HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIEKIRA XR safely and effectively. See full prescribing information for VIEKIRA XR.

VIEKIRA XR (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets, for oral use
Initial U.S. Approval: 2014

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV
See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

RECENT MAJOR CHANGES

Boxed Warning	2/2017
Dosage and Administration (2.1)	2/2017
Contraindications (4)	3/2017
Warnings and Precautions (5.1)	2/2017

INDICATIONS AND USAGE

VIEKIRA XR includes dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, and ritonavir, a CYP3A inhibitor and is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV):

- genotype 1b infection without cirrhosis or with compensated cirrhosis
- genotype 1a infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. (1)

DOSAGE AND ADMINISTRATION

Testing Prior to the Initiation of Therapy:

- Test all patients for HBV infection by measuring HBsAg and anti-HBc. (2.1)
- Assess for laboratory and clinical evidence of hepatic decompensation. (2.1)

Recommended dosage: Three tablets taken once daily. VIEKIRA XR must be taken with a meal because administration under fasting conditions may result in reduced virologic response and possible development of resistance. (2.2)

Treatment Regimen and Duration by Patient Population

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA XR + ribavirin	12 weeks
Genotype 1a, with compensated cirrhosis	VIEKIRA XR + ribavirin	24 weeks**
Genotype 1b, with or without compensated cirrhosis	VIEKIRA XR	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA XR administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[See Clinical Studies (14.3)]*.

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above. (2.2)
- Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA XR with ribavirin is 24 weeks. (2.4)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 200 mg dasabuvir, 8.33 mg ombitasvir, 50 mg paritaprevir, and 33.33 mg ritonavir (3)

CONTRAINDICATIONS

- Patients with moderate to severe hepatic impairment. (4, 5.2, 8.6, 12.3)
- If VIEKIRA XR is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. (4)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate or strong inducers of CYP3A or strong inducers of CYP2C8; and strong inhibitors of CYP2C8. (4)
- Known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome). (4)

WARNINGS AND PRECAUTIONS

- Risk of Hepatitis B Virus Reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)
- Hepatic Decompensation and Hepatic Failure in Patient with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported mostly in patients with advanced cirrhosis. Monitor for clinical signs and symptoms of hepatic decompensation. (5.2)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting VIEKIRA XR (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on VIEKIRA XR, monitor closely and follow recommendations in full prescribing information. (5.3)
- Risks Associated With Ribavirin Combination Treatment: If VIEKIRA XR is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. (5.4)
- Drug Interactions: The concomitant use of VIEKIRA XR and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA XR. (5.5)

ADVERSE REACTIONS

In subjects receiving the combination of dasabuvir with ombitasvir, paritaprevir, ritonavir with ribavirin, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving the combination of dasabuvir with ombitasvir, paritaprevir, ritonavir without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of VIEKIRA XR can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of VIEKIRA XR. The potential for drug interactions must be considered before and during treatment. Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.5, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with VIEKIRA XR. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

VIEKIRA XR is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) *[see Dosage and Administration (2.2) and Clinical Studies (14)]*:

- genotype 1b infection without cirrhosis or with compensated cirrhosis
- genotype 1a infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to the Initiation of Therapy

- Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with VIEKIRA XR *[see Warnings and Precautions (5.1)]*.
- Prior to initiation of VIEKIRA XR, assess for laboratory and clinical evidence of hepatic decompensation *[see Warnings and Precautions (5.2 and 5.3)]*.

2.2 Recommended Dosage in Adults

VIEKIRA XR is a 4-drug fixed-dose combination, extended-release tablet containing 200 mg of dasabuvir, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir.

The recommended dosage of VIEKIRA XR is three tablets taken orally once daily.

- VIEKIRA XR must be taken with a meal because administration under fasting conditions may result in reduced virologic response and possible development of resistance *[see Clinical Pharmacology (12.3)]*.
- Swallow tablets whole. Splitting, crushing, or chewing tablets may compromise the extended-release performance, efficacy, and/or safety of VIEKIRA XR.

- For optimal release of dasabuvir, alcohol should not be consumed within 4 hours of taking VIEKIRA XR.

VIEKIRA XR is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with VIEKIRA XR, the recommended dosage of RBV is based on weight: 1000 mg/day for subjects <75 kg and 1200 mg/day for those ≥75 kg, divided and administered twice-daily with food. The starting dosage and on-treatment dosage of RBV can be decreased based on changes in hemoglobin levels and/or creatinine clearance. For ribavirin dosage modifications, refer to the ribavirin prescribing information.

