphatic system disorders:	anemia, leukopenia, neutropenia
Cardiac disorders:	extrasystoles, palpitations, sinus tachycardia, tachycardia, ventricular extrasystoles

Body System	Adverse Events
Ear and labyrinth disorders:	tinnitus
Endocrine disorders:	goitre, hypothyroidism, thyroiditis, adrenal insufficiency
Eye disorders	blepharitis: ulcerative keratitis, visual impairment
Gastrointestinal disorders:	abdominal discomfort, abdominal pain, abdominal pain upper, anorectal discomfort, constipation, dental caries, diarrhoea, dry mouth, dyspepsia, dysphagia, frequent bowel movements, gastrointestinal disorder, gastrooesophageal reflux disease, haemorrhoids, hyperchlorhydria, lip ulceration, pancreatitis, retching, vomiting
General disorders and administration site conditions:	chest discomfort, chills, energy increased, exercise tolerance decreased, hunger, inflammation, influenza like illness, irritability, malaise, oedema peripheral, pain, pre-existing condition improved, product taste abnormal, pyrexia, swelling
Hepatobiliary disorders:	hyperbilirubinemia, jaundice
Immune system disorders:	seasonal allergy
Infections and infestations:	abscess, bronchitis, cellulitis, ear infection, gastroenteritis, gingival infection, herpes simplex, lower respiratory tract infection, nasopharyngitis, oral herpes, sinusitis, skin infection, upper respiratory tract infection, tooth abscess
Investigations:	alanine aminotransferase increased, blood bilirubin increased, blood bilirubin unconjugated increased, irritability, malaise, electrocardiogram abnormal, haemoglobin decreased, neutrophil count increased, reticulocyte count increased, transaminases increased, weight decreased, white blood cell count decreased
Metabolism and nutrition disorders:	decreased appetite, diabetes mellitus, gout, hyperphosphataemia, hypertriglyceridaemia, hypophosphataemia, increased appetite, lactic acidosis
Musculoskeletal and connective tissue disorders:	arthralgia, arthritis, axillary mass, back pain, bone pain, bursitis, muscle spasms, musculoskeletal chest pain, musculoskeletal stiffness, myalgia, neck pain, pain in extremity, sensation of heaviness, tendonitis
Nervous system disorders:	ataxia, cerebrovascular accident, disturbance in attention, dizziness, dysgeusia, hyperesthesia, intention tremor, lethargy, memory impairment, migraine, neuralgia, paraesthesia, presyncope, restless legs syndrome, somnolence, syncope, tension headache, tremor
Psychiatric disorders:	abnormal dreams, affect lability, agitation, anger, anxiety, anxiety disorder, depressed mood, depression, emotional disorder, euphoric mood, insomnia, libido decreased, mental status changes, mood altered, mood swings, nervousness, nightmare, sleep disorder, suicidal ideation, tearfulness, terminal insomnia
Reproductive system and breast disorders:	amenorrhoea, menorrhagia, metrorrhagia
Respiratory thoracic and mediastinal disorders:	acute respiratory failure, chronic obstructive pulmonary disease, cough, dyspnoea, dyspnoea exertional, hypoxia, respiratory depression, sleep apnoea syndrome.
Skin and subcutaneous tissue disorders:	alopecia, blister, cold sweat, dandruff, dry skin, erythema, night sweats, photodermatosis, photosensitivity reaction, pruritus, pruritus generalised, rash, rash erythematous, rash generalised, rash papular, rash pruritic, skin odour abnormal, skin reaction
Vascular disorders:	flushing, hot flush, hypertension, hypotension

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

Changes in selected laboratory parameters are described in **Table 3**. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in design.

Table 3. Selected Treatment Emergent Laboratory Abnormalities

Laboratory Parameters	SAPPHIRE I and II		PEARL II, III and IV		TURQUOISE II (subjects with cirrhosis)
	HOLKIRA™ PAK + RBV 12 Weeks N = 770 n (%)	Placebo 12 Weeks N = 255 n (%)	HOLKIRA™ PAK + RBV 12 Weeks N = 401 n (%)	HOLKIRA™ PAK 12 Weeks N = 509 n (%)	HOLKIRA™ PAK + RBV 12 or 24 Weeks N = 380 n (%)
ALT					
> 5-20 × ULN* (Grade 3)	6/765 (0.8%)	10/254 (3.9%)	3/401 (0.7%)	1/509 (0.2%)	4/380 (1.1%)
> 20 × ULN (Grade 4)	3/765 (0.4%)	0	0	0	2/380 (0.5%)
Hemoglobin					
< 10-8 g/dL (Grade 2)	41/765 (5.4%)	0	23/401 (5.7%)	0	30/380 (7.9%)
< 8-6.5 g/dL (Grade 3)	1/765 (0.1%)	0	2/401 (0.5%)	0	3/380 (0.8%)
< 6.5 g/dL (Grade 4)	0	0	0	0	1/380 (0.3%)
Total Bilirubin					
> 3-10 × ULN (Grade 3)	19/765 (2.5%)	0	23/401 (5.7%)	2/509 (0.4%)	37/380 (9.7%)
> 10 × ULN (Grade 4)	1/765 (0.1%)	0	0	0	0

* ULN: Upper Limit of Normal according to testing laboratory.

Serum ALT Elevations

Refer to the HOLKIRA™ PAK Product Monograph.

Hemoglobin

Treatment with ribavirin in combination with HOLKIRA™ PAK for HCV was associated with a gradual decrease in hemoglobin. Anemia due to hemolysis is the most significant toxicity of ribavirin therapy. The most rapid decrease in hemoglobin occurred during the first 4 weeks of therapy (see **Table 3** and **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, **Dose Modifications**).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in subjects receiving HOLKIRA™ PAK with ribavirin, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with aminotransferase elevations.

Post-Market Adverse Reactions

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

The following adverse reactions have been identified and reported during post-approval use of peginterferon alfa2a + 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)

DRUG INTERACTIONS

Overview

MODERIBA™ is to be used in combination with other products. Refer to the appropriate Product Monograph(s) for a detailed list of their drug interactions.

MODERIBA™ is not a substrate, inhibitor or inducer of cytochrome P450 enzymes. There is minimal potential for P450 enzyme-based interactions.

Co-administration of ribavirin with an antacid containing magnesium, aluminium 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 clinical trials in which the two agents were used in combination therapy. MODERIBA™ does not share common disposition pathways with HOLKIRA™ PAK and does not interact with HOLKIRA™ PAK or contribute to HOLKIRA™ PAK drug interactions.

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

Due to the long half-life of ribavirin (approximately 300 h following multiple doses) 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 Interactions

Concomitant Drug Class: Drug Name	Clinical comment
HIV-Antiviral Agents	
Nucleoside analog reverse-transcriptase inhibitor: stavudine	*In vitro* data indicate that the phosphorylation of stavudine is inhibited at relevant concentrations by ribavirin; therefore coadministration of stavudine with MODERIBA™ should be undertaken with caution.
zidovudine	Ribavirin levels could be increased by zidovudine leading to increased risk of anemia. The use of MODERIBA™ concomitantly with zidovudine in the treatment of HIV/HCV co-infected patients is not advised.
lamivudine	In a 12 week study pharmacokinetic substudy in 47 HCV/HIV co-infected patients to determine the effects of ribavirin on the intracellular phosphorykation of some nucleoside reverse transcriptase inhibitors including lamivudine, stavudine or zidovudine, no evidence of drug interaction was seen.
Nucleoside Reverse-Transcriptase Inhibitor: didanosine	Based on in vitro data, ribavirin increases the intracellular triphosphate levels of didanosine. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine and ribavirin with or without stavudine. Ribavirin is contraindicated with didanosine.

