PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrHOLKIRA® PAK

ombitasvir/paritaprevir/ritonavir
film-coated tablets (12.5/75/50 mg)

and

dasabuvir (as dasabuvir sodium monohydrate)
film-coated tablets (250 mg)

Antiviral Agent

Date of Preparation:
December 22, 2014

Date of Previous Revision:
August 10, 2017

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February 22, 2018

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Submission Control No: 211536

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[Pr]HOLKIRA PAK

ombitasvir/paritaprevir/ritonavir and dasabuvir

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	ombitasvir/paritaprevir /ritonavir film-coated tablets: 12.5/75/50 mg	None
	dasabuvir film-coated tablets: 250 mg (as dasabuvir sodium monohydrate)	Lactose monohydrate
		*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is indicated for the treatment of adults with genotype 1 chronic hepatitis C (CHC) infection, including those with compensated cirrhosis:

- with ribavirin in non-cirrhotic and cirrhotic patients with genotype 1a infection;
- without ribavirin in non-cirrhotic and cirrhotic patients with genotype 1b infection

Geriatrics (> 65 years of age):

In Phase 3 clinical trials, 8.5% (174/2053) of patients were age 65 or over. No overall differences in safety or effectiveness were observed between these patients and younger patients (see **WARNINGS AND PRECAUTIONS**).

HCV Patients Co-Infected with HIV-1:

Efficacy and safety of HOLKIRA PAK has been established in patients with hepatitis C virus (HCV) genotype 1 co-infected with HIV-1 (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Post-Liver Transplant Recipients:

Efficacy and safety of HOLKIRA PAK with ribavirin has been established in liver transplant recipients with normal hepatic function and Metavir fibrosis score of ≤ 2, regardless of the HCV genotype 1 subtype (see **DOSAGE AND ADMINISTRATION** and **CLINICAL TRIALS**).

Pediatrics (< 18 years of age):

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Patients who are hypersensitive to the medicinal ingredients of HOLKIRA PAK (ombitasvir, paritaprevir, ritonavir and dasabuvir) or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.

- If HOLKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen (see the ribavirin Product Monograph for a list of contraindications for ribavirin).

- The use of ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant, may be pregnant, or plan to become pregnant because of the risks for birth defects and fetal death associated with ribavirin (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Pregnant Women**).

- HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity.

- The following categories of drugs are contraindicated with HOLKIRA PAK:

    - Drugs for which elevated plasma concentrations are associated with serious adverse events and that are sensitive cytochrome P450 (CYP) 3A substrates;

    - Drugs that are strong CYP2C8 inhibitors, which may increase dasabuvir plasma concentrations;

    - Drugs that are moderate or strong inducers of CYP3A, which may result in substantial lowering of plasma concentrations of paritaprevir, ombitasvir and dasabuvir.

- Drugs that are strong inducers of CYP2C8, which may result in substantial lowering of plasma concentrations of dasabuvir.

Table 1. Drugs that Are Contraindicated with HOLKIRA PAK

Drug Class	Drug Name
Alpha1-adrenoreceptor antagonist	alfuzosin HCl
Antiarrhythmic	disopyramide, dronedarone
Antibiotic	fusidic acid (oral formulation)*
Anticonvulsants	carbamazepine, phenytoin, phenobarbital
Anti-gout	colchicine in patients with renal and/or hepatic impairment
Antihistamine	astemizole, terfenadine*
Antihyperlipidemic	gemfibrozil
Antimycobacterial	rifampin
Antipsychotic	lurasidone
Antiviral	efavirenz-containing regimens, including Atripla, etravirine, nevirapine
Benzodiazepines	oral midazolam, triazolam
Endothelin receptor agonist	bosentan
Ergot derivatives	ergotamine, dihydroergotamine, ergonovine*, methylergonovine*
GI Motility Agent	cisapride*
Herbal Product	St. John's Wort (*Hypericum perforatum*)
Hormonal Product	ethinyl estradiol-containing medications such as combined oral contraceptives
HMG-CoA Reductase Inhibitors	atorvastatin, lovastatin, simvastatin
Long-acting beta-adrenoceptor agonist	salmeterol
Neuroleptics	pimozide
PDE5 enzyme inhibitor	sildenafil only when used for the treatment of pulmonary arterial hypertension (PAH)
Others	modafinil

* Drugs not sold in Canada.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Potential for Hepatitis B virus (HBV) reactivation:** Screen all patients for evidence of current or prior HBV infection before initiating HOLKIRA PAK therapy. Cases of HBV reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death, have been reported during HCV treatment and/or post-treatment with regimens containing direct-acting HCV antivirals (DAAs) in patients co-infected with HBV. (See **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**)

General

If HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen (see the ribavirin Product Monograph).

HOLKIRA PAK contains ritonavir and should not be co-administered with additional ritonavir or ritonavir-containing regimens.

Co-administration of HOLKIRA PAK with other direct-acting antivirals (DAAs) against HCV has not been studied and therefore cannot be recommended.

As a fixed dose combination formulation, no dosage adjustments for HOLKIRA PAK are possible.

Retreatment of patients previously treated with HOLKIRA PAK or other DAAs is not recommended since the efficacy in these patients has not been established.

Transaminase Elevations with Concomitant Drugs

Clinically significant transaminase elevations were observed when HOLKIRA PAK was co-administered with efavirenz- or ethinyl estradiol-containing regimens and therefore these drugs are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**). When HOLKIRA PAK is co-administered with other drugs known to cause elevations of transaminases, caution should be exercised and monitoring of transaminase levels should be considered. If transaminase elevations occur, consideration should be given to whether the other drug may be discontinued. Discontinuation of HOLKIRA PAK should be considered if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, direct bilirubin or international normalized ratio (INR) (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic, ALT Elevations**).

Use with Tacrolimus, Sirolimus and Everolimus

Co-administration of HOLKIRA PAK with systemic tacrolimus, sirolimus, or everolimus increases the concentrations of the immunosuppressant via CYP3A inhibition (see **DRUG INTERACTIONS**, **Table 9**). Serious and/or life threatening adverse events have been observed with co-administration of HOLKIRA PAK with systemic tacrolimus and a similar risk can be expected with sirolimus and everolimus. Avoid concomitant use of tacrolimus or sirolimus with HOLKIRA PAK unless the benefits outweigh the risks.

If tacrolimus or sirolimus and HOLKIRA PAK are used concomitantly, caution is advised. Refer to the **DRUG INTERACTIONS** section for recommended doses and monitoring strategies. Everolimus cannot be used due to lack of suitable dose strength for dose adjustments.

Tacrolimus or sirolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with HOLKIRA PAK and the dose and/or dosing frequency should be adjusted as needed. Patients should be monitored frequently for any changes in renal function or tacrolimus or sirolimus-associated adverse events. Refer to the tacrolimus or sirolimus Product Monograph for additional dosing and monitoring instructions.

Use with Fluticasone (and other glucocorticoids metabolized by CYP3A)

Use caution when administering HOLKIRA PAK with fluticasone or other glucocorticoids that are metabolized by CYP3A4 (see **DRUG INTERACTIONS, Table 7**). Concomitant use of inhaled glucocorticoids metabolized by CYP3A can increase systemic exposures of the glucocorticoids, and cases of Cushing's syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens. Concomitant use of HOLKIRA PAK and glucocorticoids, particularly long-term use, should only be initiated if the potential benefit of treatment outweighs the risk of systemic corticosteroid effects.

Use with Quetiapine

The use of HOLKIRA PAK with quetiapine, a CYP3A4 substrate, is not recommended due to an expected increase in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose and monitor for quetiapine-associated adverse reactions (see **DRUG INTERACTIONS, Table 6** and the quetiapine Product Monograph for the recommendations on adverse reaction monitoring).

Use with Rilpivirine

Concomitant use of HOLKIRA PAK with rilpivirine, a CYP3A4 substrate, significantly increased rilpivirine exposure by 243%. Co-administration of HOLKIRA PAK with rilpivirine is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine (see **DRUG INTERACTIONS**, **Table 6**).

Use with HMG-CoA Reductase Inhibitors

Simvastatin, lovastatin, and atorvastatin, CYP3A4 substrates, are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**). For patients receiving fluvastatin, use the lowest dose or switch to low-dose pravastatin or rosuvastatin (see **DRUG INTERACTIONS**, **Table 5** and **Table 7**).

Cardiovascular

QTc Prolongation

HOLKIRA PAK was associated with concentration-dependent QTc prolongation. At therapeutic plasma concentrations, the maximum mean difference from placebo in the QTc interval was reported to be < 5 ms, with a 95% CI upper limit of < 10 ms (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacodynamics**, **Effects on Electrocardiogram**).

Caution should be exercised when drugs that prolong QTc are co-administered with HOLKIRA PAK (see **DRUG INTERACTIONS**).

Hepatic/Biliary/Pancreatic

Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported from postmarketing sources in patients treated with HOLKIRA PAK with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation. Because these events 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.

HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see **CONTRAINDICATIONS**; **DOSAGE AND ADMINISTRATION**, **Special Populations**, **Hepatic Impairment**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage).

- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter.

- Discontinue treatment in patients who develop evidence of hepatic decompensation.

ALT Elevations

During clinical trials with HOLKIRA PAK with or without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all patients (see **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**, **Laboratory Abnormalities**). **These ALT elevations were significantly more frequent in female patients who were using ethinyl estradiol-containing medications such as combined oral contraceptives or contraceptive vaginal rings (see CONTRAINDICATIONS).** ALT elevations typically occurred during the first 4 weeks of treatment and declined within approximately two weeks of onset with continued dosing of HOLKIRA PAK with or without ribavirin.

Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with HOLKIRA PAK (see CONTRAINDICATIONS). Alternative contraceptive agents or methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during HOLKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with HOLKIRA PAK.

Patients using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy, had a rate of ALT elevation similar to those not receiving any estrogens (1%). However, due to the limited number of patients taking these other estrogens (n=87), caution is warranted for co-administration with HOLKIRA PAK.

Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice and discolored feces. If elevated liver chemistries are identified, careful follow-up is recommended. HOLKIRA PAK should be discontinued if there are clinical signs of liver inflammation that are accompanied by persistent elevations in ALT, direct bilirubin or international normalized ratio (INR).

Potential for Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, including those resulting in fulminant hepatitis, hepatic failure, and death have been reported in HCV/HBV–coinfected patients who were undergoing, or completed treatment with DAA. To decrease the risk of HBV reactivation in patients co-infected with HBV, HBV screening should be performed in all patients prior to

initiation of HCV treatment. Patients with positive HBV serology (HBsAg positive) and patient with serologic evidence of resolved HBV infection (i.e. HBsAg negative and anti-HBc positive) should be monitored and treated according to current clinical practice guidelines to manage potential for HBV reactivation (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Renal

No dose adjustment of HOLKIRA PAK is required in patients with mild, moderate, or severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Renal Insufficiency**).

HOLKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin Product Monograph for information regarding use in patients with renal impairment.

Sexual Function/Reproduction

Fertility

There are no studies on the effect of HOLKIRA PAK on human fertility.

No effects on fertility were observed in animal studies with the components of HOLKIRA PAK (see **NON-CLINICAL TOXICOLOGY, Fertility**).

Use with Ribavirin in Females and Males of Reproductive Potential

Ribavirin may cause birth defects and/or death of the exposed fetus (see **CONTRAINDICATIONS**). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients when HOLKIRA PAK is administered in combination with ribavirin as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin.

HOLKIRA PAK in combination with ribavirin 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 6 months after treatment has concluded. See additional information on specific hormonal contraceptives in **CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **ALT Elevations;** and **DRUG INTERACTIONS**, **Table 5**. Routine monthly pregnancy tests must be performed during this time (see the ribavirin Product Monograph).

Special Populations

Pregnant Women

HOLKIRA PAK with Ribavirin

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin; therefore, ribavirin is contraindicated in women who are pregnant and in men whose female partners are pregnant (see **CONTRAINDICATIONS** and the ribavirin Product Monograph).

HOLKIRA PAK

There are no studies with HOLKIRA PAK in pregnant women.

No effects on embryo-fetal development have been noted in studies in animals with paritaprevir/ritonavir, ombitasvir and its major inactive human metabolites (M29, M36) or dasabuvir. For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For ombitasvir, the highest dose tested produced exposures equal to 28-fold (mouse) or 4-fold (rabbit) the exposure in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26 times higher in mice than in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures equal to 24-fold (rat) or 6-fold (rabbit) the exposure in humans at the recommended clinical dose.

Ombitasvir, paritaprevir and dasabuvir were minimally transferred through the placenta of pregnant rats.

Nursing Women

It is not known whether paritaprevir/ritonavir, ombitasvir or dasabuvir and their metabolites are excreted in human breast milk. Paritaprevir and its hydrolysis product M13, unchanged ombitasvir and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups. A risk to the newborn cannot be excluded; therefore nursing must be discontinued prior to initiation of treatment with HOLKIRA PAK. Physicians prescribing ribavirin should also refer the patient to the Product Monograph for ribavirin.

Pediatrics (< 18 years of age)

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established.

Geriatrics (> 65 years of age)

No dose adjustment of HOLKIRA PAK is needed in geriatric patients. In Phase 3 clinical trials, 8.5% (174/2053) of patients were age 65 or over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

HCV-HBV Co-infection

The safety and efficacy of HOLKIRA PAK have not been established in HCV patients co-infected with HBV. HBV reactivation has been reported during treatment and post-treatment with DAAs in patients co-infected with HBV who were not undergoing treatment for HBV infection (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

HCV-HIV Co-infection

The ritonavir component of HOLKIRA PAK is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with HOLKIRA PAK should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

HOLKIRA PAK is contraindicated with efavirenz-containing regimens (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Table 5**).

Other HCV Genotypes

The safety and efficacy of HOLKIRA PAK has not been established in patients with HCV genotypes other than genotype 1.

Use in Patients Who Have Failed Previous Therapy with Direct-Acting Antivirals against HCV

HOLKIRA PAK efficacy has not been studied in patients who have previously failed therapy with other direct-acting antiviral (DAA) agents.

Monitoring and Laboratory Tests

For patients with cirrhosis, hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter. Discontinue treatment in patients who develop evidence of hepatic decompensation.

Refer to **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic** for additional information.

Clearance of HCV may lead to increased replication of HBV in patients who are HCV/HBV coinfected. Co-infected patients should be monitored for clinical and laboratory signs (e.g. HBsAg, anti-HBc, HBV DNA, serum aminotransferase levels, bilirubin) for hepatitis flare or HBV reactivation during and at post-treatment follow-up as clinically appropriate (see **WARNINGS AND PRECAUTIONS**, **Potential for Hepatitis B Virus Reactivation**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety summary is based on pooled data from phase 2 and 3 clinical trials in more than 2,600 patients who received HOLKIRA PAK with or without ribavirin.

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

The safety profile of HOLKIRA PAK and ribavirin in patients with cirrhosis was similar to that of patients without cirrhosis.

In patients receiving HOLKIRA PAK without ribavirin, the most commonly reported treatment emergent adverse events considered related to study drug by site investigator (greater than 10% of patients) were fatigue and headache. No patients permanently discontinued treatment due to a related adverse event and no patients had a treatment interruption due to a related adverse event.

In patients with genotype 1b infection and compensated cirrhosis receiving HOLKIRA PAK without ribavirin, the most commonly reported treatment emergent adverse event considered related to study drug by site investigator (greater than 10% of patients) was fatigue. One patient (2%) had a serious adverse event. One patient (2%) interrupted treatment due to a related adverse event and no patients permanently discontinued treatment due to adverse events. Post-baseline Grade 2 increases in total bilirubin occurred in 12/60 (20%) patients.

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.*

Table 2 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.