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 1. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 shows the recommended VIEKIRA XR treatment regimen and duration based on patient population.

Table 1. Treatment Regimen and Duration by Patient Population (Treatment-Naïve or Interferon-Experienced)

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA XR + ribavirin	12 weeks
Genotype 1a, with compensated cirrhosis (Child-Pugh A)	VIEKIRA XR + ribavirin	24 weeks**
Genotype 1b, with or without compensated cirrhosis (Child-Pugh A)	VIEKIRA XR	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA XR administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[see Clinical Studies (14.3)]*.

2.3 Use in Liver Transplant Recipients

In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower), the recommended duration of VIEKIRA XR with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype *[see Clinical Studies (14.6)]*. When VIEKIRA XR is administered with calcineurin inhibitors in liver transplant recipients, dosage adjustment of calcineurin inhibitors is needed *[see Drug Interactions (7)]*.

2.4 Hepatic Impairment

VIEKIRA XR is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) *[see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablet: 200 mg of dasabuvir (equivalent to 216.2 mg of dasabuvir sodium monohydrate), 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir. The tablets are pale yellow-colored, film-coated, oblong shaped, debossed with “3QD” on one side.

4 CONTRAINDICATIONS

- VIEKIRA XR is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- If VIEKIRA XR is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of contraindications for ribavirin.
- VIEKIRA XR is contraindicated:
  - With drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - With drugs that are moderate or strong inducers of CYP3A and strong inducers of CYP2C8 and may lead to reduced efficacy of VIEKIRA XR.
  - With drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.
  - In patients with known hypersensitivity to ritonavir (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome).

Table 2 lists drugs that are contraindicated with VIEKIRA XR *[see Drug Interactions (7)]*.

Table 2. Drugs that are Contraindicated with VIEKIRA XR

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anti-anginal	Ranolazine	Potential for serious and/or life-threatening reactions.
Antiarrhythmic	Dronedarone	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	VIEKIRA XR exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA XR.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.

Antimycobacterial	Rifampin	VIEKIRA XR exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA XR.
Antipsychotic	Lurasidone Pimozide	Potential for serious and/or life-threatening reactions. Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Ergot derivatives	Ergotamine, dihydroergotamine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions (5.3)]*.
GI Motility Agent	Cisapride	Potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	VIEKIRA XR exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA XR.
HMG-CoA Reductase Inhibitors	Atorvastatin Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Immunosuppressants	Everolimus Sirolimus Tacrolimus	Increased potential for serious and/or life threatening immunosuppressant associated adverse events.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as Revatio for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA XR may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory

		depression.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients.

HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with VIEKIRA XR. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with VIEKIRA XR and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

5.2 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 postmarketing in patients treated with the components of VIEKIRA XR. Most patients with these severe outcomes had evidence of advanced 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.

VIEKIRA XR is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) *[see Contraindications (4), Adverse Reactions (6.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

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 and during the first 4 weeks of starting treatment and as clinically indicated.
- Discontinue VIEKIRA XR in patients who develop evidence of hepatic decompensation.

5.3 Increased Risk of ALT Elevations

During clinical trials with the combination of dasabuvir tablets and ombitasvir, paritaprevir, and ritonavir tablets (components of VIEKIRA XR) with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects *[see Adverse Reactions (6.1)]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing.

These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA XR *[see Contraindications (4)]*. Alternative methods of contraception (e.g., progestin only contraception or non-hormonal methods) are recommended during VIEKIRA XR therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA XR.

Women 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; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA XR *[see Adverse Reactions (6.1)]*.

Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- 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, jaundice or discolored feces.
- Consider discontinuing VIEKIRA XR if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA XR if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or INR.

5.4 Risks Associated With Ribavirin Combination Treatment

If VIEKIRA XR is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the warnings and precautions for ribavirin.

5.5 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of VIEKIRA XR and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to:

- Loss of therapeutic effect of VIEKIRA XR and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA XR.

See Table 5 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during VIEKIRA XR therapy; review concomitant medications during VIEKIRA XR therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

5.6 Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients

The ritonavir component of VIEKIRA XR 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 VIEKIRA XR should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

6 ADVERSE REACTIONS

The following adverse reaction is described below and elsewhere in the labeling:

- Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis *[see Warnings and Precautions (5.2)]*
- Increased Risk of ALT Elevations *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of VIEKIRA XR cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

If VIEKIRA XR is administered with ribavirin (RBV), refer to the prescribing information for ribavirin for a list of ribavirin-associated adverse reactions.