Concomitant Drug Class: Drug Name	Clinical comment
Other Agents	
Immunosuppressive Agents: azathioprine	Ribavirin has an inhibitory effect on azathioprine metabolism, possibly leading to an accumulation of 6-methylthioinosine monophosphate which has been associated with myelotoxicity. In individual cases where the benefit of administering MODERIBA™ concomitantly with azathioprine warrants the potential risk, it is recommended that close hematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped.

Drug-Food Interactions

Bioavailability of MODERIBA™ was increased with food. MODERIBA™ should be taken with food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption,** *Effects of Food on Oral Absorption* and **DOSAGE AND ADMINISTRATION, Administration**).

Drug-Herb Interactions

Interactions of MODERIBA™ with herbs have not been established.

Drug-Laboratory Interactions

Interactions or interferences of MODERIBA™ with laboratory tests have not been established.

Drug-Lifestyle Interactions

Patients who develop dizziness, confusion, somnolence, and fatigue should be cautioned to avoid driving or operating machinery.

Drug-Alcohol Interactions

Patients should be advised not to drink alcohol, as alcohol may exacerbate chronic hepatitis C infection.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Ribavirin monotherapy is not effective and MODERIBA™ (ribavirin tablet) must only be used in combination with other agents for the treatment of CHC.

For detailed dosage and administration instructions pertaining to the use of MODERIBA™ in combination with HOLKIRA™ PAK, consult the HOLKIRA™ PAK Product Monograph.

Recommended Dose and Dosage Adjustment

The recommended dose and treatment durations of MODERIBA™ 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 MODERIBA™ 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 daily dose of MODERIBA™ in combination with HOLKIRA™ PAK is 1000 mg for patients weighing less than 75 kg, and 1200 mg, for patients weighing more than or equal to 75 kg, administered orally in two divided doses.

To maximize absorption, MODERIBA™ in combination with HOLKIRA™ PAK should be taken with food without regard to fat or calorie content (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Absorption**, *Effects of Food on Oral Absorption*).

Table 5 shows the recommended treatment regimen and duration based on patient population.

Table 5. MODERIBA™ Combination Therapy with HOLKIRA™ PAK: Treatment Regimen and Duration by Patient Population

Patient Population	Treatment	Duration
Genotype 1a, without cirrhosis	MODERIBA™* + **HOLKIRA™** PAK	12 weeks
Genotypes 1a and 1b, with cirrhosis	MODERIBA™* + **HOLKIRA™** PAK	12 weeks†

* HOLKIRA™ PAK without ribavirin can be considered as a therapeutic option for treatment-naïve patients with genotype 1a infection without cirrhosis who are intolerant of or ineligible for ribavirin (see **CLINICAL TRIALS**). Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

† 24 weeks of MODERIBA™ + HOLKIRA™ PAK is recommended for patients with genotype 1a-infection with compensated cirrhosis who have had a previous null response to pegylated interferon (pegIFN) and ribavirin (see **CLINICAL TRIALS**).

Note: MODERIBA™ + HOLKIRA™ PAK is recommended in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

Dose Modifications

In general the MODERIBA™ dose should be adjusted according to the patient's tolerance to medication. If severe adverse reactions or laboratory abnormalities develop, the dose should be modified or therapy temporarily discontinued until the adverse reactions abate or decrease in severity. If intolerance persists after dose adjustment, discontinuation of ribavirin therapy may be needed.

Guidelines were developed for MODERIBA™ dose modification (see **Table 6**).

Table 6. MODERIBA™ Tablets Dosage Modification Guidelines for Management of Treatment-Emergent Anemia

Laboratory Values	Reduce Only MODERIBA™ Dose to 600 mg/Day[a] if:	Discontinue MODERIBA™ if:[b]
Hemoglobin in Patients with No Cardiac Disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin: Patients with History of Stable Cardiac Disease	≥ 2 g/dL decrease in hemoglobin during any 4 week period during treatment (permanent dose reduction)	< 12 g/dL despite 4 weeks at reduced dose

[a] Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg tablet in the morning and two 200 mg tablets or one 400 mg tablet in the evening.

[b] If the abnormality is reversed, ribavirin may be restarted at 600 mg daily, and further increased to 800 mg daily at the discretion of the treating physician. However, a return to higher doses is not recommended.

Pediatrics (< 18 Years of Age)

The safety and effectiveness of MODERIBA™ in children less 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Geriatrics (≥ 65 years)

No dose adjustment of MODERIBA™ is warranted in geriatric patients based upon age alone. In Phase 3 clinical trials, 8.5% (174/2053) of subjects were age 65 or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. However, caution should be exercised when administering ribavirin to elderly patients. This is due to the greater frequency of anemia, decreased hepatic, renal and cardiac function, and the greater frequency of concomitant disease and other drug therapy in the geriatric population.

Hepatic Impairment

Hepatic function does not affect the pharmacokinetics of ribavirin. Therefore, no dose adjustment of MODERIBA™ is required in patients with hepatic impairment. Safety and efficacy of ribavirin has not been established in patients with decompensated cirrhosis.

Renal Impairment

No dose adjustment of MODERIBA™ is required in patients with creatinine clearance > 50 mL/min. MODERIBA™ should not be used in patients with a creatinine clearance < 50 mL/min.

Gender

No dose adjustment is necessary for MODERIBA™ based on gender.

Race

No dose adjustment is necessary for MODERIBA™ based on race.

Discontinuation of Dosing

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

Missed Dose

If a MODERIBA™ dose is missed but remembered within 6 hours, it should be taken as soon as possible. If more than 6 hours has passed since MODERIBA™ is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule. Two doses should not be taken at the same time.

Administration

MODERIBA™ is administered orally in two divided doses with food (morning and evening). Due to the teratogenic potential of ribavirin, the tablets should not be broken or crushed.

OVERDOSAGE

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

No cases of overdose of ribavirin have been reported in clinical trials. Hypocalcemia and hypomagnesemia have been observed in persons administered greater than 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. Treatment of overdose with ribavirin should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with ribavirin. Due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ribavirin is a synthetic nucleoside analog that shows *in vitro* activity against some Ribonucleic acid (RNA) and Deoxyribonucleic acid (DNA) viruses. Ribavirin combined with HOLKIRA™ PAK demonstrated additive to synergistic inhibition of the HCV genotype 1 replicon at the majority of drug concentrations studied in short term cell culture assays.

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.

Pharmacokinetics

Absorption

Ribavirin is rapidly absorbed with T_{max} occurring between 1 and 2 hours. Following multiple twice-daily dosing, ribavirin showed extensive accumulation with steady state exposure significantly higher than single dose values. Observed ribavirin exposure in HCV genotype 1-infected subjects in Phase 3 studies who received 1000 or 1200 mg/day ribavirin in combination with HOLKIRA™ PAK showed steady state AUC_{24} of 47800 ng·hr/mL, C_{max} of 2120 ng/mL and C_{min} of 1870 ng/mL.

Effects of Food on Oral Absorption

Ribavirin absorption is enhanced by food or fatty meal. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Distribution

Ribavirin demonstrated multiphasic disposition. Ribavirin is extensively distributed with a high volume of distribution reported as approximately 4500 litres, which reflect the mechanism of cellular uptake of the drug across membranes, primarily via an es-type equilibrative nucleoside transporter found on almost all cell types. As a result ribavirin accumulates in erythrocytes, ova and spermatozoa. Ribavirin nucleotides are sequestered in erythrocytes; ribavirin concentration in whole blood is about 60 times that in plasma. Ribavirin does not bind to plasma proteins.