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

	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)	TURQUOISE III (patients 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 (%)**	**HOLKIRA PAK 12 Weeks N = 60 n (%)**
Fatigue	29 (3.8)	4 (1.6)	26 (6.5)	22 (4.3)	15 (3.9)	4 (6.7)
Nausea	26 (3.4)	2 (0.8)	2 (0.5)	2 (0.4)	8 (2.1)	0
Asthenia	22 (2.9)	3 (1.2)	6 (1.5)	1 (0.2)	12 (3.2)	0
Headache	35 (4.5)	6 (2.3)	10 (2.5)	12 (2.4)	12 (3.2)	3 (5.0)

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

HCV-HIV-1 Co-infected Patients

The overall safety profile in HCV genotype 1/HIV-1 co-infected patients was similar to that observed in HCV genotype 1 mono-infected patients. Transient elevations in total bilirubin > 3 × ULN (mostly indirect) occurred in 17/63 (27.0%) patients; 15 of these patients were receiving atazanavir. None of the patients with hyperbilirubinemia had concomitant elevations of aminotransferases.

Liver Transplant Recipients

The type of adverse events experienced by HCV genotype 1 infected liver transplant recipients who were treated with HOLKIRA PAK and ribavirin (in addition to their immunosuppressant medications) was similar to those experienced by patients treated with HOLKIRA PAK with ribavirin in Phase 3 clinical trials; however some events were increased in frequency. Adverse events occurring in > 20% of post-liver transplant patients included fatigue 50.0% (17/34), headache 44.1% (15/34), cough 32.4% (11/32), diarrhea 26.5% (9/34), insomnia 26.5% (9/34), asthenia 23.5% (8/34), nausea 23.5% (8/34), anemia 20.6% (7/34), muscle spasms 20.6% (7/34), and rash 20.6% (7/34). Ten patients (29.4%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten of 34 patients (29.4%) had dose modified due to decrease in hemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. Five patients required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No patient received a blood transfusion.

Less Common Clinical Trial Adverse Drug Events (< 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 patients in Phase 3 trials are listed below by system organ class (**Table 3**).

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

Body System	Adverse Events
Blood and lymphatic system disorders:	anaemia, leukopenia, neutropenia
Cardiac disorders:	extrasystoles, palpitations, sinus tachycardia, tachycardia, ventricular extrasystoles
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:	hyperbilirubinaemia, 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, hyperaesthesia, intention tremor, lethargy, memory impairment, migraine, neuralgia, paraesthesia, presyncope, restless legs syndrome, somnolence, syncope, tension headache, tremor

Body System	Adverse Events
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 4**. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in design.

Table 4. Selected Treatment Emergent Laboratory Abnormalities of at Least Moderate Intensity (Grades 2-4)

Laboratory Parameters	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)	TURQUOISE III (patients 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 (%)	HOLKIRA PAK 12 Weeks N = 60 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%)	1/60 (1.7%)
> 20 × ULN (Grade 4)	3/765 (0.4%)	0	0	0	2/380 (0.5%)	0
Hemoglobin						
< 10-8 g/dL (Grade 2)	41/765 (5.4%)	0	23/401 (5.7%)	0	30/380 (7.9%)	1/60 (1.7%)
< 8-6.5 g/dL (Grade 3)	1/765 (0.1%)	0	2/401 (0.5%)	0	3/380 (0.8%)	0
< 6.5 g/dL (Grade 4)	0	0	0	0	1/380 (0.3%)	0
Total Bilirubin						
> 3-10 × ULN (Grade 3)	19/765 (2.5%)	0	23/401 (5.7%)	2/509 (0.4%)	37/380 (9.7%)	0
> 10 × ULN (Grade 4)	1/765 (0.1%)	0	0	0	0	0

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

Serum ALT Elevations

During clinical trials with HOLKIRA PAK with and without ribavirin, less than 1% of patients who were not on ethinyl estradiol-containing medications experienced transient serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment (see **CONTRAINDICATIONS**). These elevations were asymptomatic, generally occurred during the first 4 weeks of treatment and resolved with ongoing therapy. Increases in ALT were not associated with simultaneous increases in bilirubin levels. Cirrhosis was not a risk factor for elevated ALT. No specific monitoring of liver chemistries is required for the majority of patients (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, **ALT Elevations**).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in patients 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. The frequency of indirect bilirubin elevations was lower among patients who did not receive ribavirin.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of HOLKIRA PAK. 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.

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).

Immune System Disorders: Anaphylactic reactions and other hypersensitivity reactions (including tongue and lip swelling).

Skin and Subcutaneous Tissue Disorders: Erythema multiforme.

DRUG INTERACTIONS

Drug-Drug Interactions

Potential for HOLKIRA PAK to Affect Other Drugs

Ritonavir is a strong inhibitor of CYP3A. Co-administration of HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of these drugs. Drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events are contraindicated (see **CONTRAINDICATIONS**).

Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of HOLKIRA PAK with drugs that are substrates of OATP1B1, OATP1B3, OATP2B1 or BCRP may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring.

While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, only slight increase was observed in the exposure of the P-gp substrate, digoxin, when administered with

HOLKIRA PAK. Monitoring for plasma concentrations of drugs that are sensitive for changed intestinal P-gp activity is recommended.

Ombitasvir, paritaprevir and dasabuvir are inhibitors of UGT1A1. Co-administration of HOLKIRA PAK with drugs that are primarily metabolized by UGT1A1 is expected to result in increased plasma concentrations of such drugs; consider clinical monitoring for narrow therapeutic index drugs (i.e. levothyroxine). See also **Table 7** for specific advice on raltegravir and buprenorphine, which have been evaluated in drug interaction studies.

Co-administration of HOLKIRA PAK can decrease exposures of drugs that are primarily metabolized by CYP2C19 (e.g., omeprazole). Clinical monitoring and/or dose increases might be needed for CYP2C19 substrates when administered with HOLKIRA PAK.

HOLKIRA PAK did not affect the exposures of the CYP2C9 substrate, warfarin, or CYP2D6/CYP1A2 substrate, duloxetine. Dose adjustment is not required for CYP2C9 or CYP2D6 or CYP1A2 substrates when administered with HOLKIRA PAK.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, ritonavir and dasabuvir are not inhibitors of organic cation transporter 2 (OCT2), organic anion transporter 3 (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations. Therefore, HOLKIRA PAK is not expected to affect drugs which are primarily excreted by the renal route via these transporters.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir are not expected to inhibit organic cation transporter 1 (OCT1) at clinically relevant concentrations.

Caution should be exercised when drugs that prolong QTc are co-administered with HOLKIRA PAK.

If HOLKIRA PAK is coadministered with vitamin K antagonist, close monitoring of International Normalised Ratio (INR) is recommended. This is due to liver function changes during treatment with HOLKIRA PAK.

Potential for Other Drugs to Affect HOLKIRA PAK

Paritaprevir and ritonavir are primarily metabolized by CYP3A, and dasabuvir is primarily metabolized by CYP2C8.

Strong inhibitors of CYP3A may significantly increase paritaprevir and ritonavir exposures when co-administered with HOLKIRA PAK. Drugs that potently inhibit CYP2C8 may significantly increase dasabuvir plasma concentrations; the co-administration of HOLKIRA PAK with a weak CYP2C8 inhibitor trimethoprim did not meaningfully affect dasabuvir exposure.

Drugs that induce CYP3A are expected to decrease dasabuvir, paritaprevir, ombitasvir and ritonavir plasma concentrations significantly and reduce their therapeutic effect. Drugs that induce CYP2C8 are expected to decrease dasabuvir plasma concentrations significantly and reduce its therapeutic effect. Drugs that are strong CYP2C8 inhibitors, CYP3A inducers or CYP2C8 inducers are contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS**).

Paritaprevir, dasabuvir, ritonavir and ombitasvir are substrates of P-gp. Paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may significantly increase exposures of the various components of HOLKIRA PAK.

Paritaprevir is a substrate of CYP3A and transport proteins. Caution is advised if co-administering HOLKIRA PAK with products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3) as it can result in clinically relevant increases in paritaprevir exposures.

Drugs that Are Contraindicated with HOLKIRA PAK

The drugs that are contraindicated with HOLKIRA PAK are listed in **Table 5**.

Table 5. Drugs that Are Contraindicated with HOLKIRA PAK

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ALPHA1-ADRENORECEPTOR ANTAGONISTS		
alfuzosin HCL	CYP3A inhibition by ritonavir	Potential for increased alfuzosin concentrations which can result in hypotension.
ANTIARRHYTHMICS		
disopyramide, dronedarone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias
ANTIBIOTICS		
fusidic acid (oral formulation)*	CYP3A4 inhibition by ritonavir	Potential for increased fusidic acid concentrations with risk of adverse events such as hepatotoxicity.
ANTICONVULSANTS		
carbamazepine, phenytoin, phenobarbital	CYP3A4 induction by carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTI-GOUT		
colchicine	CYP3A4 inhibition by ritonavir	Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For recommendations concerning patients with normal renal and hepatic function see **Table 7.**
ANTIHISTAMINES		
astemizole, terfenadine*	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
ANTIHYPERLIPIDEMICS		
gemfibrozil	CYP2C8 inhibition by gemfibrozil	Increased risk of QT prolongation due to 10-fold increase in dasabuvir AUC
ANTIMYCOBACTERIALS		
rifampin	CYP3A4/CYP2C8 induction by rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
ANTIPSYCHOTICS		
lurasidone	CYP3A inhibition by ritonavir	Potential for serious and/or life-threatening reactions.
BENZODIAZEPINES		
oral midazolam, triazolam	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
ENDOTHELIN RECEPTOR ANTAGONISTS		
bosentan	CYP3A4 induction by bosentan	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
ERGOT DERIVATIVES		
ergotamine, dihydroergotamine, ergonovine*, methylergonovine*	CYP3A4 inhibition by ritonavir	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
GI MOTILITY AGENTS		
cisapride*	CYP3A4 inhibition by ritonavir	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
HERBAL PRODUCTS		
St. John's Wort (*Hypericum perforatum*)	CYP3A4 induction by St. John's Wort	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
HIV-ANTIVIRAL AGENTS		
efavirenz-containing regimens, such as Atripla		Co-administration of efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla) with paritaprevir, ritonavir and dasabuvir was poorly tolerated and resulted in liver enzyme elevations and early study termination.
nevirapine, etravirine	CYP3A4 induction by nevirapine or etravirine	Ombitasvir, paritaprevir and ritonavir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.
HORMONAL PRODUCTS		
ethinyl estradiol-containing drugs (combined oral contraceptives, contraceptive vaginal rings, contraceptive patch)	possibly due to UGT inhibition by ombitasvir and paritaprevir	Potential for ALT elevations.
HMG CoA REDUCTASE INHIBITORS		
lovastatin, simvastatin, atorvastatin	CYP3A4 and OATP1B inhibition by ritonavir and paritaprevir, respectively	Potential for serious reactions such as myopathy including rhabdomyolysis.
LONG-ACTING BETA-ADRENOCEPTOR AGONISTS		
salmeterol	CYP3A4 inhibition by ritonavir	Potential for QT prolongation, palpitations and sinus tachycardia.
NEUROLEPTICS		
pimozide	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias.
PDE5 ENZYME INHIBITORS		
sildenafil only at the doses used daily for the treatment of pulmonary arterial hypertension	CYP3A4 inhibition by ritonavir	Potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
OTHER		
modafinil	CYP3A4 induction by modafinil	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of HOLKIRA PAK.

* Drugs not sold in Canada

Drugs that Should Not be Co-administered with HOLKIRA PAK

The drugs that should not be co-administered with HOLKIRA PAK are listed in **Table 6**.

Table 6. Drugs that Should Not be Co-administered with HOLKIRA PAK

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
ANTIARRHYTHMICS		
amiodarone, flecainide, lidocaine (systemic), propafenone, quinidine	CYP3A4 inhibition by ritonavir	Potential for cardiac arrhythmias. Physicians considering combined therapy of HOLKIRA PAK with amiodarone should refer to the amiodarone Product Monograph, carefully weigh the potential benefits and risks, and monitor patients for amiodarone-associated adverse reactions.
ANTIPSYCHOTICS		
quetiapine	CYP3A4 inhibition by ritonavir	Potential for an increase in quetiapine exposure. If the co-administration is necessary, reduce the quetiapine dose and closely monitor patients for quetiapine-associated adverse reactions (see the quetiapine Product Monograph).
HIV-ANTIVIRAL AGENTS		
darunavir/ritonavir	unknown	Potential for reduced therapeutic activity of HOLKIRA PAK. For administration of HOLKIRA PAK with darunavir without additional ritonavir, refer to **Table 7.**
rilpivirine	CYP3A4 inhibition by ritonavir	Potential for QT interval prolongation due to increased rilpivirine exposure.
ritonavir and ritonavir-containing regimens, including atazanavir/ritonavir, lopinavir/ritonavir	CYP3A4 inhibition by ritonavir	Potential for increased paritaprevir exposure. For administration of HOLKIRA PAK with atazanavir without ritonavir, refer to **Table 7**.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
IMMUNOSUPPRESSANTS		
sirolimus	CYP3A4 inhibition by ritonavir	Avoid concomitant use of sirolimus with HOLKIRA PAK unless the benefits outweigh the risks. If sirolimus and HOLKIRA PAK are used concomitantly, administer sirolimus 0.2 mg twice a week (every 3 or 4 days on the same 2 days each week). Upon initiation of HOLKIRA PAK, sirolimus whole blood concentrations should be monitored every 4 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus. Sirolimus dose and/or dosing frequency should be adjusted as needed throughout co-administration with HOLKIRA PAK (see **WARNINGS AND PRECAUTIONS**). Five days after completion of HOLKIRA PAK treatment, the sirolimus dose and dosing frequency prior to receiving HOLKIRA PAK should be resumed, along with routine monitoring of sirolimus whole blood concentrations.
everolimus	CYP3A4 inhibition by ritonavir	Should not be co-administered due to a significant increase in everolimus exposures that cannot be properly dose-adjusted with available dose strengths.
tacrolimus	CYP3A4 inhibition by ritonavir	Serious and/or life threatening adverse events have been observed with co-administration of HOLKIRA PAK with systemic tacrolimus. Avoid concomitant use of tacrolimus with HOLKIRA PAK unless the benefits outweigh the risks. If tacrolimus and HOLKIRA PAK are used concomitantly, tacrolimus should not be administered on the day HOLKIRA PAK is initiated. Beginning the day after HOLKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days (see **WARNINGS AND PRECAUTIONS**). Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with HOLKIRA PAK and the dose and/or dosing frequency should be adjusted as needed. Upon completion of HOLKIRA PAK treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus whole blood concentrations.

Drug Class: Specific Drugs	Mechanism of Interaction	Clinical Comment
OPIOID ANALGESICS		
alfentanil, fentanyl	CYP3A4 inhibition by ritonavir	Potential for increased opioid exposure.

Established and Other Potential Drug Interactions

Table 7 lists clinically relevant drug interactions where patient monitoring and/or dose adjustment are recommended. The pharmacokinetic data relevant to these drug interactions are shown in **Table 8** and **Table 9**.