The safety assessment was based on data from seven clinical trials in more than 2,000 subjects who received the components of VIEKIRA XR with or without ribavirin for 12 or 24 weeks.

Components of VIEKIRA XR with Ribavirin in GT 1-Infected Subjects without Cirrhosis

The safety of the components of VIEKIRA XR with ribavirin were assessed in 770 subjects with chronic HCV genotype 1 (GT1) infection without cirrhosis in two placebo-controlled trials (SAPPHIRE-I and -II) *[see Clinical Studies (14.1, 14.2)]*. Adverse reactions that occurred more often in subjects treated with the components of VIEKIRA XR with ribavirin compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia (see Table 3). The majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE). The proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

Table 3. Adverse Reactions with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection without Cirrhosis Treated with the Components of VIEKIRA XR with Ribavirin Compared to Placebo for 12 Weeks

	SAPPHIRE-I and -II

	Components of VIEKIRA XR + RBV 12 Weeks N = 770 %	Placebo 12 Weeks N = 255 %
Fatigue	34	26
Nausea	22	15
Pruritus*	18	7
Skin reactions[$]	16	9
Insomnia	14	8
Asthenia	14	7

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.
[$]Grouped terms: rash, erythema, eczema, rash maculo-papular, rash macular, dermatitis, rash papular, skin exfoliation, rash pruritic, rash erythematous, rash generalized, dermatitis allergic, dermatitis contact, exfoliative rash, photosensitivity reaction, psoriasis, skin reaction, ulcer, urticaria.

Components of VIEKIRA XR with and without Ribavirin in GT1-Infected Subjects without Cirrhosis

The components of VIEKIRA XR with and without ribavirin were assessed in 401 and 509 subjects with chronic HCV infection GT1 infection without cirrhosis, respectively, in three clinical trials (PEARL-II, PEARL-III and PEARL-IV) *[see Clinical Studies (14.1, 14.2)]*. Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with the components of VIEKIRA XR with ribavirin (see Table 4). The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for the components of VIEKIRA XR with or without ribavirin.

Table 4. Adverse Events with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection without Cirrhosis Treated with the Components of VIEKIRA XR with or without Ribavirin for 12 Weeks

	PEARL-II, -III and -IV	
	Components of VIEKIRA XR + RBV 12 Weeks N = 401 %	Components of VIEKIRA XR without RBV 12 Weeks N = 509 %
Nausea	16	8
Pruritus*	13	7
Insomnia	12	5
Asthenia	9	4

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

Components of VIEKIRA XR with Ribavirin in GT1-Infected Subjects with Compensated Cirrhosis

The components of VIEKIRA XR with ribavirin were assessed in 380 subjects with genotype 1 infection and compensated cirrhosis who were treated with the components of VIEKIRA XR plus ribavirin for 12 (n=208) or 24 (n=172) weeks duration (TURQUOISE-II) *[see Clinical Studies (14.1, 14.3)]*. The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with the components of VIEKIRA XR for 12 and 24 weeks who experienced SAEs were 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Components of VIEKIRA XR without Ribavirin in GT1b-Infected Subjects with Compensated Cirrhosis

The components of VIEKIRA XR without ribavirin for 12 weeks was assessed in 60 subjects with genotype 1b infection and compensated cirrhosis (TURQUOISE-III) *[see Clinical Studies (14.1, 14.3)]*. The type and severity of adverse events and laboratory abnormalities in genotype 1b-infected subjects with compensated cirrhosis were comparable to subjects in other trials without ribavirin.

Skin Reactions

In PEARL-II, -III and -IV, 7% of subjects receiving the components of VIEKIRA XR alone and 10% of subjects receiving the components of VIEKIRA XR with ribavirin reported rash-related events. In SAPPHIRE-I and -II 16% of subjects receiving the components of VIEKIRA XR with ribavirin and 9% of subjects receiving placebo reported skin reactions. In TURQUOISE-II, 18% and 24% of subjects receiving the components of VIEKIRA XR with ribavirin for 12 or 24 weeks reported skin reactions. The majority of events were graded as mild in severity. There were no serious events or severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS).