Metabolism

Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway, 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxyacid metabolite.

Excretion

Ribavirin and its triazole carboxamide and diphosphate metabolites are primarily excreted in the urine with the majority of the dose eliminated as metabolites. In HCV infected patients, ribavirin mean terminal phase half-life is reported to be approximately 300 hours.

Special Populations and Conditions

Pediatrics

The pharmacokinetics of MODERIBA™ in pediatric patients has not been established [see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pediatrics (< 18 years of age)**].

Geriatrics

Specific pharmacokinetic evaluations for elderly patients have not been performed. Population pharmacokinetic analyses 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 (Child-Pugh Classification A, B or C) are similar to those of normal controls.

Population pharmacokinetic analyses of HOLKIRA™ PAK Phase 3 studies indicated that exposures of ribavirin were comparable (< 6% difference) in HCV-infected subjects with Child-Pugh A cirrhosis compared to subjects who did not have cirrhosis. Ribavirin exposure in patients with mild, moderate and severe hepatic dysfunction was also shown to be similar to those observed in normal control subjects. No dose adjustment of MODERIBA™ is required in patients with hepatic impairment. Safety and efficacy of ribavirin have not been established in patients with decompensated cirrhosis.

Renal Insufficiency

Subjects with creatinine clearance > 50 mL/min showed minimal ribavirin exposure difference (8%) compared to normal renal function. The pharmacokinetics of single-dose ribavirin were altered in patients with renal dysfunction. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine > 2 mg/dL (> 177 micromol/L) or with creatinine clearance < 50 mL/min (0.83 mL/sec). MODERIBA™ should not be used in patients with a creatinine clearance < 50 mL/min. (see

D**OSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, **Dose Modifications,** Renal Impairment and **WARNINGS AND PRECAUTIONS, Renal)**.

STORAGE AND STABILITY

Store MODERIBA™ (ribavirin) at room temperature between 15 and 30ºC. Keep the bottle tightly closed in order to protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MODERIBA™ (ribavirin) tablets are available in three strengths: 200 mg, 400 mg, and 600 mg.

MODERIBA™ 200 mg tablets are supplied as light blue coloured, capsule-shaped, film-coated tablet, debossed with "200" on one side and the logo "3RP" on the other side. Each bottle contains 168 tablets.

MODERIBA™ 400 mg tablets are supplied as medium blue coloured, capsule-shaped, film-coated tablet, debossed with "400" on one side and the logo "3RP" on the other side. Each bottle contains 56 tablets.

MODERIBA™ 600 mg tablets are supplied as dark blue coloured, capsule-shaped, film-coated tablet, debossed with "600" on one side and the logo "3RP" on the other side. Each bottle contains 56 tablets.

Listing of Non-Medicinal Ingredients

Each MODERIBA™ 200 mg tablet contains 200 mg of ribavirin with the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, partially hydrolyzed polyvinyl alcohol, polyethylene glycol 3350, povidone, talc, titanium dioxide, and indigo carmine aluminum lake.

Each MODERIBA™ 400 mg tablet contains 400 mg of ribavirin with the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, partially hydrolyzed polyvinyl alcohol, polyethylene glycol 3350, povidone, talc, titanium dioxide, and brilliant blue FCF aluminum lake.

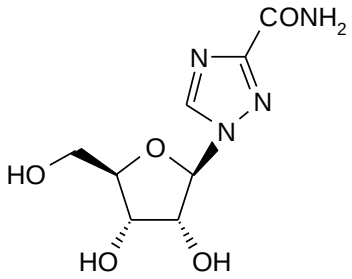
Each MODERIBA™ 600 mg tablet contains 600 mg of ribavirin with the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, partially hydrolyzed polyvinyl alcohol, polyethylene glycol 3350, povidone, talc, titanium dioxide, and brilliant blue FCF aluminum lake.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper name:	ribavirin
Chemical name:	1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide
Molecular formula and molecular mass:	$C_8H_{12}N_4O_5$ 244.21

Structural formula:



Physicochemical properties:	Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol.

CLINICAL TRIALS

Consult the respective Product Monograph(s) of products used in combination with MODERIBA™ (ribavirin) for information on the relevant clinical studies.

Clinical Trials: Ribavirin in Combination Therapy with HOLKIRA™ PAK

Trial Design

The efficacy and safety of ribavirin in combination with HOLKIRA™ PAK was evaluated in six randomized Phase 3 clinical trials, including one trial exclusively in subjects with cirrhosis (Child-Pugh A), in over 2300 subjects with genotype 1 chronic hepatitis C infection, as summarized in **Table 7**.

Table 7. Summary of Clinical Trial Designs in Treatment of Genotype 1 Chronic Hepatitis C Infection

Study #	Number of Subjects Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
Treatment-Naïve[c], without Cirrhosis				
SAPPHIRE-I (M11-646)	631	GT1	Double-blind, randomized, placebo controlled	ombitasvir/paritaprevir /ritonavir tablet: 25/150/100 mg or placebo QD; dasabuvir tablet: 250 mg or placebo BID; RBV tablet: 1000 or 1200 mg or placebo QD (divided BID); Oral 12 weeks
PEARL-III (M13-961)	419	GT1b	Double-blind, randomized (RBV or RBV placebo)	ombitasvir/ paritaprevir /ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1000 to 1200 mg or placebo QD (divided BID); Oral 12 weeks

Study #	Number of Subjects Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
PEARL-IV (M14-002)	305	GT1a	Double-blind, randomized (RBV or RBV placebo)	ombitasvir/ paritaprevir /ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1000 to 1200 mg or placebo QD (divided BID) Oral 12 weeks
Treatment-Experienced[d], without Cirrhosis				
SAPPHIRE-II (M13-098)	394	GT1	Double-blind, randomized, placebo controlled	ombitasvir/ paritaprevir /ritonavir tablet: 25/150/100 mg or placebo QD; dasabuvir tablet: 250 mg or placebo BID; RBV tablet: 1000 or 1200 mg or placebo QD (divided BID) Oral 12 weeks
PEARL-II (M13-389)	179	GT1b	Open-label, randomized (with or without RBV)	ombitasvir/ paritaprevir /ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1000 or 1200 mg QD (divided BID) Oral 12 weeks
Treatment-Naïve and Treatment-Experienced, with Cirrhosis				
TURQUOISE -II (M13-099)	380	GT1	Open-label, randomized to 12 or 24 weeks	ombitasvir/ paritaprevir /ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet: 1000 to 1200 mg or placebo QD (divided BID) Oral 12 or 24 weeks

Study #	Number of Subjects Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]

BID = twice daily, QD = daily, pegIFN = pegylated interferon, RBV = ribavirin

a. Treated is defined as subjects who were randomized and received at least one dose of HOLKIRA™ PAK.

b. For subjects who received ribavirin, the ribavirin dose was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg.

c. Treatment naïve was defined as not having received any prior therapy for HCV infection.

d. Treatment-experienced subjects were defined as either: prior relapsers (subjects with HCV RNA undetectable at or after the end of at least 36 weeks of pegIFN/RBV treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up) or prior partial responders (received at least 20 weeks of pegIFN/RBV and achieved a greater than or equal to 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12, but not achieving HCV RNA undetectable at end of treatment) or prior null-responders (received at least 12 weeks of pegIFN/RBV treatment and failed to achieve a 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 or, for PEARL-III and PEARL-IV, received at least 4 weeks of pegIFN/RBV treatment and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4).

Sustained virologic response (SVR) (virologic cure) was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR_{12}) in the Phase 3 trials. Treatment duration was fixed in each trial and was not guided by subjects' 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.