Table 7. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
ANGIOTENSIN RECEPTOR BLOCKERS		
candesartan, losartan and valsartan	↑ candesartan, ↑ losartan ↑ valsartan	Decrease the dose of the angiotensin receptor blockers and monitor patients.
ANTIARRHYTHMICS		
digoxin	↑ digoxin	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
ANTICOAGULANTS		
warfarin	↓ warfarin	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalized ratio (INR) is recommended.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole ↑ paritaprevir	Caution is warranted, and patients should be monitored for adverse reactions to ketoconazole and HOLKIRA PAK. The maximum daily dose of ketoconazole should not exceed 200 mg.
itraconazole and posaconazole (not studied, theoretical)	↑ itraconazole ↑ posaconazole ↑ paritaprevir	Drug interactions similar to ketoconazole are expected; monitor patients for adverse reactions and reduce the dose of the co-administered drug as appropriate.
voriconazole (not studied, theoretical)	↓ voriconazole ↑ paritaprevir	Co-administration of HOLKIRA PAK with voriconazole is expected to decrease voriconazole exposure and to increase paritaprevir exposure. Co-administration is not recommended unless the assessment of the benefit-to-risk ratio justifies the use of voriconazole.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
ANTI-GOUT		
colchicine		Contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions (see **CONTRAINDICATIONS**). A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with HOLKIRA PAK is required (see also the colchicine Product Monograph).
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Caution is warranted and a 50% reduction in the dose of amlodipine should be considered.
diltiazem, nifedipine and verapamil	↑ diltiazem ↑ nifedipine ↑ verapamil	Decrease the dose of the calcium channel blocker. Clinical monitoring of patients is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone		Concomitant use of HOLKIRA PAK with inhaled or nasal fluticasone may decrease serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported with ritonavir-containing regimens. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide	Caution and monitoring for furosemide clinical effects are recommended; decrease the dose of furosemide by up to 50% if clinically indicated.
HIV-ANTIVIRAL AGENTS		
atazanavir	atazanavir administered in the morning ↔ atazanavir ↑ paritaprevir	Atazanavir without ritonavir should be co-administered at the same time as HOLKIRA PAK. The ritonavir in HOLKIRA PAK will provide atazanavir boosting. Atazanavir plus ritonavir is not recommended with HOLKIRA PAK.
darunavir	↓ darunavir (C_{trough})	Darunavir without ritonavir should be co-administered at the same time as HOLKIRA PAK. The ritonavir in HOLKIRA PAK will provide darunavir boosting. Because of decreased darunavir trough concentrations, patients should be monitored for HIV-1viral breakthrough.
raltegravir	↑ raltegravir	No dose adjustment is necessary for raltegravir.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
HMG CoA REDUCTASE INHIBITORS		
fluvastatin	↑ fluvastatin	The lowest dose of fluvastatin should be used. Monitor patients for fluvastatin side effects such as myopathy/rhabdomyolysis.
rosuvastatin	↑ rosuvastatin	Co-administration of rosuvastatin with HOLKIRA PAK should be avoided. If used together, caution should be exercised and patients should be monitored for rosuvastatin side effects such as myopathy/rhabdomyolysis. Rosuvastatin dose should not exceed 5 mg per day.
pravastatin	↑ pravastatin	Pravastatin dose should not exceed 40 mg per day. Patients should be monitored for pravastatin side effects such as myopathy/rhabdomyolysis.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When starting co-administration with HOLKIRA PAK, give one fifth of the total daily dose of cyclosporine once daily with HOLKIRA PAK. Monitor cyclosporine levels and adjust dose and/or dosing frequency as needed.
MUSCLE RELAXANTS		
carisoprodol	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)	Monitor patients for decreased efficacy of carisoprodol; increase the carisoprodol dose if clinically indicated.
cyclobenzaprine	↓ cyclobenzaprine ↓ norcyclobenzaprine (metabolite of cyclobenzaprine)	Monitor patients for decreased efficacy of cyclobenzaprine; increase the cyclobenzaprine dose if clinically indicated.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine (metabolite of buprenorphine)	No dose adjustment of buprenorphine/naloxone is required.
hydrocodone (when co-administered as a fixed-dose combination of 300 mg acetaminophen/5 mg hydrocodone)	↑ hydrocodone	Hydrocodone dose should be reduced by 50%. Monitor patients for respiratory depression and sedation at frequent intervals.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of omeprazole; increase the omeprazole dose if clinically indicated.

Concomitant Drug Class: Drug Name	Effect on Concentration of HOLKIRA PAK or Concomitant Drug	Clinical comments
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Caution is warranted and clinical monitoring of patients for alprazolam-associated side effects is recommended. A decrease in alprazolam dose can be considered based on clinical response.
diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)	Monitor patients for decreased efficacy of diazepam; increase the diazepam dose if clinically indicated.

The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC)

Drugs with No Observed Interactions with HOLKIRA PAK

Drug interaction studies in patients reveal no clinically significant interaction between HOLKIRA PAK and the following commonly co-prescribed medications. No dose adjustments are required when co-administering these drugs with HOLKIRA PAK: abacavir, acetaminophen, dolutegravir, duloxetine, emtricitabine, escitalopram, lamivudine, metformin, methadone, naloxone, norethindrone, sofosbuvir, sulfamethoxazole, tenofovir disoproxil fumarate, trimethoprim, zolpidem.

Pharmacokinetic Parameters for Clinically Relevant Drug Interactions

Change in pharmacokinetic parameters for drug interaction for drug interactions resulting in contraindications, dose modification or clinical monitoring is presented in **Table 8** and **Table 9**. **Table 8** provides the magnitude of interaction on the concomitant medication. For information regarding clinical recommendations, see **Table 7**.

Table 8. Drug Interactions: Change in Pharmacokinetic Parameters of the Individual Components of HOLKIRA PAK in the Presence of co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
ANTIARRHYTHMICS						
digoxin	0.5 single dose	12	dasabuvir	0.99 (0.92-1.07)	0.97 (0.91-1.02)	0.99 (0.92-1.07)
			ombitasvir	1.03 (0.97-1.10)	1.00 (0.98-1.03)	0.99 (0.96-1.02)
			paritaprevir	0.92 (0.80-1.06)	0.94 (0.81-1.08)	0.92 (0.82-1.02)
			ritonavir	1.01 (0.94, 1.08)	0.98 (0.94, 1.03)	0.96 (0.89, 1.04)
ANTICOAGULANTS						
warfarin	5 single dose	12	dasabuvir	0.97 (0.89-1.06)	0.98 (0.91-1.06)	1.03 (0.94-1.13)
			ombitasvir	0.94 (0.89-1.00)	0.96 (0.93-1.00)	0.98 (0.95-1.02)
			paritaprevir	0.98 (0.82-1.18)	1.07 (0.89-1.27)	0.96 (0.85-1.09)
			ritonavir	0.94 (0.89, 1.00)	0.97 (0.94. 1.00)	1.10 (1.03, 1.17)
ANTICONVULSANTS						
carbamazepine	200 once daily followed by 200 twice daily	12	dasabuvir	0.45 (0.41, 0.50)	0.30 (0.28, 0.33)	NA
			ombitasvir	0.69 (0.61, 0.78)	0.69 (0.64, 0.74)	NA
			paritaprevir	0.34 (0.25, 0.48)	0.30 (0.23, 0.38)	NA
			ritonavir	0.17 (0.12, 0.24)	0.13 (0.09, 0.17)	NA
ANTIFUNGALS						
ketoconazole	400 once daily	12	dasabuvir	1.16 (1.03, 1.32)	1.42 (1.26, 1.59)	NA
			ombitasvir	0.98 (0.90, 1.06)	1.17 (1.11, 1.24)	NA
			paritaprevir	1.37 (1.11, 1.69)	1.98 (1.63, 2.42)	NA
			ritonavir	1.27 (1.04, 1.56)	1.57 (1.36, 1.81)	NA
ANTIHYPERLIPIDEMIC AGENT						
gemfibrozil[a]	600 twice daily	11	dasabuvir	2.01 (1.71, 2.38)	11.25 (9.05, 13.99)	NA
			ombitasvir	NA	NA	NA
			paritaprevir	1.21 (0.94, 1.57)	1.38 (1.18, 1.61)	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	0.84 (0.69, 1.03)	0.90 (0.78, 1.04)	NA
CALCIUM CHANNEL BLOCKERS						
amlodipine	5 single dose	14	dasabuvir	1.05 (0.97, 1.14)	1.01 (0.96, 1.06)	0.95 (0.89, 1.01)
			ombitasvir	1.00 (0.95, 1.06)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
			paritaprevir	0.77 (0.64, 0.94)	0.78 (0.68, 0.88)	0.88 (0.80, 0.95)
			ritonavir	0.96 (0.87, 1.06)	0.93 (0.89, 0.98)	0.95 (0.89, 1.01)
CONTRACEPTIVES						
ethinylestradiol/ norgestimate	0.035/0.25 once daily	7[b]	dasabuvir	0.51 (0.22-1.18)	0.48 (0.23-1.02)	0.53 (0.30- 0.95)
			ombitasvir	1.05 (0.81-1.35)	0.97 (0.81-1.15)	1.00 (0.88- 1.12)
			paritaprevir	0.70 (0.40-1.21)	0.66 (0.42-1.04)	0.87 (0.67-1.14)
			ritonavir	0.80 (0.53, 1.21)	0.71 (0.54, 0.94)	0.79 (0.68, 0.93)
nor-ethindrone (progestin only pill)	0.35 once daily	12	dasabuvir	1.01 (0.90-1.14)	0.96 (0.85-1.09)	0.95 (0.80-1.13)
			ombitasvir	1.00 (0.93-1.08)	0.99 (0.94-1.04)	0.97 (0.90-1.03)
			paritaprevir	1.24 (0.95-1.62)	1.23 (0.96-1.57)	1.43 (1.13-1.80)
			ritonavir	1.01 (0.89, 1.13)	1.08 (0.95, 1.23)	1.27 (1.06, 1.51)
DIURETICS						
furosemide	20 single dose	12	dasabuvir	1.12 (0.96, 1.31)	1.09 (0.96, 1.23)	1.06 (0.98, 1.14)
			ombitasvir	1.14 (1.03, 1.26)	1.07 (1.01, 1.12)	1.12 (1.08, 1.16)
			paritaprevir	0.93 (0.63, 1.36)	0.92 (0.70, 1.21)	1.26 (1.16, 1.38)
			ritonavir	1.10 (0.96, 1.27)	1.04 (0.92, 1.18)	1.07 (0.99, 1.17)
HIV-ANTIVIRAL AGENTS						
atazanavir/ ritonavir[c]	Atazanavir 300 and ritonavir 100 once daily in the evening	11	dasabuvir	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)
			ombitasvir	0.83 (0.72, 0.96)	0.90 (0.78, 1.02)	1.00 (0.89, 1.13)
			paritaprevir	2.19 (1.61, 2.98)	3.16 (2.40, 4.17)	11.95 (8.94, 15.98)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
			ritonavir	1.60 (1.38, 1.86)	3.18 (2.74, 3.69)	24.65 (18.64, 32.60)
darunavir[d]	800 once daily	9	dasabuvir	1.10 (0.88, 1.37)	0.94 (0.78, 1.14)	0.90 (0.76, 1.06)
			ombitasvir	0.86 (0.77, 0.95)	0.86 (0.79, 0.94)	0.87 (0.82, 0.92)
			paritaprevir	1.54 (1.14, 2.09)	1.29 (1.04, 1.61)	1.30 (1.09, 1.54)
			ritonavir	0.84 (0.72, 0.98)	0.85 (0.78, 0.93)	1.07 (0.93, 1.23)
darunavir/ ritonavir[e]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	7	dasabuvir	0.84 (0.67, 1.05)	0.73 (0.62, 0.86)	0.54 (0.49, 0.61)
			ombitasvir	0.76 (0.65, 0.88)	0.73 (0.66, 0.80)	0.73 (0.64, 0.83)
			paritaprevir	0.70 (0.43, 1.12)	0.59 (0.44, 0.79)	0.83 (0.69, 1.01)
			ritonavir	1.61 (1.30, 2.00)	1.28 (1.12, 1.45)	0.88 (0.79, 0.99)
darunavir/ ritonavir[f]	Darunavir 800 and ritonavir 100 once daily in the evening	12	dasabuvir	0.75 (0.64, 0.88)	0.72 (0.64, 0.82)	0.65 (0.58, 0.72)
			ombitasvir	0.87 (0.82, 0.93)	0.87 (0.81, 0.93)	0.87 (0.80, 0.95)
			paritaprevir	0.70 (0.50, 0.99)	0.81 (0.60, 1.09)	1.59 (1.23, 2.05)
			ritonavir	1.19 (1.06, 1.33)	1.70 (1.54, 1.88)	14.15 (11.66, 17.18)
lopinavir/ ritonavir	400/100 twice daily	6	dasabuvir	0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
			ombitasvir	1.14 (1.01, 1.28)	1.17 (1.07, 1.28)	1.24 (1.14, 1.34)
			paritaprevir	2.04 (1.30, 3.20)	2.17 (1.63, 2.89)	2.36 (1.00, 5.55)
			ritonavir	1.55 (1.16, 2.09)	2.05 (1.49, 2.81)	5.25 (3.33, 8.28)
lopinavir/ ritonavir[g]	800/200 once daily	12	dasabuvir	0.56 (0.47, 0.66)	0.54 (0.46, 0.65)	0.47 (0.39, 0.58)
			ombitasvir	0.87 (0.83, 0.92)	0.97 (0.94, 1.02)	1.11 (1.06, 1.16)
			paritaprevir	0.99 (0.79, 1.25)	1.87 (1.40, 2.52)	8.23 (5.18, 13.07)
			ritonavir	1.57 (1.34, 1.83)	2.62 (2.32, 2.97)	19.46 (15.93, 23.77)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
rilpivirine	25 once daily (morning)[g]	10	dasabuvir	1.18 (1.02, 1.37)	1.17 (0.99, 1.38)	1.10 (0.89, 1.37)
			ombitasvir	1.11 (1.02, 1.20)	1.09 (1.04, 1.14)	1.05 (1.01, 1.08)
			paritaprevir	1.30 (0.94, 1.81)	1.23 (0.93, 1.64)	0.95 (0.84, 1.07)
			ritonavir	1.10 (0.98, 1.24)	1.08 (0.93, 1.27)	0.97 (0.91, 1.04)
HMG CoA REDUCTASE INHIBITORS						
pravastatin	10 once daily	12	dasabuvir	1.00 (0.87, 1.14)	0.96 (0.85, 1.09)	1.03 (0.91, 1.15)
			ombitasvir	0.95 (0.89-1.02)	0.89 (0.83-0.95)	0.94 (0.89-0.99)
			paritaprevir	0.96 (0.69, 1.32)	1.13 (0.92, 1.38)	1.39 (1.21, 1.59)
			ritonavir	0.89 (0.73, 1.09)	0.95 (0.86, 1.05)	1.08 (0.98, 1.19)
rosuvastatin	5 once daily	11	dasabuvir	1.07 (0.92, 1.24)	1.08 (0.92, 1.26)	1.15 (1.05, 1.25)
			ombitasvir	0.92 (0.82, 1.04)	0.89 (0.83, 0.95)	0.88 (0.83, 0.94)
			paritaprevir	1.59 (1.13, 2.23)	1.52 (1.23, 1.90)	1.43 (1.22, 1.68)
			ritonavir	0.98 (0.84, 1.15)	1.02 (0.93, 1.12)	1.00 (0.90, 1.12)
IMMUNOSUPPRESSANTS						
cyclosporine	30 single dose[i]	10	dasabuvir	0.66 (0.58, 0.75)	0.70 (0.65, 0.76)	0.76 (0.71, 0.82)
			ombitasvir	0.99 (0.92, 1.07)	1.08 (1.05, 1.11)	1.15 (1.08, 1.23)
			paritaprevir	1.44 (1.16, 1.78)	1.72 (1.49, 1.99)	1.85 (1.58, 2.18)
			ritonavir	0.90 (0.78, 1.04)	1.11 (1.04, 1.19)	1.49 (1.28, 1.74)
tacrolimus	2 single dose	12	dasabuvir	0.85 (0.73, 0.98)	0.90 (0.80, 1.02)	1.01 (0.91, 1.11)
			ombitasvir	0.93 (0.88, 0.99)	0.94 (0.89, 0.98)	0.94 (0.91, 0.96)
			paritaprevir	0.57 (0.42, 0.78)	0.66 (0.54, 0.81)	0.73 (0.66, 0.80)
			ritonavir	0.76 (0.63, 0.91)	0.87 (0.79, 0.97)	1.03 (0.89, 1.19)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
MUSCLE RELAXANTS						
carisoprodol	250 single dose	14	dasabuvir	0.96 (0.91, 1.01)	1.02 (0.97, 1.07)	1.00 (0.92, 1.10)
			ombitasvir	0.98 (0.92, 1.04)	0.95 (0.92, 0.97)	0.96 (0.92, 0.99)
			paritaprevir	0.88 (0.75, 1.03)	0.96 (0.85, 1.08)	1.14 (1.02, 1.27)
			ritonavir	0.94 (0.87, 1.02)	0.94 (0.88, 0.99)	0.95 (0.89, 1.03)
cyclobenzaprine	5 single dose	14	dasabuvir	0.98 (0.90, 1.07)	1.01 (0.96, 1.06)	1.13 (1.07, 1.18)
			ombitasvir	0.98 (0.92, 1.04)	1.00 (0.97, 1.03)	1.01 (0.98, 1.04)
			paritaprevir	1.14 (0.99, 1.32)	1.13 (1.00, 1.28)	1.13 (1.01, 1.25)
			ritonavir	0.93 (0.87, 0.99)	1.00 (0.95, 1.06)	1.13 (1.05, 1.21)
NARCOTIC ANALGESICS						
hydrocodone/ acetaminophen	5/300 single dose	15	dasabuvir	1.13 (1.01, 1.26)	1.12 (1.05, 1.19)	1.16 (1.08, 1.25)
			ombitasvir	1.01 (0.93, 1.10)	0.97 (0.93, 1.02)	0.93 (0.90, 0.97)
			paritaprevir	1.01 (0.80, 1.27)	1.03 (0.89, 1.18)	1.10 (0.97, 1.26)
			ritonavir	1.01 (0.90, 1.13)	1.03 (0.96, 1.09)	1.01 (0.93, 1.10)
PROTON PUMP INHIBITORS						
omeprazole	40 once daily	11	dasabuvir	1.13 (1.03, 1.25)	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)
			ombitasvir	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.04 (0.98, 1.11)
			paritaprevir	1.19 (1.04, 1.36)	1.18 (1.03, 1.37)	0.92 (0.76, 1.12)
			ritonavir	1.04 (0.96, 1.12)	1.02 (0.97, 1.08)	0.97 (0.89, 1.05)

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
SEDATIVES/HYPNOTICS						
alprazolam	0.5 single dose	12	dasabuvir	0.93 (0.83, 1.04)	0.98 (0.87, 1.11)	1.00 (0.87, 1.15)
			ombitasvir	0.98 (0.93, 1.04)	1.00 (0.96, 1.04)	0.98 (0.93, 1.04)
			paritaprevir	0.91 (0.64, 1.31)	0.96 (0.73, 1.27)	1.12 (1.02, 1.23)
			ritonavir	0.92 (0.84, 1.02)	0.96 (0.89, 1.03)	1.01 (0.94, 1.09)

a. Study was conducted with paritaprevir, ritonavir and dasabuvir.

b. N = 3 for dasabuvir

c. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of the components of HOLKIRA PAK.

d. Darunavir administered with the components of HOLKIRA PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.

e. Darunavir administered with the components of HOLKIRA PAK in the morning and with 100 mg ritonavir in the evening was compared to darunavir administered with 100 mg ritonavir in the morning and evening.

f. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after the morning dose of the components of HOLKIRA PAK compared to darunavir administered with 100 mg ritonavir in the evening.

g. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of the components of HOLKIRA PAK.

h. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.

i. 30 mg cyclosporine was administered with the components of HOLKIRA PAK in the test arm and 100 mg cyclosporine was administered in the reference arm without the components of HOLKIRA PAK.

NA: not available/not applicable; DAA: Direct-acting antiviral agent; CI: Confidence interval

Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures). Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg.

Dasabuvir was dosed twice daily and ombitasvir, paritaprevir and ritonavir were dosed once daily in all the above studies except studies with gemfibrozil, ketoconazole and carbamazepine that used single doses.

Table 9 summarizes the effects of HOLKIRA PAK on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see **Table 7**.

Table 9. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Components of HOLKIRA PAK

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
alprazolam	0.5	1 day	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
amlodipine	5	1 day	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
buprenorphine	Buprenorphine: 4 to 24 once daily and Naloxone 1 to 6 once daily	14 days	10	2.18 (1.78, 2.68)[c]	2.07 (1.78, 2.40)[c]	3.12 (2.29, 4.27)[c]
naloxone				1.18 (0.81, 1.73)	1.28 (0.92, 1.79)[c]	NA
carisoprodol	250	1 day	14	0.54 (0.47, 0.63)	0.62 (0.55, 0.70)	NA
carisoprodol's metabolite, mepobramate				1.17 (1.10, 1.25)	1.09 (1.03, 1.16)	NA
cyclobenzaprine	5	1 day	14	0.68 (0.61, 0.75)	0.60 (0.53, 0.68)	NA
cyclobenzaprine's metabolite norcyclobenzaprine				1.03 (0.87, 1.23)	0.74 (0.64, 0.85)	NA
cyclosporine	30[h]	1 day	10	1.01 (0.85, 1.20)	5.69 (4.67, 6.93)	15.80 (13.81, 18.09)[a, b]
everolimus	0.75	1 day	12	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)[g]
darunavir	800 once daily	14 days	8	0.92 (0.87, 0.98)[d]	0.76 (0.71, 0.82)[d]	0.52 (0.47, 0.58)[d]
darunavir/ ritonavir[e]	Darunavir 800 and ritonavir 100 once daily in the evening	14 days	10	0.79 (0.70, 0.90)[d]	1.34 (1.25, 1.43)[d]	0.54 (0.48, 0.62)[d]
darunavir/ ritonavir[d]	Darunavir 600 twice daily and ritonavir 100 once daily in the evening	14 days	7	0.87 (0.79, 0.96)[b]	0.80 (0.74, 0.86)[b]	0.57 (0.48, 0.67)[b]

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
diazepam	2	1 day	13	1.18 (1.07, 1.30)	0.78 (0.73, 0.82)	NA
diazepam's metabolite nordiazepam				1.10 (1.03, 1.19)	0.56 (0.45, 0.70)	NA
digoxin	0.5	1 day	12	1.15 (1.04,1.27)	1.16 (1.09,1.23)	1.01 (0.97,1.05)
ethinylestradiol	0.035/0.25 once daily	12 days	9	1.16 (0.90,1.50)	1.06 (0.96,1.17)	1.12 (0.94,1.33)
norgestimate				2.26 (1.91,2.67)	2.54 (2.09,3.09)	2.93 (2.39,3.57)
norgestimate metabolites: norgestrel and norelgestromin				2.01 (1.77,2.29)	2.60 (2.30,2.95)	3.11 (2.51,3.85)
furosemide	20	1 day	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
hydrocodone	5	1 day	15	1.27 (1.14, 1.40)	1.90 (1.72, 2.10)	NA
ketoconazole	400	1 day	12	1.15 (1.09, 1.21)	2.17 (2.05, 2.29)	NA
lopinavir/ ritonavir	400/100 twice daily	14 days	6	0.87 (0.76, 0.99)[d]	0.94 (0.81, 1.10)[d]	1.15 (0.93, 1.42)[d]
lopinavir/ ritonavir	800/200 once daily	14 days	12	0.86 (0.80, 0.93)[d]	0.94 (0.87, 1.01)[d]	3.18 (2.49, 4.06)[d]
omeprazole	40	1 day	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
pravastatin	10	14 days	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
rilpivirine	25 (morning)	14 days	20	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
	25 (evening)	14 days	20	2.16 (1.79, 2.61)	2.50 (2.05, 3.06)	2.87 (2.28, 3.62)
	25 (night: 4 hrs after dinner)	14 days	20	3.00 (2.50, 3.59)	3.43 (3.03, 3.89)	3.73 (3.16, 4.40)
rosuvastatin	5	14 days	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without Components of HOLKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
sirolimus	0.5[e]	1 day	11	6.40 (5.34, 7.68)[c]	37.99 (31.5, 45.8)[c]	19.55 (16.7, 22.9)[c, b]
tacrolimus	2	1 day	12	3.99 (3.21, 4.97)	57.13 (45.5, 71.7)	16.56 (12.97, 21.16)[a, b]
R-warfarin	5	1 day	12	1.05 (0.95,1.17)	0.88 (0.81,0.95)	0.94 (0.84,1.05)
S-warfarin				0.96 (0.85,1.08)	0.88 (0.81,0.96)	0.95 (0.88,1.02)

NA: Not available

a. Dose normalized parameters reported.

b. C_{24}: concentration at 24 hours following single dose of cyclosporine, digoxin, sirolimus or tacrolimus.

c. Atazanavir or darunavir or lopinavir parameters are reported.

d. Darunavir administered with HOLKIRA™ PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.

e. 0.5 mg sirolimus was administered with ombitasvir/paritaprevir/ritonavir plus dasabuvir in the test arm and 2 mg sirolimus was administered in the reference arm without ombitasvir/paritaprevir/ritonavir plus dasabuvir.

f. C_{12}: concentration at 12 hours following single dose of everolimus.

g. 30 mg cyclosporine was administered with ombitasvir/paritaprevir/ritonavir plus dasabuvir in the test arm and 100 mg cyclosporine was administered in the reference arm without ombitasvir/paritaprevir/ritonavir plus dasabuvir.

Drug-Food Interactions

Food increased the exposure (AUC) of paritaprevir, ombitasvir, ritonavir, and dasabuvir by up to 211%, 82%, 49%, and 30% respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal). To maximize absorption, HOLKIRA PAK should be taken with food without regard to fat or calorie content (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions

Co-administration of St. John's wort *(Hypericum perforatum)*, a potent hepatic and intestinal CYP3A4 and/or P-gp inducer, may decrease HOLKIRA PAK plasma concentrations, which may result in loss of therapeutic effect.

St. John's wort *(Hypericum perforatum)* is contraindicated with HOLKIRA PAK (see **CONTRAINDICATIONS**).

Drug-Laboratory Interactions

Interactions of HOLKIRA PAK with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is ombitasvir/paritaprevir/ritonavir fixed dose combination tablets copackaged with dasabuvir tablets. Ombitasvir/paritaprevir/ritonavir tablets must be administered with dasabuvir tablets.

- HOLKIRA PAK is used in combination with ribavirin in patients with genotype 1a infection. HOLKIRA PAK is used without ribavirin in patients with genotype 1b infection (see **Table 10**).

- Prior to initiation of therapy, assess for laboratory and clinical evidence of hepatic decompensation (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

- Prior to initiation of therapy, HBV screening should be performed in all patients to decrease the risk of HBV reactivation in patients co-infected with HBV.

Recommended Dose and Dosage Adjustment

The recommended oral dose of HOLKIRA PAK is two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening). HOLKIRA PAK is used in combination with ribavirin in certain patient populations (see **Table 10**).

As a fixed dose combination formulation, no dosage adjustments for HOLKIRA PAK are possible.

HOLKIRA PAK tablets should be swallowed whole, with water if required, and not chewed, broken, or crushed. To maximize absorption, 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 10 shows the recommended treatment regimen and duration based on patient population.

Table 10. Treatment Regimen and Duration by Patient Population

Patient Population	HCV Genotype and Subtype	Treatment	Duration
HCV mono-infected subjects **Or** **HCV patients co-infected with HIV**	**Genotype 1a, without cirrhosis or with compensated cirrhosis**	HOLKIRA PAK + ribavirin	12 weeks
	Genotype 1b, without cirrhosis or with compensated cirrhosis	HOLKIRA PAK	12 weeks
Liver transplant recipients: Only patients with normal hepatic function and Metavir fibrosis score ≤ 2	**HCV Genotype 1 regardless of the subtype 1a or 1b**	HOLKIRA PAK + ribavirin	24 weeks
HCV genotype 1a with cirrhosis and with previous null response to pegylated interferon (pegIFN) and ribavirin	**Genotype 1a**	HOLKIRA PAK + ribavirin	24 weeks

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

For specific dosage instructions for ribavirin, including dose modification, refer to the ribavirin Product Monograph.

HOLKIRA PAK should be taken as directed for the prescribed duration, without interruption or dose modification. If HOLKIRA PAK is used in combination with ribavirin, ribavirin should be administered for the same duration as HOLKIRA PAK.

Special Populations

Pediatrics (< 18 years of age)

Safety and effectiveness of HOLKIRA PAK in children less than 18 years of age have not been established.

Geriatrics (≥ 65 years of age)

No dose adjustment of HOLKIRA PAK is warranted in geriatric patients (see **INDICATIONS AND CLINICAL USE**; **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

HCV-HIV-1 Co-infection

For patients with HCV-HIV-1 co-infection, follow the dosage recommendations in **Table 10**. Refer to **DRUG INTERACTIONS** for dosage recommendations for concomitant HIV-1 antiviral drugs.

Liver Transplant Recipients

HOLKIRA PAK in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. Lower ribavirin dose at initiation may be appropriate. In the post liver transplant study, ribavirin dosing was individualized and most patients received 600 to 800 mg per day (see **CLINICAL TRIALS**). For dosing recommendations with calcineurin inhibitors refer to **DRUG INTERACTIONS**.

Hepatic Impairment

No dose adjustment of HOLKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). HOLKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**; **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Hepatic Insufficiency**).

Renal Impairment

No dose adjustment of HOLKIRA PAK is required in patients with mild, moderate or severe renal impairment (see **WARNINGS AND PRECAUTIONS**, **Renal and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**)

Missed Dose

Patients should be informed that in case a dose of ombitasvir/paritaprevir/ritonavir is missed, the prescribed dose can be taken within 12 hours of the scheduled time for the dose that was missed.

In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours of the scheduled time for the dose that was missed.

If more than 12 hours has passed since ombitasvir/paritaprevir/ritonavir is usually taken or more than 6 hours has passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

OVERDOSAGE

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

The highest documented single dose administered to healthy subjects was 350 mg for ombitasvir, 400 mg for paritaprevir (with 100 mg ritonavir), 200 mg for ritonavir (with 100 mg paritaprevir), and 2000 mg for dasabuvir. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately. ECG monitoring is recommended.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) combines three direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action, and non-overlapping resistance profiles, to target HCV at multiple steps in the viral lifecycle (see **MICROBIOLOGY**, **Mechanism of Action**).

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication. Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. The stopping of viral replication leads to a rapid decline of HCV viral load and clearing of HCV levels in the body.

Ritonavir is not active against HCV. Ritonavir is a pharmacokinetic enhancer that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

Pharmacodynamics

Effects on Electrocardiogram

In a double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects, a single dose of paritaprevir/ritonavir/ombitasvir 200/150/25 mg co-administered with dasabuvir 250 mg resulted in statistically significant QTcF prolongation from 3 to 8 hours post-dosing, with a maximum mean difference from placebo of 3.6 msec (90% CI 1.8, 5.4) at 5 hours. A single dose of paritaprevir/ritonavir/ombitasvir 350/150/50 mg co-administered with dasabuvir 500 mg (providing concentrations approximately 1.8, 6 and 2 times the therapeutic concentrations of ombitasvir, paritaprevir and dasabuvir) resulted in statistically significant QTcF prolongation from 3 to 8 hours post-dosing, with a maximum mean difference from placebo of 5.9 msec (90% CI 4.1, 7.7) at 5 hours. These combination treatments had no noteworthy effect on the QRS duration, the PR interval, or heart rate.

Pharmacokinetics

The pharmacokinetic properties of the combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. **Table 11** shows mean C_{max} and AUC of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy subjects.

Table 11. Geometric Mean C_{max}, C_{trough}, AUC of Multiple Doses of Ombitasvir/Paritaprevir/Ritonavir 25/150/100 mg Once Daily with Dasabuvir 250 mg Twice Daily with Food in HCV-Infected Patients and Healthy Subjects

Compound/Population	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC (ng*hr/mL)
HCV-Infected Patients[a]			
Ombitasvir	68	24	1000
Paritaprevir	262	22	2220
Dasabuvir	667	74	3240
Ritonavir	682	35	6180
Healthy Subjects[b]			
Ombitasvir	127	29	1420
Paritaprevir	1470	20	6990
Dasabuvir	1030	269	6840
Ritonavir	1600	33	9470

a. median values

b. geometric mean values

Absorption

Ombitasvir/paritaprevir/ritonavir and dasabuvir were absorbed after oral administration with mean T_{max} of approximately 4 to 5 hours. While ombitasvir and dasabuvir exposures increased in a dose proportional manner, paritaprevir and ritonavir exposures increased in a more than dose proportional manner. Accumulation is minimal for ombitasvir and dasabuvir and approximately 1.5- to 2-fold for ritonavir and paritaprevir. Pharmacokinetic steady state for the combination is achieved after approximately 12 days of dosing.

The absolute bioavailability of ombitasvir and paritaprevir when administered with ritonavir as 25/150/100 mg ombitasvir/paritaprevir/ritonavir was approximately 48% and 53%, respectively. The absolute bioavailability of dasabuvir when administered alone is estimated to be approximately 70%.

Effects of Food on Oral Absorption

Food increased the exposure (AUC) of ombitasvir, paritaprevir, ritonavir, and dasabuvir by up to 82, 211, 49, and 30% respectively relative to the fasting state. The increase in exposure was similar regardless of meal type (e.g., high-fat versus moderate-fat) or calorie content (approximately 600 Kcal versus approximately 1000 Kcal).