Clinical Trials in Treatment-Naïve Adults

SAPPHIRE-I was a randomized, global multicenter, double-blind, placebo-controlled trial conducted in 631 treatment-naïve adults with genotype 1 chronic hepatitis C virus infection without cirrhosis. HOLKIRA™ PAK was given for 12 weeks of treatment in combination with ribavirin (RBV). Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received open-label HOLKIRA™ PAK in combination with ribavirin for 12 weeks.

PEARL-III and PEARL-IV were randomized, global, multicenter, double-blind, controlled trials conducted in 419 treatment-naïve adults with genotype 1b chronic hepatitis C virus infection without cirrhosis (PEARL-III) and 305 treatment-naïve adults with genotype 1a chronic hepatitis C virus infection without cirrhosis (PEARL-IV). Subjects were randomized, in a 1:1 ratio (PEARL-III) or a 1:2 ratio (PEARL-IV), to receive HOLKIRA™ PAK with or without ribavirin for 12 weeks of treatment.

Demographic and baseline characteristics for treatment-naïve subjects in SAPPHIRE-I, PEARL-III and PEARL-IV are provided in **Table 8**.

Table 8. Demographic and Baseline Characteristics of Treatment-Naïve Subjects without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV

Characteristics	SAPPHIRE-I N=631	PEARL-III N=419	PEARL-IV N=305
Age (years)			
Median (range)	52 (18 – 70)	50 (19 – 70)	54 (19 – 70)
Gender, n (%)			
Male	344 (54.5)	192 (45.8)	199 (65.2)
Female	287 (45.5)	227 (54.2)	106 (34.8)
Race, n (%)			
White	572 (90.6)	394 (94.3)	257 (84.3)
Black or African American	34 (5.4)	20 (4.8)	36 (11.8)
Asian	14 (2.2)	2 (0.5)	4 (1.3)
Other	11 (1.7)	2 (0.5)	8 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (5.1)	7 (1.7)	28 (9.2)
None of the above	599 (94.9)	412 (98.3)	277 (90.8)
Body mass index, n (%)			
< 30 kg/m^2	529 (83.8)	350 (83.5)	245 (80.3)
≥ 30 kg/m^2	102 (16.2)	69 (16.5)	60 (19.7)
HCV genotype, n (%)			
1a	427 (67.7)	N/A	304 (99.7)
1b	204 (32.3)	419 (100)	1 (0.3)

Characteristics	SAPPHIRE-I N=631	PEARL-III N=419	PEARL-IV N=305
Baseline HCV RNA			
Mean ± SD (log_{10} IU/mL)	6.42 ± 0.63	6.31 ± 0.72	6.57 ± 0.63
< 800000 IU/mL, n (%)	132 (20.9)	112 (26.7)	41 (13.4)
≥ 800000 IU/mL, n (%)	499 (79.1)	307 (73.3)	264 (86.6)
IL28B, n (%)			
CC	194 (30.7)	88 (21.0)	94 (30.8)
Non-CC	437 (69.3)	331 (79.0)	211 (69.2)
Baseline fibrosis stage, n (%)			
F0-F1	479 (75.9)	291 (69.6)	195 (63.9)
F2	97 (15.4)	85 (20.3)	56 (18.4)
≥ F3	55 (8.7)	42 (10.0)	54 (17.7)
History of depression or bipolar disorder, n (%)			
No	535 (84.8)	380 (90.7)	242 (79.3)
Yes	96 (15.2)	39 (9.3)	63 (20.7)

N/A = Not Applicable.

Study Results

Table 9 shows the SVR12 rates for genotype 1-infected, treatment-naïve subjects receiving HOLKIRA™ PAK with or without ribavirin for 12 weeks in SAPPHIRE-I, PEARL-III and PEARL-IV. All treatment groups met the primary efficacy endpoint. In study PEARL-III, HOLKIRA™ PAK without ribavirin had similar SVR12 rates (99.0%) compared to HOLKIRA™ PAK with ribavirin (99.5%). In study PEARL-IV, HOLKIRA™ PAK without ribavirin did not meet the pre-specified criteria for non-inferiority to HOLKIRA™ PAK with ribavirin.

Table 9. SVR12 for Genotype 1-Infected Treatment-Naïve Subjects without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV

Treatment Outcome	SAPPHIRE-I Genotype 1	PEARL-III Genotype 1b		PEARL-IV Genotype 1a	
	HOLKIRA™ PAK + RBV N=473 % (n/N)	HOLKIRA™ PAK + RBV N=210 % (n/N)	HOLKIRA™ PAK N=209 % (n/N)	HOLKIRA™ PAK + RBV N=100 % (n/N)	HOLKIRA™ PAK N=205 % (n/N)
Overall SVR12	96 (455/473)	99 (209/210)	99 (207/209)	97 (97/100)	90 (185/205)
95% CI	94.5 to 97.9	98.6 to 100	97.7 to 100	93.7 to 100	86.2 to 94.3
HCV genotype 1a	95 (307/322)	N/A	N/A	97 (97/100)	90 (184/204)
HCV genotype 1b	98 (148/151)	99 (209/210)	99 (207/209)	N/A	
Outcome for subjects without SVR12					
On-treatment VF[a]	<1 (1/473)[d]	<1 (1/210)	0	1 (1/100)	3 (6/205)
Relapse[b]	2 (7/463)[d]	0	0	1 (1/98)	5 (10/194)
Other[c]	2 (10/473)	0	1 (2/209)	1 (1/100)	2 (4/205)

CI = confidence interval, VF = virologic failure, N/A = Not Applicable

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

d. No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and one subject with HCV genotype 1b infection experienced relapse.

Table 10 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-naïve subjects in studies SAPPHIRE-I, PEARL-III and PEARL-IV.

Table 10. SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Naïve Subjects without Cirrhosis in SAPPHIRE-I, PEARL-III and PEARL-IV

Treatment Outcome	SAPPHIRE-I Genotype 1	PEARL-III Genotype 1b		PEARL-IV Genotype 1a	
	HOLKIRA™ PAK + RBV N=473 % (n/N)	HOLKIRA™ PAK + RBV N=210 % (n/N)	HOLKIRA™ PAK N=209* % (n/N)	HOLKIRA™ PAK + RBV N=100** % (n/N)	HOLKIRA™ PAK N=205 % (n/N)
IL28B					
CC	97 (139/144)	100 (44/44)	98 (43/44)	100 (31/31)	97 (61/63)
Non-CC	96 (316/329)	99 (165/166)	99 (164/165)	96 (66/69)	87 (124/142)
Sex					
Female	98 (197/202)	99 (103/104)	100 (123/123)	100 (30/30)	95 (72/76)
Male	95 (258/271)	100 (106/106)	98 (84/86)	96 (67/70)	88 (113/129)
Age					
< 65 years	96 (437/454)	99 (195/196)	99 (188/190)	97 (87/90)	90 (172/192)
≥ 65 years	95 (18/19)	100 (14/14)	100 (19/19)	100 (10/10)	100 (13/13)
Race					
Black	96 (27/28)	100 (11/11)	100 (11/11)	100 (10/10)	85 (23/27)
Non-black	96 (428/445)	99 (198/199)	99 (196/197)	97 (87/90)	91 (162/178)
Ethnicity					
Hispanic or Latino	93 (25/27)	100 (2/2)	80 (4/5)	90 (9/10)	89 (16/18)
None of the above	430/446 (96.4)	99 (207/208)	99 (203/204)	98 (88/90)	90 (169/187)
Body mass index					
< 30 kg/m^2	97 (390/402)	100 (182/182)	100 (168/168)	99 (78/79)	92 (153/166)
≥ 30 kg/m^2	92 (65/71)	96 (27/28)	95 (39/41)	90 (19/21)	82 (32/39)
Baseline HCV RNA					
< 800000 IU/mL	98 (102/104)	100 (51/51)	100 (61/61)	100 (8/8)	91 (30/33)
≥ 800000 IU/mL	96 (353/369)	99 (158/159)	99 (146/148)	97 (89/92)	90 (155/172)
Baseline fibrosis stage					
F0-F1	97 (352/363)	99 (149/150)	100 (141/141)	97 (61/63)	92 (122/132)
F2	94 (66/70)	100 (38/38)	100 (47/47)	95 (20/21)	83 (29/35)
≥ F3	93 (37/40)	100 (22/22)	90 (18/20)	100 (16/16)	89 (34/38)
History of depression or bipolar disorder					
No	97 (389/403)	99 (189/190)	99 (189/190)	96 (80/83)	89 (142/159)
Yes	94 (66/70)	100 (20/20)	95 (18/19)	100 (17/17)	93 (43/46)

* For subjects with GT1b infection without cirrhosis, HOLKIRA™ PAK alone for 12 weeks is the recommended regimen.

** For subjects with GT1a infection without cirrhosis, HOLKIRA™ PAK with RBV for 12 weeks is the recommended regimen.

These baseline viral (genotype 1 subtype, baseline viral load) and host factors (gender, race, ethnicity, age, IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage) were not associated with lower SVR12 rates across subgroups.

In addition, subjects who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trials in Treatment-Experienced Adults

SAPPHIRE-II was a randomized, global multicenter, double-blind, placebo-controlled trial conducted in 394 subjects with genotype 1 chronic hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with peginterferon and ribavirin (pegIFN/RBV). HOLKIRA™ PAK in combination with ribavirin was given for 12 weeks of treatment. Subjects randomized to the placebo arm received placebo for 12 weeks, after which they received HOLKIRA™ PAK in combination with ribavirin for 12 weeks.

PEARL-II was a randomized, global, multicenter, open-label trial conducted in 179 adults with chronic genotype 1b hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Subjects were randomized, in a 1:1 ratio, to receive HOLKIRA™ PAK with or without ribavirin for 12 weeks of treatment.

Demographic and baseline characteristics for treatment-experienced subjects in SAPPHIRE-II and PEARL-II are provided in **Table 11**.

Table 11. Demographic and Baseline Characteristics of Treatment-Experienced Subjects without Cirrhosis in SAPPHIRE-II and PEARL-II

Characteristics	SAPPHIRE-II N=394	PEARL-II N=179
Age (years)		
Median (range)	54 (19 – 71)	57 (26 – 70)
Gender, n (%)		
Male	227 (57.6)	97 (54.2)
Female	167 (42.4)	82 (45.8)
Race, n (%)		
White	355 (90.1)	165 (92.2)
Black or African American	32 (8.1)	7 (3.9)
Asian	6 (1.5)	3 (1.7)
Other	1 (0.3)	4 (2.3)
Ethnicity, n (%)		
Hispanic or Latino	25 (6.3)	3 (1.7)
None of the above	369 (93.7)	176 (98.3)

Characteristics	SAPPHIRE-II N=394	PEARL-II N=179
Body mass index, n (%)		
< 30 kg/m^2	316 (80.2)	140 (78.2)
≥ 30 kg/m^2	78 (19.8)	39 (21.8)
HCV genotype, n (%)		
1a	230 (58.4)	N/A
1b	163 (41.4)	179 (100)
Baseline HCV RNA		
Mean ± SD (log_{10} IU/mL)	6.55 ± 0.52	6.51 ± 0.55
< 800000 IU/mL, n (%)	51 (12.9)	22 (12.3)
≥ 800000 IU/mL, n (%)	343 (87.1)	157 (87.7)
IL28B, n (%)		
CC	41 (10.4)	17 (9.5)
Non-CC	353 (89.6)	162 (90.5)
Type of response to previous pegIFN/RBV treatment, n (%)		
Null responder	193 (49.0)	63 (35.2)
Nonresponder/partial responder	86 (21,8)	51 (28.5)
Relapser	115 (29.2)	65 (36.3)
Baseline fibrosis stage, n (%)		
F0-F1	267 (67.8)	122 (68.2)
F2	70 (17.8)	32 (17.9)
≥ F3	57 (14.5)	25 (14.0)
History of depression or bipolar disorder, n (%)		
No	313 (79.4)	156 (87.2)
Yes	81 (20.6)	23 (12.8)

N/A = Not Applicable

Study Results

Table 12 shows the SVR12 rates for treatment-experienced subjects with genotype 1-infection receiving HOLKIRA™ PAK in combination with ribavirin for 12 weeks in SAPPHIRE-II and PEARL-II and HOLKIRA™ PAK alone in PEARL-II. All the treatment groups met the primary efficacy endpoint.

Table 12. SVR12 for Genotype 1-Infected Treatment-Experienced Subjects without Cirrhosis in SAPPHIRE-II and PEARL-II

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA™ PAK + RBV N=297 % (n/N)	HOLKIRA™ PAK + RBV N=88 % (n/N)	HOLKIRA™ PAK* N=91 % (n/N)
Overall SVR12	96 (286/297)	97 (85/88)	100 (91/91)
95% CI	94.1 to 98.4	92.8 to 100	95.9 to 100
HCV genotype 1a	96 (166/173)	N/A	N/A
Prior pegIFN/RBV null responder	95 (83/87)	N/A	N/A
Prior pegIFN/RBV partial responder	100 (36/36)	N/A	N/A
Prior pegIFN/RBV relapser	94 (47/50)	N/A	N/A
HCV genotype 1b	97 (119/123)	97 (85/88)	100 (91/91)
Prior pegIFN/RBV null responder	95 (56/59)	94 (29/31)	100 (32/32)
Prior pegIFN/RBV partial responder	100 (28/28)	96 (24/25)	100 (26/26)
Prior pegIFN/RBV relapser	97 (35/36)	100 (32/32)	100 (33/33)
Outcome for subjects without SVR12			
On-treatment VF[a]	0	0	0
Relapse[b]	2 (7/293)	0	0
Other[c]	1 (4/297)	3 (3/88)	0

CI = confidence interval, VF = virologic failure, N/A = Not Applicable

***** For subjects with GT1b infection without cirrhosis, HOLKIRA™ PAK alone for 12 weeks is the recommended regimen.

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Table 13 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-experienced subjects in studies SAPPHIRE-II and PEARL-II.

Table 13. SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Experienced Subjects without Cirrhosis in SAPPHIRE-II and PEARL-II

Treatment Outcome	SAPPHIRE-II Genotype 1	PEARL-II Genotype 1b	
	HOLKIRA™ PAK + RBV N=297 % (n/N)	HOLKIRA™ PAK + RBV N=88 % (n/N)	HOLKIRA™ PAK* N=91 % (n/N)
IL28B			
CC	91 (31/34)	100 (10/10)	100 (7/7)
Non-CC	97 (255/263)	96 (75/78)	100 (84/84)
Sex			
Female	97 (126/130)	98 (44/45)	100 (37/37)
Male	96 (160/167)	95 (41/43)	100 (54/54)
Age			
< 65 years	97 (269/277)	96 (70/73)	100 (76/76)
≥ 65 years	85 (17/20)	100 (15/15)	100 (15/15)
Race			
Black	95 (21/22)	100 (3/3)	100 (5/5)
Non-black	96 (265/275)	96 (82/85)	100 (86/86)
Ethnicity			
Hispanic or Latino	95 (21/22)	50 (1/ 2)	100 (1/ 1)
None of the above	96 (265/275)	98 (84/86)	100 (90/90)
Body mass index			
< 30 kg/m^2	97 (231/238)	96 (68/71)	100 (69/69)
≥ 30 kg/m^2	93 (55/59)	100 (17/17)	100 (22/22)
Baseline HCV RNA			
< 800000 IU/mL	100 (42/42)	100 (13/13)	100 (9/9)
≥ 800000 IU/mL	96 (244/255)	96 (72/75)	100 (82/82)
Baseline fibrosis stage			
F0-F1	98 (197/202)	97 (61/63)	100 (59/59)
F2	94 (50/53)	100 (13/13)	100 (19/19)
≥ F3	93 (39/42)	92 (11/12)	100 (13/13)
History of depression or bipolar disorder			
No	96 (220/229)	97 (71/73)	100 (83/83)
Yes	97 (66/68)	93 (14/15)	100 (8/8)

* For subjects with GT1b infection without cirrhosis, HOLKIRA™ PAK alone for 12 weeks is the recommended regimen.