Distribution

Ombitasvir, paritaprevir, ritonavir and dasabuvir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood to plasma concentration ratios in humans were 0.49, 0.7, 0.6, and 0.7 for ombitasvir, paritaprevir, ritonavir and dasabuvir, indicating that preferential distribution in the plasma compartment of whole blood.

Ombitasvir

Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 mcg per mL.

Paritaprevir

Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 mcg per mL.

Ritonavir

Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 mcg per mL.

Dasabuvir

Dasabuvir was greater than 99.5% bound to human plasma proteins over a concentration range of 0.15 to 5 mcg per mL.

In animals, paritaprevir liver levels are significantly higher than plasma levels (e.g. liver: plasma ratio of greater than 300:1 in mouse). *In vitro* data indicate that paritaprevir is a substrate for the human hepatic uptake transporters, OATP1B1 and OATP1B3.

Metabolism

Ombitasvir

Ombitasvir is metabolized via amide hydrolysis followed by oxidative metabolism. Following a 25 mg single dose of ^{14}C-ombitasvir given alone, unchanged parent drug accounted for 8.9% of total radioactivity in human plasma; a total of 13 metabolites were identified in human plasma. These metabolites are not expected to have antiviral activity or off-target pharmacologic activity.

Paritaprevir

Paritaprevir is metabolized predominantly by CYP3A4 and to a lesser extent CYP3A5. Following administration of a single 200/100 mg oral dose of ^{14}C-paritaprevir/ritonavir to humans, the parent drug was the major circulating component accounting for approximately 90% of the plasma radioactivity. At least 5 minor metabolites of paritaprevir have been identified in circulation that accounted for approximately 10% of plasma radioactivity. These metabolites are not expected to have antiviral activity.

Dasabuvir

Dasabuvir is predominantly metabolized by CYP2C8 and to a lesser extent by CYP3A. Following a 400 mg ^{14}C-dasabuvir dose in humans, unchanged dasabuvir was the major component (approximately 60%) of drug related radioactivity in plasma; seven metabolites were identified in plasma. The most abundant plasma metabolite was M1, which represented 21% of drug-related radioactivity (AUC) in circulation and has similar activity (after correction for plasma protein binding) as the parent drug against genotype 1 *in vitro*.

Ritonavir

Ritonavir is predominantly metabolized by CYP3A and to a lesser extent, by CYP2D6. Nearly the entire plasma radioactivity after a single 600 mg dose of ^{14}C-ritonavir oral solution in humans was attributed to unchanged ritonavir.

Excretion

Ombitasvir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of ombitasvir was approximately 21 to 25 hours. Following a 25 mg ^{14}C-ombitasvir dose, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine. Unchanged ombitasvir accounted for 87.8% of the radioactivity in the feces and 0.03% in the urine.

Paritaprevir

Following dosing of ombitasvir/paritaprevir/ritonavir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C-paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in feces with limited radioactivity (8.8%) in urine. Unchanged paritaprevir accounted for 1.1% of the radioactivity in the feces and 0.05% in the urine. Unchanged parent drug and M29, the product of fecal hydrolysis, accounted for 87.8% of total radioactivity recovered in feces, indicating that biliary excretion of parent drug is a major elimination pathway for paritaprevir.

Dasabuvir

Following dosing of dasabuvir with ombitasvir/paritaprevir/ritonavir, mean plasma half-life of dasabuvir was approximately 5.5 to 6 hours. Following a 400 mg ^{14}C-dasabuvir dose, approximately 94.4% of the radioactivity was recovered in feces with limited radioactivity (approximately 2%) in urine. Unchanged dasabuvir accounted for 26% of the radioactivity in the feces and 0.03% in the urine.

Ritonavir

Following dosing of paritaprevir/ritonavir/ombitasvir, mean plasma half-life of ritonavir was approximately 4 hours. Following a 600 mg dose of ^{14}C-ritonavir oral solution, 86.4% of the radioactivity was recovered in the feces and 11.3% of the dose was excreted in the urine.

Special Populations and Conditions

Pediatrics

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

Geriatrics (> 65 years of age)

Population pharmacokinetic analysis of data from Phase 3 clinical studies with HOLKIRA PAK showed that a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would result in approximately 10% change in ombitasvir exposures, ≤ 20% change in paritaprevir exposures and < 10% change in dasabuvir exposures. Age was not a significant predictor for ritonavir exposures. There is no pharmacokinetic information in patients > 75 years. Phase 3 studies of HOLKIRA PAK included 174 patients aged 65 and over. The response rates observed for patients ≥ 65 years of age (97%) were similar to those of patients < 65 years of age (96%), across treatment groups (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics (> 65 years of age)**.

Gender

Population pharmacokinetic analysis of data from Phase 3 clinical studies with HOLKIRA PAK showed that female patients would have approximately 55% higher ombitasvir exposures, 100% higher paritaprevir exposures, 15% higher ritonavir exposures and 14 to 30% higher dasabuvir exposures than male patients. The relationship between gender and HOLKIRA PAK exposures was not considered clinically relevant as high response rates (SVR > 90%) were achieved in male and female patients across the Phase 3 studies.

Race

Based on population pharmacokinetic analyses, exposures of ombitasvir, paritaprevir, dasabuvir and ritonavir were not significantly different in patients of Black race compared to patients of other races. Population pharmacokinetic analysis of data from Phase 3 clinical studies with

HOLKIRA PAK showed that Asian patients had 18 to 21% higher ombitasvir exposures, 37 to 39% higher paritaprevir exposures and 29 to 39% higher dasabuvir exposures than non-Asian patients. The ritonavir exposures were comparable between Asians and non-Asians. These differences in exposures were not clinically significant.

Hepatic Insufficiency

The single dose pharmacokinetics of the combination of paritaprevir 200 mg, ritonavir 100 mg, ombitasvir 25 mg, and dasabuvir 400 mg were evaluated in healthy subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

In patients with mild hepatic impairment, ombitasvir, paritaprevir and ritonavir mean AUC values decreased by 8, 29 and 34%, respectively, and dasabuvir mean AUC values were 17% higher compared to patients with normal hepatic function. No dose adjustment for HOLKIRA PAK is recommended for HCV-infected patients with mild hepatic impairment.

In patients with moderate hepatic impairment, ombitasvir and ritonavir mean AUC values decreased by 30%, paritaprevir mean AUC value increased by 62% and dasabuvir mean AUC values were 16 % lower compared to patients with normal hepatic function. HOLKIRA PAK is contraindicated in patients with moderate hepatic impairment (Child Pugh B) (see **WARNINGS AND PRECAUTIONS** and **CONTRAINDICATIONS**).

In patients with severe hepatic impairment, paritaprevir and dasabuvir mean AUC values increased by 945% and 325%, respectively, ritonavir mean AUC value was 13% higher, and ombitasvir mean AUC value decreased by 54% compared to patients with normal hepatic function. HOLKIRA PAK is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see **CONTRAINDICATIONS**).

Renal Insufficiency

Pharmacokinetics of the combination of ombitasvir 25 mg, paritaprevir 150 mg and ritonavir 100 mg, with or without dasabuvir 400 mg were evaluated in patients with mild (creatinine clearance [CrCl]: 60 to 89 mL per min), moderate (CrCl: 30 to 59 mL per min) and severe (CrCl: 15 to 29 mL per min) renal impairment.

In patients with mild renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 19, 42, and 21% higher, respectively, compared to subjects with normal renal function.

In patients with moderate renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 33, 80, and 37% higher, respectively, compared to subjects with normal renal function.

In patients with severe renal impairment, the mean AUC values of ombitasvir, paritaprevir, ritonavir and dasabuvir were < 1, 45, 114, and 50% higher, respectively, compared to subjects with normal renal function.

Consult the ribavirin Product Monograph for patients with renal impairment.

STORAGE AND STABILITY

Store between 2 and 30°C. Protect from moisture.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

HOLKIRA PAK (ombitasvir/paritaprevir/ritonavir and dasabuvir) is ombitasvir/paritaprevir/ritonavir fixed dose combination tablets co-packaged with dasabuvir tablets.

- Ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with "AV1" on one side.

- Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with "AV2" on one side.

HOLKIRA PAK is dispensed in a convenient monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each daily dose pack contains four tablets: two 12.5/75/50 mg ombitasvir/paritaprevir/ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening.

Listing of Non-Medicinal Ingredients

Each ombitasvir/paritaprevir/ritonavir fixed dose combination tablet contains 12.5 mg ombitasvir /75 mg paritaprevir/50 mg ritonavir with the following non-medicinal ingredients: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, and vitamin E polyethylene glycol succinate. The film-coating ingredients include: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide. The tablets do not contain gluten.

Each dasabuvir immediate release tablet contains 250 mg dasabuvir (as dasabuvir sodium monohydrate) with the following non-medicinal ingredients: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose. The film-coating ingredients include: iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide. The tablets do not contain gluten.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

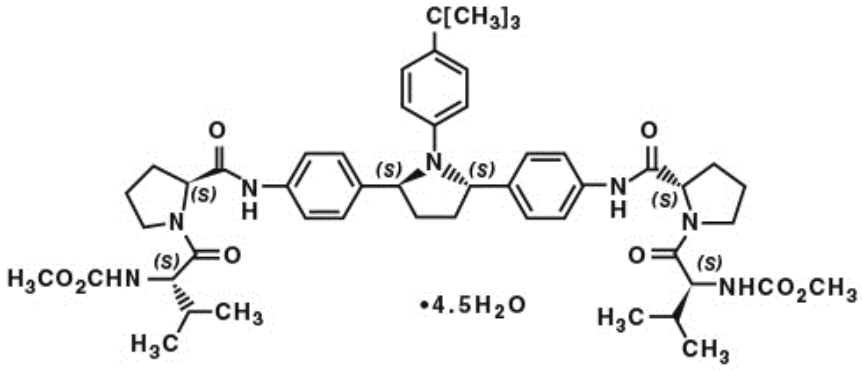
Ombitasvir Hydrate

Common name: ombitasvir

Chemical name: Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate

Molecular formula and molecular mass: $C_{50}H_{67}N_7O_8 \bullet 4.5H_2O$ (hydrate) 975.20 (hydrate)

Structural formula:



Physicochemical properties:

Appearance: Ombitasvir Hydrate is a white to light yellow to light pink powder.

Solubility: Ombitasvir Hydrate is practically insoluble in aqueous buffers but is soluble in ethanol.

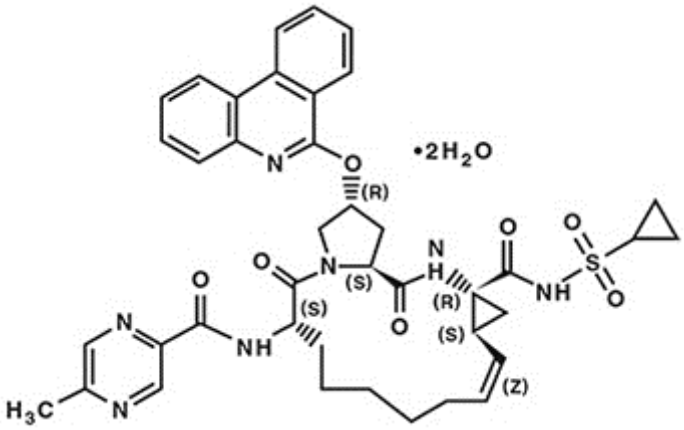
Paritaprevir Hydrate

Common name: paritaprevir

Chemical name: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate

Molecular formula and molecular mass: $C_{40}H_{43}N_7O_7S \bullet 2H_2O$ (dihydrate) 801.91 (dihydrate)

Structural formula:

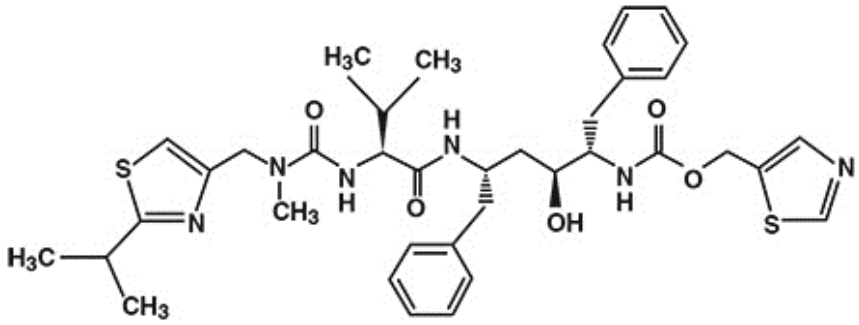


Physicochemical properties:

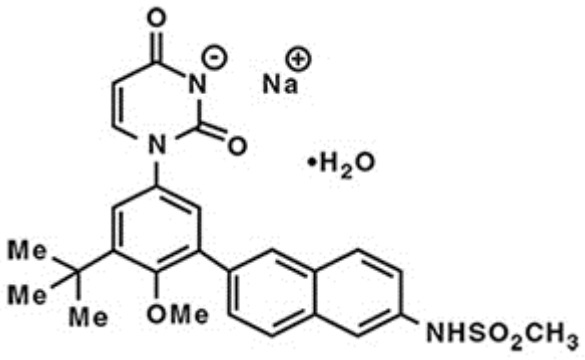
Appearance: Paritaprevir Hydrate is a white to off white powder.

Solubility: Paritaprevir Hydrate has very low water solubility.

Ritonavir

Proper name:	ritonavir
Chemical name:	[5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester
Molecular formula and molecular mass:	$C_{37}H_{48}N_6O_5S_2$ 720.95
Structural formula:	
Physicochemical properties:	
Appearance	Ritonavir is a white to off white to light tan powder.
Solubility	Ritonavir is insoluble in water and freely soluble in methanol and ethanol.

Dasabuvir

Common name:	dasabuvir sodium monohydrate	
Chemical name:	Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)	
Molecular formula and molecular mass:	$C_{26}H_{26}N_3O_5S•Na•H_2O$ (monosodium, monohydrate)	533.57 (monosodium, monohydrate)
	$C_{26}H_{27}N_3O_5S$ (free acid, anhydrate)	493.57 (free acid, anhydrate)
Structural formula:		

Physicochemical properties:

Appearance	Dasabuvir is white to pale yellow to pink powder.
Solubility	Dasabuvir is slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol.

CLINICAL TRIALS

Trial Design

The efficacy and safety of HOLKIRA PAK was evaluated in seven Phase 3 clinical trials, including two trials exclusively in patients with cirrhosis (Child-Pugh A), in over 2,300 patients with genotype 1 chronic hepatitis C infection, as summarized in **Table 12**. HOLKIRA PAK was also evaluated in patients with HCV GT1 co-infected with HIV-1 and in HCV GT1-infected liver transplant recipients.

Table 12. Summary of Clinical Trial Designs in Treatment of Genotype 1 Chronic Hepatitis C Infection

Study #	Number of Patients 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: 1,000 or 1,200 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: 1,000 to 1,200 mg or placebo QD (divided BID); Oral 12 weeks
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: 1,000 to 1,200 mg or placebo QD (divided BID) Oral 12 weeks

Study #	Number of Patients Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
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: 1,000 or 1,200 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: 1,000 or 1,200 mg QD (divided BID) Oral 12 weeks
Treatment-Naïve and Treatment-Experienced[d], 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: 1,000 to 1,200 mg or placebo QD (divided BID) Oral 12 or 24 weeks
TURQUOISE-III (M14-490)	60	GT1b	Open-label	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; Oral 12 weeks
Patients with HCV GT1 Infection-HIV-1 Co-infection				
TURQUOISE-I (M14-004)	63	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: 1,000 to 1,200 mg QD (divided BID) Oral 12 or 24 weeks

Study #	Number of Patients Treated[a]	HCV Genotype (GT)	Trial Design	Dosage, Route of Administration and Duration[b]
Liver Transplant Recipients				
CORAL-I (M12-999)	34	GT1	Open-label	ombitasvir/paritaprevir/ritonavir tablet: 25/150/100 mg QD; dasabuvir tablet: 250 mg BID; RBV tablet[c]: 600 to 800 mg Oral 24 weeks

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

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

b. For patients who received ribavirin, the ribavirin dose was 1000 mg per day for patients weighing less than 75 kg or 1200 mg per day for patients 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 patients were defined as either: prior relapsers (patients 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 SAPPHIRE-II and TURQUOISE-II, received at least 4 weeks of pegIFN/RBV treatment and achieved a < 1 $\log_{10}$ IU/mL reduction in HCV RNA at week 4). TURQUOISE-III also enrolled less well characterized failures of pegIFN/RBV treatment.

e. Ribavirin dosing was managed at the discretion of the investigator with 600 to 800 mg per day being the most frequently selected starting doses.

Sustained virologic response (SVR) (virologic cure) was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12) in the Phase 3 trials. Treatment duration was fixed in each trial and was not guided by patients' HCV RNA levels (no response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL.

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). Patients 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). Patients 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 patients in SAPPHIRE-I, PEARL-III and PEARL-IV are provided in **Table 13**.

Table 13. Demographic and Baseline Characteristics of Treatment-Naïve Patients 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)
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)

Characteristics	SAPPHIRE-I N=631	PEARL-III N=419	PEARL-IV N=305
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 14 shows the SVR12 rates for genotype 1-infected, treatment-naïve patients 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 (100%) 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 14. SVR12 for Genotype 1-Infected Treatment-Naïve Patients 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 (456/473)	99 (209/210)	100 (209/209)	97 (97/100)	90 (185/205)
95% CI	94.7 to 98.1	98.6 to 100	98.2 to 100	93.7 to 100	86.2 to 94.3
HCV genotype 1a	96 (308/322)	N/A	N/A	97 (97/100)	90 (184/204)
HCV genotype 1b	98 (148/151)	99 (209/210)	100 (209/209)	N/A	
Outcome for patients 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 (9/473)	0	0 (0/209)	1 (1/100)	2 (4/205)

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

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

** For patients with GT1a infection without cirrhosis, HOLKIRA PAK with RBV 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 patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

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

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

Table 15 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-naïve patients in studies SAPPHIRE-I, PEARL-III and PEARL-IV.

Table 15. SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Naïve Patients 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)	100 (44/44)	100 (31/31)	97 (61/63)
Non-CC	96 (317/329)	99 (165/166)	100 (165/165)	96 (66/69)	87 (124/142)
Sex					
Female	98 (197/202)	99 (103/104)	100 (123/123)	100 (30/30)	95 (72/76)
Male	96 (259/271)	100 (106/106)	100 (86/86)	96 (67/70)	88 (113/129)
Age					
< 65 years	97 (438/454)	99 (195/196)	100 (190/190)	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 (429/445)	99 (198/199)	100 (197/197)	97 (87/90)	91 (162/178)
Ethnicity					
Hispanic or Latino	93 (25/27)	100 (2/2)	100 (5/5)	90 (9/10)	89 (16/18)
None of the above	97 (431/446)	99 (207/208)	100 (204/204)	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)	100 (41/41)	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 (354/369)	99 (158/159)	100 (148/148)	97 (89/92)	90 (155/172)
Baseline fibrosis stage					
F0-F1	97 (353/363)	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)	100 (20/20)	100 (16/16)	89 (34/38)

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)
History of depression or bipolar disorder					
No	97 (390/403)	99 (189/190)	100 (190/190)	96 (80/83)	89 (142/159)
Yes	94 (66/70)	100 (20/20)	100 (19/19)	100 (17/17)	93 (43/46)

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

** For patients 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, patients 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 patients 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. Patients 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. Patients 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 patients in SAPPHIRE-II and PEARL-II are provided in **Table 16**.

Table 16. Demographic and Baseline Characteristics of Treatment-Experienced Patients 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)

Characteristics	SAPPHIRE-II N=394	PEARL-II N=179
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)
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 17 shows the SVR12 rates for treatment-experienced patients 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 17. SVR12 for Genotype 1-Infected Treatment-Experienced Patients 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)	98 (86/88)	100 (91/91)
95% CI	94.1 to 98.4	94.6 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)	98 (86/88)	100 (91/91)
Prior pegIFN/RBV null responder	95 (56/59)	97 (30/31)	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 patients without SVR12			
On-treatment VF[a]	0	0	0
Relapse[b]	2 (7/293)	0	0
Other[c]	1 (4/297)	2 (2/88)	0

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

* For patients 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 patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.

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

Table 18 presents the SVR12 rates by selected subgroups for genotype 1-infected, treatment-experienced patients in studies SAPPHIRE-II and PEARL-II.

Table 18. SVR12 rates for Selected Subgroups of Genotype 1-infected, Treatment-Experienced Patients 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)	97 (76/78)	100 (84/84)
Sex			
Female	97 (126/130)	98 (44/45)	100 (37/37)
Male	96 (160/167)	98 (42/43)	100 (54/54)
Age			
< 65 years	97 (269/277)	97 (71/73)	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)	98 (83/85)	100 (86/86)
Ethnicity			
Hispanic or Latino	95 (21/22)	50 (1/ 2)	100 (1/ 1)
None of the above	96 (265/275)	99 (85/86)	100 (90/90)
Body mass index			
< 30 kg/m^2	97 (231/238)	97 (69/71)	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)	97 (73/75)	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)	100 (12/12)	100 (13/13)
History of depression or bipolar disorder			
No	96 (220/229)	99 (72/73)	100 (83/83)
Yes	97 (66/68)	93 (14/15)	100 (8/8)

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)

* For patients 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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trials in Patients with Cirrhosis

TURQUOISE-II was a randomized, global multicenter, open-label trial conducted exclusively in 380 genotype 1-infected patients 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.

TURQUOISE-III is a Phase 3b, open-label, single-arm, multicenter study evaluating the efficacy and safety of HOLKIRA PAK administered for 12 weeks in HCV genotype 1b-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis.

Demographic and baseline characteristics for genotype 1-infected patients with cirrhosis in studies TURQUOISE-II and TURQUOISE-III are provided in **Table 19**.

Table 19. Demographic and Baseline Characteristics of Patients with Cirrhosis in TURQUOISE-II and TURQUOISE-III

Characteristics	TURQUOISE-II HOLKIRA PAK + RBV N = 380	TURQUOISE-III HOLKIRA PAK N = 60
Age (years)		
Median (range)	58 (21 – 71)	60.5 (26 – 78)
Gender, n (%)		
Male	267 (70.3)	37 (61.7)
Female	113 (29.7)	23 (38.3)
Race, n (%)		
White	360 (94.7)	52 (86.7)
Black or African American	12 (3.2)	7 (11.7)
Asian	8 (2.1)	0

Characteristics	TURQUOISE-II HOLKIRA PAK + RBV N = 380	TURQUOISE-III HOLKIRA PAK N = 60
Ethnicity		
Hispanic or Latino	45 (11.8)	3 (5.0)
None of the above	335 (88.2)	57 (95.0)
Body mass index		
< 30 kg/m^2	272 (71.6)	43 (71.7)
≥ 30 kg/m^2	108 (28.4)	17 (28.3)
HCV genotype, n (%)		
1a	261 (68.7)	0
1b	119 (31.3)	60 (100)
Baseline HCV RNA		6.57 (0.6)
Mean ± SD (log_{10} IU/mL)	6.47 ± 0.58	5 (8.3)
< 800000 IU/mL, n (%)	53 (13.9)	55 (91.7)
≥ 800000 IU/mL, n (%)	327 (86.1)	
Prior HCV Therapy		
Treatment-Naive	160 (42.1)	27 (45.0)
Treatment-experienced with pegIFN/RBV, n (%)	220 (57.9)	33 (55.0)
Null responder	137 (36.1)	7 (21.2)
Partial responder	31 (8.2)	5 (15.2)
Relapser	52 (13.7)	3 (9.1)
Other pegIFN/RBV failures	N/A	18 (54.5)[+]
IL28B, n (%)		
CC	69 (18.2)	10 (16.7)
CT	237 (62.4)	36 (60.0)
TT	74 (19.5)	14 (23.3)
Baseline platelet count, n (%)		
< 90 $x10^9/L$	56 (14.7)	13 (21.7)
≥ 90 $x10^9/L$	324 (85.3)	47 (78.3)
Baseline albumin, n (%)		
< 35 g/L	43 (11.3)	10 (16.7)
≥ 35 g/L	337 (88.7)	50 (83.3)
History of depression or bipolar disorder, n (%)		
No	286 (75.3)	43 (71.7)
Yes	94 (24.7)	17 (28.3)

N/A = Not Applicable.

[+] Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Study Results

Table 20 shows the SVR12 rates for genotype 1-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV in studies TURQUOISE-II and TURQUOISE-III. All the treatment groups met the primary efficacy endpoint.

Table 20. SVR12 for Genotype 1-Infected Patients with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II and TURQUOISE-III

Treatment Outcome	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK with RBV		HOLKIRA PAK
	12 Weeks*	12 Weeks	12 Weeks
	% (n/N)	% (n/N)	% (n/N)
Overall SVR12	92 (191/208)[d]	97 (166/172)[d]	100 (60/60)
97.5% CI	87.6 to 96.1	93.4 to 99.6	N/A
95% CI	N/A	N/A	94.0 to 100.0
HCV genotype 1a	89 (124/140)	95 (115/121)	N/A
Treatment naïve	92 (59/64)	95 (53/56)	N/A
Prior pegIFN/RBV null responders	80 (40/50)	93 (39/42)**	N/A
Prior pegIFN/RBV partial responders	100 (11/11)	100 (10/10)	N/A
Prior pegIFN/RBV prior relapsers	93 (14/15)	100 (13/13)	N/A
HCV genotype 1b	99 (67/68)	100 (51/51)	100 (60/60)
Treatment naïve	100 (22/22)	100 (18/18)	100 (27/27)
Prior pegIFN/RBV null responders	100 (25/25)	100 (20/20)	100 (7/7)
Prior pegIFN/RBV partial responders	86 (6/7)	100 (3/3)	100 (5/5)
Prior pegIFN/RBV prior relapsers	100 (14/14)	100 (10/10)	100 (3/3)
Other pegIFN/RBV failures	N/A	N/A	100 (18/18)[+]

Treatment Outcome	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK with RBV		HOLKIRA PAK
	12 Weeks*	12 Weeks	12 Weeks
	% (n/N)	% (n/N)	% (n/N)
Outcome for patients without SVR12			
On-treatment VF[a]	<1 (1/208)	2 (3/172)	0
Relapse[b]	6 (12/203)	<1 (1/164)	0
Other[c]	2 (4/208)	1 (2/172)	0

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

* 12 weeks of HOLKIRA PAK with RBV is the recommended regimen for all patients 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.

+ Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

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 patients with HCV RNA < 25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for patients assigned to 12 or 24 weeks of treatment, respectively.

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

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

Table 21 presents the SVR12 rates by selected subgroups for genotype 1-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 21. SVR12 rates for Selected Subgroups of Genotype 1-infected Patients with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV in TURQUOISE-II and TRUQUOISE-III

	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK + RBV		HOLKIRA PAK
	12 Weeks N = 208	24 Weeks N = 172	12 Weeks N = 60
Subgroup	% (n/N)	% (n/N)	% (n/N)
IL28B			
CC	94 (33/35)	97 (33/34)	100 (10/10)
Non-CC	91 (158/173)	96 (133/138)	100 (50/50)
Sex			
Female	94 (58/62)	98 (50/51)	100 (23/23)
Male	91 (133/146)	96 (116/121)	100 (37/37)

	TURQUOISE-II		TURQUOISE-III
	HOLKIRA PAK + RBV		HOLKIRA PAK
	12 Weeks N = 208	24 Weeks N = 172	12 Weeks N = 60
Subgroup	**% (n/N)**	**% (n/N)**	**% (n/N)**
Age			
< 65 years	91 (166/182)	96 (143/149)	100 (45/45)
≥ 65 years	96 (25/26)	100 (23/23)	100 (15/15)
Race			
Black	100 (6/6)	83 (5/6)	100 (7/7)
Nonblack	92 (185/202)	97 (161/166)	100 (53/53)
Ethnicity			
Hispanic or Latino	84 (21/25)	95 (19/20)	100 (3/3)
None of the above	93 (170/183)	97 (147/152)	100 (57/57)
Body mass index			
< 30 kg/m^2	92 (135/146)	98 (123/126)	100 (43/43)
≥ 30 kg/m^2	90 (56/62)	93 (43/46)	100 (17/17)
Baseline HCV RNA			
< 800000 IU/mL	91 (31/34)	89 (17/19)	100 (5/5)
≥ 800000 IU/mL	92 (160/174)	97 (149/153)	100 (55/55)
Baseline platelet count			
< 90 x 10^9/L	83 (25/30)	96 (25/26)	100 (13/13)
≥ 90 x 10^9/L	93 (166/178)	97 (141/146)	100 (47/47)
Baseline albumin			
< 35 g/L	84 (21/25)	89 (16/18)	100 (10/10)
≥ 35 g/L	93 (170/183)	97 (150/154)	100 (50/50)
History of depression or bipolar disorder			
No	91 (143/157)	97 (125/129)	100 (43/43)
Yes	94 (48/51)	95 (41/43)	100 (17/17)

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

Pooled Analyses of Clinical Trials

Durability of Response

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

Pooled Efficacy Analysis

In Phase 3 clinical trials, 1088 patients (including 194 with cirrhosis) received the recommended regimen for their HCV subtype, cirrhosis status and previous treatment. **Table 22** shows SVR rates for these patients. Among patients who received the recommended regimen in Phase 3 clinical trials, 97% achieved SVR (95% with cirrhosis and 97% without cirrhosis), while 0.6% demonstrated virologic breakthrough and 1.5% experienced post-treatment relapse.

Table 22. 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**
	12 weeks	**12 weeks***	**12 weeks**	**12 weeks**
Treatment-naïve	96% (403/420)	92% (61/66)	100% (210/210)	100% (27/27)
Treatment-experienced	96% (166/173)	94% (64/68)*	100% (91/91)	100% (33/33)+
Prior pegIFN/RBV relapser	94% (47/50)	93% (14/15)	100% (33/33)	100% (3/3)
Prior pegIFN/RBV partial responder	100% (36/36)	100% (11/11)	100% (26/26)	100% (5/5)
Prior pegIFN/RBV null responder	95% (83/87)	93% (39/42) (24 weeks)	100% (32/32)	100% (7/7)
Other pegIFN/RBV failures	0	0	0	100 % (18/18)+
TOTAL	96% (569/593)	93% (125/134)*	100% (301/301)	100% (60/60)

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

+ Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Impact of Ribavirin Dose Adjustment on Probability of SVR

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

Clinical Trial in Patients with HCV Genotype 1 Infection-HIV-1 Co-infection (TURQUOISE-I)

In an open-label clinical trial (TURQOISE-I) the safety and efficacy of 12 or 24 weeks of treatment with HOLKIRA PAK and ribavirin was evaluated in 63 patients with genotype 1 chronic hepatitis C co-infected with HIV-1. See **DOSAGE AND ADMINISTRATION** for dosing recommendations in HCV-HIV-1 co-infected patients. Patients were on a stable HIV-1 antiretroviral therapy (ART) regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine.

Treated patients (N = 63) had a median age of 51 years (range: 31 to 69); 24% of patients were Black; 81% of patients had IL28B non-CC genotype; 19% of patients had compensated cirrhosis; 67% of patients were HCV treatment-naïve; 33% of patients had failed prior treatment with pegIFN/RBV; 89% of patients had HCV genotype 1a infection.

Study Results

Table 23 shows the SVR12 rates for patients with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

Table 23. SVR12 for HIV-1 Co-infected Patients in TURQUOISE-I

	Arm A 12 Weeks N = 31	**Arm B 24 Weeks N = 32**
SVR12, n/N (%) 95% CI	29/31 (93.5) 79.3, 98.2	29/32 (90.6) 75.8, 96.8
Outcome of patients not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment virologic failure was defined as confirmed HCV RNA ≥ 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 treatment.

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

c. These virologic failures appear to have resulted from reinfection based on phylogenetic analyses of baseline and virologic failure samples.

d. Other includes patients not achieving SVR12 but not experiencing on-treatment virologic failure or relapse (e.g., missing HCV RNA values in the SVR12 window).