These baseline viral (genotype 1 subtype, baseline viral load) and host factors (prior treatment response, sex, race, ethnicity, age, IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage) were not associated with lower SVR12 rates across subgroups.

In addition, subjects who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trial in Subjects with Cirrhosis

TURQUOISE-II was a randomized, global multicenter, open-label trial conducted exclusively in 380 genotype 1-infected subjects with cirrhosis (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. HOLKIRA™ PAK in combination with ribavirin was administered for either 12 or 24 weeks of treatment.

Demographic and baseline characteristics for genotype 1-infected subjects with cirrhosis in study TURQUOISE-II are provided in **Table 14**.

Table 14. Demographic and Baseline Characteristics of Subjects with Cirrhosis in TURQUOISE-II

Characteristics	TURQUOISE-II HOLKIRA™ PAK + RBV N = 380
Age (years)	
Median (range)	58 (21 – 71)
Gender, n (%)	
Male	267 (70.3)
Female	113 (29.7)
Race, n (%)	
White	360 (94.7)
Black or African American	12 (3.2)
Asian	8 (2.1)
Ethnicity	
Hispanic or Latino	45 (11.8)
None of the above	335 (88.2)
Body mass index	
< 30 kg/m^2	272 (71.6)
≥ 30 kg/m^2	108 (28.4)
HCV genotype, n (%)	
1a	261 (68.7)
1b	119 (31.3)

Characteristics	TURQUOISE-II HOLKIRA™ PAK + RBV N = 380
Baseline HCV RNA	
Mean ± SD (log_{10} IU/mL)	6.47 ± 0.58
< 800000 IU/mL, n (%)	53 (13.9)
≥ 800000 IU/mL, n (%)	327 (86.1)
Prior HCV Therapy	
Treatment-Naive	160 (42.1)
Treatment-experienced with pegIFN/RBV, n (%)	220 (57.9)
Null responder	137 (36.1)
Partial responder	31 (8.2)
Relapser	52 (13.7)
IL28B, n (%)	
CC	69 (18.2)
CT	237 (62.4)
TT	74 (19.5)
Baseline platelet count, n (%)	
< 90 $x10^9$/L	56 (14.7)
≥ 90 $x10^9$/L	324 (85.3)
Baseline albumin, n (%)	
< 35 g/L	43 (11.3)
≥ 35 g/L	337 (88.7)
History of depression or bipolar disorder, n (%)	
No	286 (75.3)
Yes	94 (24.7)

Study Results

Table 15 shows the SVR12 rates for genotype 1-infected subjects with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV. Both treatment groups met the primary efficacy endpoint.

Table 15. SVR12 for Genotype 1-Infected Subjects with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II

Treatment Outcome	HOLKIRA™ PAK with RBV	
	12 Weeks*	24 Weeks
	% (n/N)	% (n/N)
Overall SVR12	92 (191/208)[d]	96 (165/172)[d]
97.5% CI	87.6 to 96.1	92.6 to 99.3
HCV genotype 1a	89 (124/140)	94 (114/121)
Treatment naïve	92 (59/64)	93 (52/56)
Prior pegIFN/RBV null responders	80 (40/50)	93 (39/42)**
Prior pegIFN/RBV partial responders	100 (11/11)	100 (10/10)
Prior pegIFN/RBV prior relapsers	93 (14/15)	100 (13/13)
HCV genotype 1b	99 (67/68)	100 (51/51)
Treatment naïve	100 (22/22)	100 (18/18)
Prior pegIFN/RBV null responders	100 (25/25)	100 (20/20)
Prior pegIFN/RBV partial responders	86 (6/7)	100 (3/3)
Prior pegIFN/RBV prior relapsers	100 (14/14)	100 (10/10)
Outcome for subjects without SVR12		
On-treatment VF[a]	<1 (1/208)	2 (3/172)
Relapse[b]	6 (12/203)	<1 (1/164)
Other[c]	2 (4/208)	2 (3/172)

CI = confidence interval, VF = virologic failure

* 12 weeks of HOLKIRA™ PAK with RBV is the recommended regimen for all subjects with cirrhosis,except those with genotype 1a infection and prior null response to pegIFN/RBV.

** 24 weeks of HOLKIRA™ PAK + ribavirin is recommended for patients with genotype 1a-infection with cirrhosis who have had a previous null response to pegIFN/RBV.

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for subjects assigned to 12 or 24 weeks of treatment, respectively.

c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

d. Based on logistic regression, the difference between treatment arms was not statistically significant (p value = 0.089).

Table 16 presents the SVR12 rates by selected subgroups for genotype 1-infected subjects with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 16. SVR12 rates for Selected Subgroups of Genotype 1-infected Subjects with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II

	TURQUOISE-II	
	HOLKIRA™ PAK + RBV	
	12 Weeks N = 208	24 Weeks N = 172
Subgroup	**n/N (%)**	**n/N (%)**
IL28B		
CC	94 (33/35)	97 (33/34)
Non-CC	91 (158/173)	96 (132/138)
Sex		
Female	94 (58/62)	96 (49/51)
Male	91 (133/146)	96 (116/121)
Age		
< 65 years	91 (166/182)	95 (142/149)
≥ 65 years	96 (25/26)	100 (23/23)
Race		
Black	100 (6/6)	83 (5/6)
Nonblack	92 (185/202)	96 (160/166)
Ethnicity		
Hispanic or Latino	84 (21/25)	95 (19/20)
None of the above	93 (170/183)	96 (146/152)
Body mass index		
< 30 kg/m^2	92 (135/146)	97 (122/126)
≥ 30 kg/m^2	90 (56/62)	93 (43/46)
Baseline HCV RNA		
< 800000 IU/mL	91 (31/34)	89 (17/19)
≥ 800000 IU/mL	92 (160/174)	97 (148/153)
Baseline platelet count		
< 90 x 10^9/L	83 (25/30)	96 (25/26)
≥ 90 x 10^9/L	93 (166/178)	96 (140/146)
Baseline albumin		
< 35 g/L	84 (21/25)	89 (16/18)
≥ 35 g/L	93 (170/183)	97 (149/154)
History of depression or bipolar disorder		
No	91 (143/157)	96 (124/129)
Yes	94 (48/51)	95 (41/43)

Subjects who underwent ribavirin dose modifications did not have lower SVR12 rates.

Pooled Analyses of Clinical Trials

Durability of Response

Overall, 660 subjects in Phase 2 and 3 clinical trials had HCV RNA results for both the SVR12 and SVR24 time points. Among these subjects, the positive predictive value of SVR12 on SVR24 was 99.8%.