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected patients were consistent with SVR12 rates in the Phase 3 trials of HCV mono-infected patients. Fifty-one of 56 (91.1%) patients with genotype 1a infection and 7 of 7 (100%) patients with genotype 1b infection achieved SVR12. Five of 6 (83.3%) patients with compensated cirrhosis in each arm achieved SVR12.

Clinical Trial in Liver Transplant Recipients (CORAL-I)

The safety and efficacy of HOLKIRA PAK with ribavirin was studied in 34 HCV genotype 1-infected liver transplant recipients who were at least 12 months post transplantation at enrollment. The primary objectives of this study were to assess the safety and the percentage of patients achieving SVR12 following 24 weeks of treatment with HOLKIRA PAK and ribavirin. The initial dose of ribavirin was left to the discretion of the investigator with 600 to 800 mg per day being the most frequently selected dose range at initiation of HOLKIRA PAK and at the end of treatment.

Study Results

Thirty-four patients (29 with HCV genotype 1a infection and 5 with HCV genotype 1b infection) who had not received treatment for HCV infection after transplantation and had a METAVIR fibrosis score of F2 or less were enrolled. Thirty-three out of the 34 patients (97.1%) achieved SVR12 (96.6% in patients with genotype 1a infection and 100% in patients with genotype 1b infection). One patient with HCV genotype 1a infection relapsed post-treatment.

MICROBIOLOGY

Mechanism of Action

HOLKIRA PAK combines three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is essential for viral replication. In replicon cell culture assays, ombitasvir has half maximal effective concentration (EC_{50}) values of 14.1 and 5.0 pM against HCV genotypes 1a and 1b, respectively.

Paritaprevir

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, paritaprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a and 1b NS3/4A protease enzymes with half maximal inhibitory concentration (IC_{50}) values of 0.18 and 0.43 nM, respectively.

Dasabuvir

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. In a biochemical assay, dasabuvir inhibited the polymerase activity of the recombinant HCV genotype 1a and 1b HCV NS5B enzymes with IC_{50} values of 2.8 and 10.7 nM, respectively.

Activity in Cell Culture and/or Biochemical Studies

Ombitasvir

The EC_{50} of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 14.1 and 5 pM, respectively. The activity of ombitasvir was attenuated 11- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of ombitasvir against replicons containing NS5A from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.66 pM (range 0.35 to 0.88 pM; n = 11) and 1.0 pM (range 0.74 to 1.5 pM; n = 11), respectively. Ombitasvir has EC_{50} values of 12, 4.3, 19, 1.7, 0.38, 3.2, and 366 pM against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 4d, 5a, and 6a, respectively.

Paritaprevir

The EC_{50} of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 1.0 and 0.21 nM, respectively. The activity of paritaprevir was attenuated 24- to 27-fold in the presence of 40% human plasma. The mean EC_{50} of paritaprevir against replicons containing NS3 from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.06 nM (range 0.03 to 0.09 nM; n = 9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the 2a-JFH-1 replicon cell line, and EC_{50} values of 19, 0.09, 0.015, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, 4d, and 6a, respectively. In a biochemical assay, paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 2a, 2b, 3a, and 4a with IC_{50} values of 2.4, 6.3, 14.5, and 0.16 nM, respectively. .

Dasabuvir

The EC_{50} of dasabuvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 7.7 and 1.8 nM, respectively. The replicon activity of dasabuvir was attenuated 12- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of dasabuvir against replicons containing NS5B from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2 nM; n = 10), respectively. In biochemical assays, dasabuvir inhibited a panel of genotype 1a and 1b polymerases with a mean IC_{50} value of 4.2 nM (range 2.2 to 10.7 nM; n = 7).

Ritonavir

Ritonavir did not exhibit a direct antiviral effect on the replication of HCV subgenomic replicons, and the presence of ritonavir did not affect the *in vitro* antiviral activity of paritaprevir.

Combination Activity *in vitro*

All two-drug combinations of paritaprevir, ombitasvir, dasabuvir and ribavirin demonstrated additive to synergistic inhibition of HCV genotype 1 replicon at the majority of drug concentrations studied in short term cell culture assays. In long term replicon survival assays, the ability of drug-resistant cells to form colonies in the presence of a single drug or drugs in

combination was evaluated. In pair-wise combinations of paritaprevir, ombitasvir, and dasabuvir at concentrations 10-fold over their respective EC_{50}, colony numbers were reduced by more than 100-fold by two drugs as compared to each drug alone. When all three drugs were combined at concentrations of 5-fold above their respective EC_{50}, no drug-resistant colonies survived.

Resistance in Cell Culture

Resistance to paritaprevir, ombitasvir, or dasabuvir conferred by variants in NS3, NS5A, or NS5B, respectively, selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in the appropriate genotype 1a or 1b replicons.

In genotype 1a, substitutions F43L, R155K, A156T, and D168A/H/V/Y in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1a replicon, the activity of paritaprevir was reduced 20-, 37-, and 17-fold by the F43L, R155K and A156T substitutions, respectively. The activity of paritaprevir was reduced 96-fold by D168V, and 50- to 219-fold by each of the other D168 substitutions. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions V36A/M, V55I, Y56H, Q80K or E357K. Double variants including combinations of V36M, Y56H, or E357K with R155K or with a D168 substitution reduced the activity of paritaprevir by an additional 2- to 3-fold relative to the single R155K or D168 substitution. In genotype 1b, substitutions R155Q, D168H, D168V, and Y56H in combination with D168V in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1b replicon, the activity of paritaprevir was reduced 76- and 159-fold by D168H and D168V, respectively. Y56H alone could not be evaluated due to poor replication capacity, however, the combination of Y56H and D168V reduced the activity of paritaprevir by 2472-fold.

In genotype 1a, substitutions M28T/V, Q30R, H58D, Y93C/H/N, and M28V + Q30R in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1a replicon, the activity of ombitasvir was reduced by 58- and 243-fold against the M28V and H58D substitutions, respectively, and 800- and 1675-fold by the Q30R and Y93C substitutions, respectively. Y93H, Y93N or M28V in combination with Q30R reduced the activity of ombitasvir by more than 40,000-fold. In genotype 1b, substitutions L31F/V, as well as Y93H alone or in combination with L28M, R30Q, L31F/M/V or P58S in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1b replicon, the activity of ombitasvir was reduced by less than 10-fold by variants at amino acid positions 30 and 31. The activity of ombitasvir was reduced by 77-, 284- and 142-fold against the genotype 1b substitutions Y93H, R30Q in combination with Y93H, and L31M in combination with Y93H, respectively. All other double substitutions of Y93H in combination with substitutions at positions 28, 31, or 58 reduced the activity of ombitasvir by more than 400-fold.

In genotype 1a, substitutions C316Y, M414T, Y448H, A553T, G554S, S556G/R, and Y561H in HCV NS5B reduced susceptibility to dasabuvir. In the genotype 1a replicon, the activity of dasabuvir was reduced 21- to 32-fold by the M414T, S556G or Y561H substitutions; 152- to 261-fold by the A553T, G554S or S556R substitutions; and 1472- and 975-fold by the C316Y and Y448H substitutions, respectively. G558R and D559G/N were observed as treatment-emergent substitutions but the activity of dasabuvir against these variants could not be evaluated due to poor replication capacity. In genotype 1b, substitutions C316N, C316Y,

M414T, Y448H, and S556G in HCV NS5B reduced susceptibility to dasabuvir. The activity of dasabuvir was reduced by 5- and 11-fold by C316N and S556G, respectively; 46-fold by M414T or Y448H; and 1569-fold by the C316Y substitutions in the genotype 1b replicon. Dasabuvir retained full activity against replicons containing substitutions S282T in the nucleoside binding site, M423T in the lower thumb site, and P495A/S, P496S or V499A in the upper thumb site.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

A pooled analysis of patients in the Phase 2b and 3 clinical trials treated with paritaprevir, ombitasvir, and dasabuvir with or without ribavirin was conducted to explore the association between the baseline NS3/4A, NS5A or NS5B substitutions/polymorphisms and treatment outcome in recommended regimens.

In the greater than 500 genotype 1a baseline samples in this analysis, the most frequently observed resistance-associated variants were M28V (7.4%) in NS5A and S556G (2.9%) in NS5B. Q80K, although a highly prevalent polymorphism in NS3 (41.2% of samples), confers minimal resistance to paritaprevir. Resistance-associated variants at amino acid positions R155 and D168 in NS3 were rarely observed (less than 1%) at baseline. In the greater than 200 genotype 1b baseline samples in this analysis, the most frequently observed resistance-associated variants observed were Y93H (7.5%) in NS5A, and C316N (17.0%) and S556G (15%) in NS5B. Given the low virologic failure rates observed with recommended treatment regimens for HCV genotype 1a- and 1b-infected patients, the presence of baseline variants appears to have little impact on the likelihood of achieving SVR.

Resistance in Clinical Studies

Of the 2,510 HCV genotype 1 infected patients in the Phase 2b and 3 clinical trials treated with regimens containing paritaprevir, ombitasvir, and dasabuvir with or without ribavirin (for 8, 12, or 24 weeks), a total of 74 patients (3%) experienced virologic failure (primarily post-treatment relapse). Treatment-emergent variants and their prevalence in these virologic failure populations are shown in **Table 24**. In the 67 genotype 1a infected patients, NS3 variants were observed in 50 patients, NS5A variants were observed in 46 patients, NS5B variants were observed in 37 patients, and treatment-emergent variants were seen in all 3 drug targets in 30 patients. In the 7 genotype 1b infected patients, treatment-emergent variants were observed in NS3 in 4 patients, in NS5A in 2 patients, and in both NS3 and NS5A in 1 patient. No genotype 1b infected patients had treatment-emergent variants in all 3 drug targets.

Table 24. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of HOLKIRA PAK with and without Ribavirin Regimens in Phase 2b and Phase 3 Clinical Trials (N = 2510)

Target	Emergent Amino Acid Substitutions[a]	Genotype 1a N = 67[b] % (n)	Genotype 1b N = 7 % (n)
NS3	V55I[c]	6 (4)	-
	Y56H[c]	9 (6)	42.9 (3)[d]
	I132V[c]	6 (4)	-
	R155K	13.4 (9)	-
	D168A	6 (4)	-
	D168V	50.7 (34)	42.9 (3)[d]
	D168Y	7.5 (5)	-
	V36A[c], V36M[c], F43L[c], D168H, E357K[c]	< 5%	-
NS5A	M28T	20.9 (14)	-
	M28V[e]	9 (6)	-
	Q30R[e]	40.3 (27)	-
	Y93H		28.6 (2)
	H58D, H58P, Y93N	< 5%	-
NS5B	A553T	6.1 (4)	-
	S556G	33.3 (22)	-
	C316Y, M414T, G554S, S556R, G558R, D559G, D559N, Y561H	< 5%	-

a. Observed in at least 2 patients of the same subtype.

b. N = 66 for the NS5B target.

c. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.

d. Observed in combination in genotype 1b-infected patients.

e. Observed in combination in 6% (4/67) of the patients.

Note: The following variants were selected in cell culture but were not treatment-emergent: NS3 variants A156T in genotype 1a, and R155Q and D168H in genotype 1b; NS5A variants Y93C/H in genotype 1a, and L31F/V or Y93H in combination with L28M, L31F/V or P58S in genotype 1b; and NS5B variants Y448H in genotype 1a, and M414T and Y448H in genotype 1b.

Persistence of Resistance-Associated Substitutions

The persistence of paritaprevir, ombitasvir, and dasabuvir resistance-associated amino acid substitutions in NS3, NS5A, and NS5B, respectively, was assessed in genotype 1a-infected patients in Phase 2b trials. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 patients. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 patients. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 patients.

NS3 variants V36A/M and R155K and NS5B variants M414T and S556G remained detectable at post-treatment Week 48, whereas NS3 variant D168V and all other NS5B variants were not observed at post-treatment Week 48. All treatment-emergent variants in NS5A remained

detectable at post-treatment Week 48. Due to high SVR rates in genotype 1b, trends in persistence of treatment-emergent variants in this genotype could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing HOLKIRA PAK-resistance-associated substitutions is unknown.

Cross-resistance

Cross-resistance is expected among NS5A inhibitors, NS3/4A protease inhibitors, and non-nucleoside NS5B inhibitors by class. The impact of prior ombitasvir, paritaprevir or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied.

NON-CLINICAL TOXICOLOGY

General Toxicity

Paritaprevir/ritonavir

Paritaprevir/ritonavir was well tolerated in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 9-months). The safety margins for studies in the rat, mouse and dog were 15-, 60-, and 210-fold the exposure in human at the recommended dose.

Paritaprevir/ritonavir associated adverse effects were limited to the gallbladder in mice and dogs. In a 6 month mouse study, the adverse findings included focal erosion/ulceration, inflammation (both acute and chronic active), and epithelial hypertrophy/hyperplasia at paritaprevir exposures of 30-fold the exposure in humans at the recommended dose. Gallbladder findings in the dog were limited to minimal epithelial degeneration/necrosis. No evidence of disruption of the epithelial integrity was noted, despite achieving exposures of up to 210-fold the exposure in humans at the recommended dose. The severity and character of the gallbladder change in the dog did not progress from the 1-month to the 9 month toxicology study, despite achieving higher exposures in the 9-month study as compared to the 1-month study.

Ombitasvir

Ombitasvir was well tolerated without adverse effects in repeated-dose oral toxicity studies in mice (up to 6-months duration), rats (up to 3-months) and dogs (up to 6-months). Maximum achieved ombitasvir plasma exposures in the longest duration studies were at least 20-fold or higher as compared to human exposure at the recommended dose.

Both inactive, major, disproportionate human metabolites of ombitasvir (M29, M36) did not cause adverse effects in 1 month repeated-dose studies at AUC exposures that were ≥ 25-fold relative to anticipated human exposures.

Dasabuvir

Dasabuvir was well tolerated in repeated-dose oral toxicity studies in mice (up to 3-months duration), rats (up to 6-months), dogs (up to 9-months) and monkeys (up to 1-month). The safety margins were approximately 30-fold for the rodent (mouse and rat), 120-fold for the dog, and 15-fold for the monkey as compared to human exposure at the recommended dose.

Mutagenicity and Carcinogenicity

Ombitasvir

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in bacterial mutagenicity, human lymphocyte chromosome aberration and *in vivo* mouse micronucleus assays.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study up to AUC exposures approximately 26- and 16-fold the exposure in humans at the recommended dose.

Paritaprevir/ritonavir

Paritaprevir was positive for genotoxicity in an *in vitro* human chromosome aberration test but negative in a bacterial mutation assay, and in two *in vivo* genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

Ritonavir was not genotoxic in bacterial mutation assay, mouse lymphoma assay, chromosomal aberration assay and in vivo mouse micronucleus test.

Paritaprevir/ritonavir was not carcinogenic in a 6-month transgenic mouse study up to AUC exposures approximately 38- and 4-fold the exposure in humans at the recommended dose. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to AUC exposures approximately 8- and 4-fold the exposure in humans at the recommended dose.

Dasabuvir

Dasabuvir was not genotoxic in bacterial mutagenicity, human lymphocyte chromosome aberration and *in vivo* rat micronucleus assays.

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study and a 2-year rat study up to AUC exposures approximately 19-fold the exposure in humans at the recommended dose.

Use with Ribavirin

Ribavirin was shown to be genotoxic in several *in vitro* and *in vivo* assays. Ribavirin was not carcinogenic in a 6-month p53+/- transgenic mouse study or a 2-year rat study. See the Product Monograph for ribavirin for additional information.

Fertility

Ombitasvir

Ombitasvir had no effects on fertility when evaluated in mice up to AUC exposures approximately 25-fold the exposure in humans at the recommended clinical dose.

Paritaprevir/ritonavir

Paritaprevir/ritonavir had no effects on fertility when evaluated in rats up to AUC exposures approximately 8- and 2-fold higher than the exposure in humans at the recommended clinical dose.

Dasabuvir

Dasabuvir had no effects on fertility when evaluated in rats up to AUC exposures approximately 16-fold the exposure in humans at the recommended clinical dose.

Use with Ribavirin

In fertility studies in male animals, ribavirin induced reversible testicular toxicity. Refer to Product Monograph for ribavirin for additional information.