Pooled Efficacy Analysis

In Phase 3 clinical trials, 1096 subjects (including 202 with cirrhosis) received the recommended regimen for their HCV subtype, cirrhosis status and previous treatment. **Table 17** shows SVR rates for these subjects. Among subjects who received the recommended regimen in Phase 3 clinical trials, 97% achieved SVR (95% with cirrhosis and 97% without cirrhosis), while 0.5% demonstrated virologic breakthrough and 1.6% experienced post-treatment relapse.

Table 17. SVR12 Rates for Recommended Treatment Regimens

	Genotype 1a		Genotype 1b	
	No Cirrhosis HOLKIRA ™ PAK with RBV	**With Cirrhosis HOLKIRA ™ PAK with RBV**	**No Cirrhosis HOLKIRA ™ PAK**	**With Cirrhosis HOLKIRA ™ PAK with RBV**
	12 weeks	**12 weeks***	**12 weeks**	**12 weeks**
Treatment-naïve	96% (402/420)	92% (61/66)	99% (208/210)	100% (22/22)
Treatment-experienced	96% (166/173)	94% (64/68)*	100% (91/91)	98% (45/46)
Prior pegIFN/RBV relapser	94% (47/50)	93% (14/15)	100% (33/33)	100% (14/14)
Prior pegIFN/RBV partial responder	100% (36/36)	100% (11/11)	100% (26/26)	86% (6/7)
Prior pegIFN/RBV null responder	95% (83/87)	93% (39/42) (24 weeks)	100% (32/32)	100% (25/25)
TOTAL	96% (568/593)	93% (125/134)*	99% (299/301)	99% (67/68)

RBV = ribavirin

* All subjects received 12 weeks of therapy except for genotype 1a infected prior null responders with cirrhosis who received 24 weeks of therapy.

Impact of Ribavirin Dose Adjustment on Probability of SVR

In Phase 3 clinical trials, 91.5% of subjects did not require ribavirin dose adjustments during therapy. In the 8.5% of subjects who had ribavirin dose adjustments during therapy, the SVR rate (98.5%) was comparable to subjects who maintained their starting ribavirin dose throughout treatment.

DETAILED PHARMACOLOGY

Pharmacodynamics

Ribavirin is a synthetic nucleoside analogue which has shown in vitro activity against some Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) viruses. It is not incorporated into RNA or DNA. Inhibition of Hepatitis C Virus (HCV)-specific enzymes or HCV replication is also not seen with ribavirin or its intracellular nucleotide metabolites at physiologic concentrations.

TOXICOLOGY

Acute Toxicity

Single dose studies were conducted. The oral lethal dose (LD50) was ≥5000 mg/kg in rodents, >480 mg/kg in dogs and > 10,000 mg/kg in monkeys. When administered parenterally (intramuscular, intraperitoneal or intravenous), the LD50 was ≥800 mg/kg for those species evaluated.

Long-Term Toxicity

General toxicology studies were conducted in mice, rats, dogs and monkeys. The longest term studies along with the high dose and relationship to maximal recommended human dose (1400 mg) on a mg/m^2 basis are listed in tabular format below.

Species and Duration	High Dose (mg/kg/day)	Multiple Compared to 1400 mg Clinical Dose (Based on mg/m^2)
Mouse (13 weeks)	600	2
Rat (26 weeks)	75	0.5
Dog (26 weeks)	20	0.5
Monkey (39 weeks)	60	0.8

Primary toxicities included effects on the erythron and testes. Erythroid effects (reduced red blood cell counts, hemoglobin, and/or hematocrit) were observed in the repeat-dose rodent studies. Anemia was indicated at the higher doses. The observed erythroid effects are similar to those reported in the literature for monkeys and patients following administration of ribavirin although it has been suggested that these erythroid effects are both dose- and duration-dependent,

reversible upon dose reduction or withdrawal, and interspecies differences exist. In repeat dose studies in mice, abnormalities in sperm occurred at doses approximating human therapeutic doses. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity occurred within one or two spermatogenic cycles. Effects on erythroid parameters and testes occurred at dosages similar to below the maximal human dose of ribavirin.

Mutagenicity and Carcinogenicity

Mutagenicity

Genotoxic activity has been observed in Balb/3T3 in vitro cell transformation assays, the in vitro mouse lymphoma assay and in vivo mouse micronucleus assays. The high dose in the in vivo micronucleus assay was 2000 mg/kg. The estimated human equivalent of this dose was 167 mg/kg, based on a body surface area adjustment for a 60 kg adult, approximately 7 times the maximum recommended dose of ribavirin on a mg/m^2 basis. Ribavirin was negative in the reverse bacterial mutation assay (Ames assay). In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg. The estimated human equivalent of this dose was 33 mg/kg, based on a body surface area adjustment for a 60 kg adult, approximately 1.4 times the maximum recommended human daily dose of ribavirin.

Carcinogenicity

Ribavirin was not carcinogenic in a two-year study in rats at doses up to 60 mg/kg/day or in a 6-month study in p53 knockout mice at doses up to 100 mg/kg/day. The estimated human equivalents of these doses were 10 and 8.3 mg/kg, respectively, based on a body surface area adjustment for a 60 kg adult, approximately 0.4 times the maximum recommended human daily dose of ribavirin.

Reproduction and Teratology

Fertility has been assessed in a study in which males were administered ribavirin orally for 8 weeks, females for 2 weeks, prior to mating, during mating (males) and until gestation day 14 (females). Males in the 60 and 90 mg/kg/day groups exhibited paternal toxicity which consisted of decreased body weight gain; there was no evidence of maternal toxicity. There were no effects on male or female fertility in terms of mating parameters and the number of animals becoming pregnant at ribavirin doses as high as 90 mg/kg/day. Resorptions were increased at 90 mg/kg/day as evaluated on gestation day 14. The no observed adverse effect levels (NOAELs) for paternal and maternal toxicity were 30 and 90 mg/kg/day, respectively. The adult male and female NOAEL in rats for mating and fertility parameters was 90 mg/kg/day.

Ribavirin produces embryolethality and/or teratogenicity in most species tested and the dose levels at which such effects are seen are below the recommended human dose. Malformations observed in more than one rodent species included cleft palate, skeletal anomalies and CNS anomalies. The incidence and severity of teratogenic effects increased with escalation of the dose. The no observed adverse effect level (NOAEL) for embryo-fetal developmental toxicity in rats was 1 mg/kg/day.

While no effects on parturition or on lactation have been reported in terms of maternal responses in a study with prenatal and postnatal development endpoints, there was an increase in stillbirths and postnatal loss from birth to weaning on postnatal day 21 at 60 and 90 mg/kg/day. These are consistent with the findings in the developmental toxicity studies and are just later manifestations of the same activity. The NOAEL for viability and growth in the offspring in this study was 30 mg/kg/day.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

[Pr]MODERIBA™

ribavirin, tablets

Read this carefully before you start taking MODERIBA™ (ribavirin) and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MODERIBA™.

What is MODERIBA™ used for?

MODERIBA™ is used for the treatment of chronic (lasting a long time) hepatitis C virus (HCV) in adults in combination with other medications.

When you have hepatitis C, you have the virus in your blood and in your liver. Chronic hepatitis C can lead to cirrhosis (liver scarring), liver failure and even liver cancer later in life.

Also read the patient information for the other medications prescribed by your doctor for the treatment of chronic hepatitis C, before taking MODERIBA™.

How does MODERIBA™ work?

MODERIBA™ when taken with other medications may cure chronic hepatitis C infection in the majority of patients. Cure means the hepatitis C virus is cleared from your blood (remains at an undetectable level) when measured three months after finishing all treatment.

Curing chronic hepatitis C can help reduce the risk of illness and death associated to liver disease.

Does MODERIBA™ reduce the risk of passing HCV to others?