REFERENCES

1. Public Health Agency of Canada. Hepatitis C in Canada: 2005-2010 Surveillance Report. Centre for Communicable Diseases and Infection Control, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada; 2011.

2. Wong T, Lee SS. Hepatitis C: A review for primary care physicians. *Can Med Assoc J* 2006 28 Feb;174(5):649-659.

3. Al Naamani K, Al Sinani S, Deschênes M. Epidemiology and treatment of hepatitis C genotypes 5 and 6. *Can J Gastroenterol* 2013 Jan;27(1):e8-12.

4. Andonov A, Chaudhary RK. Genotyping of Canadian hepatitis C virus isolates by PCR. *J Clin Microbiol* 1994;32:2031-4.

5. Murphy DG, Willems B, Delage G, et al. Hepatitis C virus genotypes in patients and blood donors – Quebec. *Can Commun Dis Rep* 1995;21:129-32.

6. Bernier L, Willems B, Delage G, Murphy DG. Identification of numerous hepatitis C virus genotypes in Montreal, Canada. *J Clin Microbiol* 1996;34:2815-8.

7. Chaudhary R, Tepper M, Eisaadany S, Gully PR. Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System. *Can J Infect Dis* 1999 Jan;10(1):53-6.

8. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto, ON: Canadian Cancer Society; 2013.

9. Remis R. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007 final report. Public Health Agency of Canada. 2007.

10. Myers RP1, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. *Can J Gastroenterol* 2012 Jun;26(6):359-75.

11. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *N Engl J Med* 2014 May 22; 370(21):1973-82

12. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014 Apr 24;370(17):1594-603.

13. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014 Apr 24;370(17):1604-14.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrHOLKIRA® PAK

ombitasvir/paritaprevir/ritonavir film-coated tablets and dasabuvir film-coated tablets

Read this carefully before you start taking HOLKIRA PAK and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your doctor about your medical condition and treatment and ask if there is any new information about HOLKIRA PAK.

Serious Warnings and Precautions

Hepatitis B activity (e.g., inflamed liver) may increase when taking antiviral drugs like HOLKIRA PAK, sometimes leading to liver failure and death. (See the "To help avoid side effects…" section, *Hepatitis B Reactivation*)

What is HOLKIRA PAK used for?

HOLKIRA PAK treats long-lasting hepatitis C virus (HCV) infection in adults 18 years and older. It treats one kind of HCV infection called HCV genotype 1.

HOLKIRA PAK is sometimes used with ribavirin, but not always. Read the ribavirin patient medication information if your doctor says you should also take ribavirin.

How does HOLKIRA PAK work?

HOLKIRA PAK with ribavirin can cure HCV infection in most patients. Cure means HCV is cleared from your blood 3 months after finishing the medicine.

HOLKIRA PAK has 3 types of HCV medicines. These 3 medicines stop HCV from multiplying in different ways.

Curing HCV infection can help lower the chance you will have problems or die from HCV.

Taking HOLKIRA PAK does not keep you from getting infected again. Talk with your doctor about ways to avoid getting infected again with HCV.

Can I still pass on HCV to others if I take HOLKIRA PAK?

Yes, you can still pass on HCV to others while you are taking HOLKIRA PAK. For example, some ways that HCV can be passed on is by sharing needles or through unprotected sex. Talk with your doctor about ways to avoid passing on HCV.

What are the ingredients in HOLKIRA PAK?

Ombitasvir/paritaprevir/ritonavir tablets

Each tablet contains the following medicinal ingredients: ombitasvir, paritaprevir and ritonavir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, propylene glycol monolaurate, sodium stearyl fumarate, sorbitan monolaurate, vitamin E polyethylene glycol succinate.

Each tablet is covered with the following ingredients that are not medicines: iron oxide red, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide.

The tablets do not contain gluten.

Dasabuvir film-coated tablets

Each tablet contains the following medicinal ingredients: dasabuvir.

Each tablet has the following ingredients that are not medicines: colloidal silicon dioxide/anhydrous colloidal silica, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Each tablet is covered with the following ingredients that are not medicines: iron oxide black, iron oxide red, iron oxide yellow, polyethylene glycol/macrogol, polyvinyl alcohol, purified water, talc, and titanium dioxide.

The tablets do not contain gluten.

HOLKIRA PAK comes in the following dosage forms:

HOLKIRA PAK has two different tablets. One tablet has 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir. The other tablet has 250 mg of dasabuvir.

Do not use HOLKIRA PAK if:

- your doctor says you should also use ribavirin and you are pregnant or want to be pregnant (or your partner is pregnant or wants to become pregnant). Ribavirin may cause birth defects or death of your unborn baby.
- you are allergic to any of the medicines or other ingredients in HOLKIRA PAK (see the section **What are the ingredients in HOLKIRA PAK?** to see all the medicines and ingredients).
- your doctor has told you that you have moderate or severe loss of liver function.

- you are taking any of the following medicines or natural substances:
    - alfuzosin hydrochloride (Xatral®)
    - astemizole*
    - atorvastatin (Lipitor®)
    - bosentan (Tracleer®)
    - carbamazepine (Tegretol®)
    - cisapride*
    - colchicine for patients who have certain kidney or liver problems
    - disopyramide (Rythmodan®)
    - dronedarone (Multaq®)
    - efavirenz-containing medicines (Sustiva®, Atripla®)
    - ergot-containing medicines including:
        - ergonovine*
        - ergotamine tartrate*
        - ergotamine (Bellergal Spacetabs®)
        - dihydroergotamine mesylate (Migranal®)
        - methylergonovine*
    - ethinyl estradiol-containing medicines such as those contained in most contraceptive pills and vaginal rings used for contraception
    - etravirine (Intelence®)
    - fusidic acid (systemic)*
    - gemfibrozil
    - lovastatin
    - lurasidone (Latuda®)
    - midazolam (when taken by mouth)
    - modafinil (Alertec®)
    - nevirapine (Viramune®)
    - phenytoin (Dilantin®)
    - phenobarbital
    - pimozide (Orap®)
    - rifampin (Rifadin®, Rifater®, Rofact®)
    - salmeterol (Advair Diskus®, Serevent Diskus®)
    - sildenafil citrate (Revatio®) for the lung problem, pulmonary artery hypertension (PAH)
    - simvastatin
    - St. John's wort (*Hypericum perforatum*) or products containing St. John's wort
    - terfenadine*
    - triazolam

*** Drugs not sold in Canada.**

To help avoid side effects and make sure you are using your medicines correctly, talk to your doctor before you take HOLKIRA PAK. Talk about any health problems you may have, including if you:

- are taking birth control medicines of any kind or using a medicine that has ethinyl estradiol. Ethinyl estradiol is usually found in birth control pills. However, not all birth control pills have ethinyl estradiol. You must not use medicines that have ethinyl estradiol while taking HOLKIRA PAK. Your doctor will ask you to stop or change to a different type of birth control while you are taking HOLKIRA PAK.
- have any other medical condition.
- have had a kidney and/or liver transplant.
    - You should not take HOLKIRA PAK if you are taking everolimus. The dose of everolimus cannot be adjusted to maintain the correct drug levels when given with HOLKIRA PAK.
    - If you are taking tacrolimus or sirolimus you should talk to your doctor about the risks and benefits of taking HOLKIRA PAK at the same time and consider:
        - Serious and life-threatening side effects have occurred when taking HOLKIRA PAK with tacrolimus or sirolimus
        - Your doctor may order blood tests to check tacrolimus or sirolimus levels in your blood at the beginning and during treatment with HOLKIRA PAK
    - Talk with your doctor if you are taking cyclosporine for your transplant. The levels of this medicine can change when taken with HOLKIRA PAK. Your doctor will choose how much cyclosporine you need to take:
        - with HOLKIRA PAK.
        - when you have completed HOLKIRA PAK.
        - if you have to stop taking HOLKIRA PAK for any reason.
- have liver problems other than HCV infection.
- also have HIV infection.
- are breastfeeding or plan to breastfeed. It is not known if HOLKIRA PAK passes into your breast milk. You and your doctor should decide if you will take HOLKIRA PAK or breastfeed. You should not do both.

Hepatitis B Reactivation

Taking antiviral drugs such as HOLKIRA PAK may increase hepatitis B activity. This can lead to liver problems such as liver failure and death. Contact your doctor if:

- you have never been tested for hepatitis B
- you know you have a current hepatitis B infection
- you have had a previous hepatitis B infection

Your healthcare professional may do blood tests:

- before hepatitis C treatment
- to see the hepatitis B levels in your blood
- and may order hepatitis B treatment

Pregnancy and Birth Control

- Females must have negative pregnancy test before starting HOLKIRA PAK and ribavirin, every month while on the medicine, and for 6 months after stopping them.
- You or your partner should not become pregnant while taking HOLKIRA PAK with ribavirin and for 6 months after you have stopped taking them.
- You and your partner must use 2 kinds of birth control while taking HOLKIRA PAK and ribavirin and for 6 months after you have stopped taking them.
- Talk with your doctor about the kind of birth control that you can use.
- If you or your partner becomes pregnant while taking HOLKIRA PAK and ribavirin or within 6 months after you stop taking them, tell your doctor right away.

Other warnings you should know about:

HOLKIRA PAK may cause severe liver problems, especially in people with advanced cirrhosis (liver scarring). These severe liver problems can lead to the need for a liver transplant, or can lead to death.

Rises in liver tests have occurred when the medicines that are in HOLKIRA PAK were taken in studies. Contact your doctor right away if you have symptoms like those listed below since these may mean you have a serious problem with your liver:

- loss of appetite (do not feel like eating)
- stomachache

- swelling of your stomach area
- nausea (feeling sick in the stomach)
- vomiting
- feeling tired or weak
- yellowing of the skin and eyes
- confusion
- dark urine and pale stool.

It is not known if taking HOLKIRA PAK is safe or will work in children under 18 years of age.

Your doctor may do blood tests before you start taking, and while you are on your medicines. This is to help check if the medicines are working for you.

Tell your doctor all the medicines, drugs, vitamins and minerals, natural supplements or alternative medicines you are already taking. Also tell your doctor if you stop any of these or start any new ones.

Do not take HOLKIRA PAK with the following medicines:

- other ritonavir-containing medicines (Norvir®, Kaletra®). When given with HOLKIRA PAK, atazanavir and darunavir should be taken without ritonavir.
- amiodarone (Cordarone®)
- alfentanil
- everolimus (Affinitor®, Affinitor® Disperz)
- fentanyl (Abstral®, Duragesic®)
- flecainamide
- lidocaine (systemic)
- propafenone (Rythmol®)
- quetiapine (Seroquel®)
- quinidine
- rilpivirine (Edurant®, Complera®)
- sirolimus (Rapamune®)

The following medicines may interact with HOLKIRA PAK:

- alprazolam (Xanax®)
- amlodipine (Norvasc®)
- atazanavir (Reyataz®)
- atorvastatin (Lipitor®)
- carisoprodol*
- candesartan (Atacand®/Atacand® Plus)

- cyclobenzaprine
- cyclosporine (Neoral®, Sandimmune®)
- darunavir (Prezista®)
- diazepam (Valium®)
- digoxin (Lanoxin®)
- diltiazem (Cardizem® CD)
- fluticasone (Advair®, Flonase®, Flovent Diskus®, Flovent HFA®)
- fluvastatin (Lescol®)
- furosemide (Lasix®)
- hydrocodone (Hycodan®, Novahistex®, Novahistine ®, Tussionex®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- losartan (Cozaar®/Hyzaar®)
- nifedipine (Adalat® XL)
- omeprazole (Losec®)
- pitavastatin*****
- posaconazole (Posanol®)
- pravastatin (Pravachol®)
- rosuvastatin (Crestor®)
- tacrolimus (Prograf®)
- valsartan (Diovan®/ Diovan® HCT)
- verapamil (Isoptin® SR)
- voriconazole (Vfend®)
- warfarin (Coumadin®), or other similar medicines called vitamin K antagonists

*** Drugs not sold in Canada.**

Ask your doctor or pharmacist if you are not sure if your medicine is one that is listed above.

Keep a list of all the medicines you take. Show it to your doctor or pharmacist when you get a new medicine or stop a medicine.

If you change or stop one of your other medicines while you are taking HOLKIRA PAK, ask your doctor about changing back when you are finished taking HOLKIRA PAK.

How to take HOLKIRA PAK:

- Take HOLKIRA PAK exactly as your doctor tells you. Do not change your dose or stop unless your doctor tells you to.
- Take HOLKIRA PAK at about the same time every day with food. The type of food is not important.
- Swallow HOLKIRA PAK tablets whole with water or another liquid if needed.
- Do not chew, break, or crush HOLKIRA PAK tablets.

Usual Adult Dose:

- Every day in the morning, take the two pink ombitasvir/paritaprevir/ritonavir tablets and one beige dasabuvir tablet with food.
- Every day in the evening, take the remaining beige dasabuvir tablet with food.
- HOLKIRA PAK is taken for either 12 or 24 weeks. Your doctor will tell you exactly how long you need to take HOLKIRA PAK.
- If your doctor has also prescribed ribavirin, your doctor will provide you dosage directions for the ribavirin.

Overdose:

If you think you have taken too much HOLKIRA PAK, contact your doctor or pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if you do not have symptoms.

Missed Dose:

- If you miss a dose of the pink ombitasvir/paritaprevir/ritonavir tablets and it is:
    - less than 12 hours from the time you usually take ombitasvir/paritaprevir/ritonavir, you should take the missed dose with food as soon as possible. Then take your next dose at your usual time.
    - more than 12 hours from the time you usually take ombitasvir/paritaprevir/ritonavir, you should not take the missed dose. Take your next dose as usual with food.
- If you miss a dose of the beige dasabuvir tablets and it is:
    - less than 6 hours from the time you usually take dasabuvir, you should take the missed dose with food as soon as possible. Then take your next dose at your usual time.
    - more than 6 hours from the time you usually take dasabuvir, you should not take the missed dose. Take your next dose as usual with food.

What are possible side effects from using HOLKIRA PAK?

If your side effect is not listed here, contact your doctor or pharmacist. Also see **Other warnings you should know about**.

Common side effects of HOLKIRA PAK:

- feeling tired or weak
- headache

Common side effects of HOLKIRA PAK when used with ribavirin:

- feeling tired or weak
- headache
- itching
- nausea (feeling sick in the stomach)
- trouble sleeping

If you have a side effect that is not listed here or becomes bad enough to get in the way of your daily tasks, talk to your doctor.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Erythema multiforme: serious or life-threatening skin rashes and blisters			✓
Serious allergic reactions: difficulty breathing or swallowing; dizziness or light-headedness which may be due to low blood pressure; swelling of the face, lips, tongue or throat; severe itching of the skin, with a red rash or raised bumps			✓

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.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting);

- 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 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting).

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

Storage:

Store between 2 and 30°C. Keep away from moisture.

Keep HOLKIRA PAK out of the reach and sight of children.

If you want more information about HOLKIRA PAK:

- Talk to your doctor.
- 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.canada.ca/en/health-canada); the manufacturer's website (abbvie.ca), or by calling 1-888-704-8271.

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Abstral, Adalat XL, Advair, Advair Diskus, Affinitor, Affinitor Disperz, Alertec, Atacand, Atacand Plus, Atripla, Bellergal Spacetabs, Cardizem CD, Complera, Cordarone, Coumadin, Cozaar, Crestor, Dilantin, Diovan, Diovan HCT, Duragesic, Edurant, Flonase, Flovent Diskus,

Flovent HFA, Hycodan,Hyzaar, Intelence, Isoptin SR, Lanoxin, Lasix, Latuda, Lescol, Lipitor, Losec, Migranal, Multaq, Neoral, Nizoral, Norvasc, Novahistex, Novahistine ,Orap, Posanol, Pravachol, Prezista, Prograf, Rapamune, Revatio, Reyataz, Rifadin, Rifater, Rofact, Rythmodan, Rythmol, Sandimmune, Serevent Diskus, Seroquel, Sporanox, Sustiva, Tegretol, Tracleer, Tussionex, Valium, Vfend, Viramune, Xanax, Xatral are trademarks of their respective owners and are not trademarks of AbbVie Corporation. The makers of these brands are not affiliated with and do not endorse AbbVie or its products.