Hepatitis C can be passed to other individuals through contact with infected blood. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

What are the ingredients in MODERIBA™?

Medicinal ingredients: ribavirin

Non-medicinal ingredients:

MODERIBA™ 200 mg tablets also contain carnauba wax, croscarmellose sodium, indigo carmine aluminum lake lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, titanium dioxide.

MODERIBA™ 400 mg tablets also contain brilliant blue FCF aluminum lake, carnauba wax, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, titanium dioxide.

MODERIBA™ 600 mg tablets also contain brilliant blue FCF aluminum lake, carnauba wax, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, talc, titanium dioxide.

MODERIBA™ comes in the following dosage forms:

MODERIBA™ tablets come in three strengths: 200 mg, 400 mg or 600 mg of ribavirin.

Do not use MODERIBA™ if:

- **you ever had an allergic reaction to ribavirin or any component of MODERIBA™ (see Non-medicinal ingredients).**
- **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 Serious Warnings and Precautions and Pregnancy).**
- **you have anemia. MODERIBA™ may cause your red blood cell count to decrease (anemia). This can be dangerous, especially if you have heart or breathing problems. This may cause a worsening of heart (cardiovascular) or circulatory problems.**
- **you have hemoglobinopathies (blood disorders) including thalassemia or sickle cell anemia.**
- **you are taking didanosine. Fatal hepatic failure (liver failure resulting in death), peripheral neuropathy (tingling, pain, numbness or weakness in the arms or legs), pancreatitis (inflammation of the pancreas), symptomatic hyperlactatemia/lactic acidosis (a build-up of lactic acid in the body, leading to the blood becoming acidic) have been reported in patients receiving both didanosine and ribavirin.**

Serious Warnings and Precautions

- **MODERIBA™ (ribavirin) taken alone is not effective treatment for chronic hepatitis C infection.**
- **MODERIBA™ 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 disease you should not take MODERIBA™.**
- **MODERIBA™ may cause birth defects or death of your unborn baby. Do not take MODERIBA™ if you are pregnant. Male partners must not take MODERIBA™ if their female partners are pregnant. Females and female partners of males taking MODERIBA™, must avoid pregnancy during MODERIBA™ therapy and for 6 months after stopping MODERIBA™.**

Pregnancy:

If you are a **woman** of childbearing age who is taking MODERIBA™, you must have a negative pregnancy test before treatment, each month during therapy and for the six months after treatment is stopped. You must use two methods of effective birth control during the time you are taking the treatment and for six months after stopping treatment. This can be discussed with your doctor.

If you are a **man** who is taking MODERIBA™ and your female partner is not pregnant but is of childbearing age, she must be tested for pregnancy each month during treatment and for the six months after treatment has stopped. You or your partner must use two methods of effective birth control during the time you are taking the treatment and for six months after stopping treatment. This can be discussed with your doctor.

If you or your female partner becomes pregnant while taking MODERIBA™ in combination with other medicines or within six months after you stop taking these medicines, tell your healthcare provider.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MODERIBA™. Talk about any health conditions or problems you may have, including if you:

- have been withdrawn from previous therapy for hepatitis C because of anemia or low blood count.
- are co-infected with HIV (the virus that causes AIDS) or the hepatitis B virus (HBV). Tell your doctor if you are being treated for HIV or HBV.
- have liver problems other than hepatitis C infection.

- have any other medical condition.
- have a heart problem or a history of heart disease. In this case your doctor will monitor you carefully.
- have a problem with your kidneys. Your doctor may decide that MODERIBA™ treatment should be decreased or stopped.
- have had an organ transplant (such as liver or kidney) and are taking medicine that keeps your body from rejecting your transplant (suppresses your immune system). Or you have one planned in the near future.
- are pregnant, planning to become pregnant, breastfeeding or plan to breastfeed. It is not known if MODERIBA™ passes into your breast milk. You and your healthcare provider should decide if you will take MODERIBA™ or breastfeed. You should not do both.

Other warnings you should know about:

MODERIBA™ is administered with other medications. The Patient Medication Information(s) of medications used in combination with ribavirin should be consulted before starting treatment with MODERIBA™.

It is not known if taking MODERIBA™ with other medications is safe and effective in children under 18 years of age.

Your doctor may do blood tests before you start your treatment and regularly during your treatment. These blood tests are done to help your doctor to check if the treatment is working for you and to check for side effects.

MODERIBA™ can make you feel tired, dizzy, or confused. You should not drive or operate machinery if you have any of these symptoms.

Do not drink alcohol, including beer, wine, and liquor. This may make your liver disease worse.

Let your doctor know if you are taking didanosine. Lactic acidosis (a build-up of lactic acid) in body, leading to the blood becoming acidic) and worsening liver function are side effects associated with didanosine.

When ribavirin is taken with azathioprine, pancytopenia (decreased red blood cells, white blood cells and platelets) and bone marrow suppression (tissue in the bones that makes these blood cells) have been seen. This was reversible when these treatments were stopped.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

For detailed information on drugs interactions refer to the Patient Medication Information(s) of medications used in combination with ribavirin.

Drugs that may interact with MODERIBA™ include: didanosine (e.g., Videx EC®), stavudine (e.g., Zerit®), zidovudine (e.g., Retrovir®), azathioprine (e.g., Imuran®), lamivudine (e.g., Heptovir®).

Know all the medicines that you take. Keep a list of them with you to show healthcare provider and pharmacist when you get a new medicine.

While MODERIBA™ when taken with other medications may cure chronic hepatitis C infection, it does not protect you from HCV reinfection. Talk with your healthcare provider about ways to prevent reinfection with the hepatitis C virus.

How to take MODERIBA™

- Take MODERIBA™ exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking MODERIBA™ to ensure that your medicine continues to work against the virus, unless your doctor tells you to. If you think there is a reason to stop taking MODERIBA™, talk to your healthcare provider before doing so.
- Take MODERIBA™ at about the same time every day.
- Take MODERIBA™ tablets with food. The type of food is not important.
- Swallow MODERIBA™ tablets whole, with water as required. Do not chew, break, or crush MODERIBA™ tablets.

Usual dose:

- Your healthcare provider will determine the correct dose of MODERIBA™ tablets based on your weight and the genotype of the disease you have.
- Your healthcare provider will tell you exactly how long you need to take MODERIBA™ combination therapy.

Overdose:

If you think you have taken too much MODERIBA™ contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of MODERIBA™ tablets and remember **within 6 hours**, it should be taken as soon as possible. If more than 6 hours has passed since MODERIBA™ is usually taken, the missed dose should NOT be taken and you should take the next dose as

per the usual dosing schedule. Do not take two doses at the same time.

What are possible side effects from using MODERIBA™?

These are not all the possible side effects you may feel when taking MODERIBA™. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Other warnings you should know about**.

Side effects of MODERIBA™ when taken with other medications:

- feeling tired (fatigue)
- itching
- feeling weak or lack of energy (asthenia)
- low red blood cell count (anemia)
- nausea
- trouble sleeping

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

SERIOUS SIDE EFFECTS 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 blood platelet count (thrombocytopenia) when used with azathioprine, with symptoms such as bruising or increased bleeding		✓	
	Low white blood cell count (neutropenia) when used with azathioprine, with symptoms such as increased infection		✓	

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

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701D
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.healthcanada.gc.ca/medeffect).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15 and 30°C. Keep the bottle tightly closed in order to protect from moisture.

Keep MODERIBA™ out of the reach and sight of children.

If you want more information about MODERIBA™:

- Talk to your healthcare professional
- Find the most recent version of the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website abbvie.ca, or by calling 1-888-704-8271.

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