Laboratory Abnormalities

Serum ALT Elevations

Approximately 1% of subjects treated with the components of VIEKIRA XR experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. The incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol containing medication *[see Contraindications (4) and Warnings and Precautions (5.3)]*. The incidence of clinically relevant ALT elevations among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy was 3% (2/59).

ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range 8-57 days) and most resolved with ongoing therapy. The majority of these ALT elevations were assessed as drug-related liver injury. Elevations in

ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT *[see Warnings and Precautions (5.3)]*.

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15% of subjects receiving the components of VIEKIRA XR with ribavirin compared to 2% in those receiving the components of VIEKIRA XR without ribavirin. These bilirubin increases were predominately indirect and 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 serum ALT elevations.

Anemia/Decreased Hemoglobin

Across all Phase 3 studies, the mean change from baseline in hemoglobin levels in subjects treated with the components of VIEKIRA XR with ribavirin was -2.4 g/dL and the mean change in subjects treated with the components of VIEKIRA XR without ribavirin was -0.5 g/dL. Decreases in hemoglobin levels occurred early in treatment (Week 1-2) with further reductions through Week 3. Hemoglobin values remained low during the remainder of treatment and returned towards baseline levels by post-treatment Week 4. Less than 1% of subjects treated with the components of VIEKIRA XR with ribavirin had hemoglobin levels decrease to less than 8.0 g/dL during treatment. Seven percent of subjects treated with the components of VIEKIRA XR with ribavirin underwent a ribavirin dose reduction due to a decrease in hemoglobin levels; three subjects received a blood transfusion and five required erythropoietin. One patient discontinued therapy due to anemia. No subjects treated with the components of VIEKIRA XR without ribavirin had a hemoglobin level less than 10 g/dL.

Components of VIEKIRA XR with Ribavirin in HCV/HIV-1 Co-infected Subjects

The components of VIEKIRA XR with ribavirin were assessed in 63 subjects with HCV/HIV-1 co-infection who were on stable antiretroviral therapy. The most common adverse events occurring in at least 10% of subjects were fatigue (48%), insomnia (19%), nausea (17%), headache (16%), pruritus (13%), cough (11%), irritability (10%), and ocular icterus (10%).

Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) subjects. Fifteen of these subjects were also receiving atazanavir at the time of bilirubin elevation and nine also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. None of the subjects with hyperbilirubinemia had concomitant elevations of aminotransferases *[see Warnings and Precautions (5.6), Adverse Reactions (6.1) and Clinical Studies (14.6)]*. No subject experienced a grade 3 ALT elevation.

Seven subjects (11%) had at least one post-baseline hemoglobin value of less than 10 g/dL, and six of these subjects had a ribavirin dose modification; no subject in this small cohort required a blood transfusion or erythropoietin.

Median declines in CD4+ T-cell counts of 47 cells/mm^3 and 62 cells/mm^3 were observed at the end of 12 and 24 weeks of treatment, respectively, and most returned to baseline levels post-treatment. Two subjects had CD4+ T-cell counts decrease to less than 200 cells/mm^3 during treatment without a decrease in CD4%. No subject experienced an AIDS-related opportunistic infection.

Components of VIEKIRA XR with Ribavirin in Selected Liver Transplant Recipients

The components of VIEKIRA XR with ribavirin were assessed in 34 post-liver transplant subjects with recurrent HCV infection. Adverse events occurring in more than 20% of subjects included fatigue 50%, headache 44%, cough 32%, diarrhea 26%, insomnia 26%, asthenia 24%, nausea 24%, muscle spasms 21% and rash 21%. Ten subjects (29%) had at least one post-baseline hemoglobin value of less than 10 g/dL. Ten subjects underwent a ribavirin dose modification due to decrease in hemoglobin and 3% (1/34) had an interruption of ribavirin. Five subjects received erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion *[see Clinical Studies (14.5)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of the components of VIEKIRA XR. 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.

Immune System Disorders: Hypersensitivity reactions (including angioedema).

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Potential for VIEKIRA XR to Affect Other Drugs

Dasabuvir, ombitasvir, and paritaprevir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and dasabuvir, paritaprevir, and ritonavir are inhibitors of BCRP. Co-administration of VIEKIRA XR with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs *[see also Contraindications (4), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)]*.

7.2 Potential for Other Drugs to Affect One or More Components of VIEKIRA XR

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of VIEKIRA XR with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes. Co-administration of VIEKIRA XR with drugs that inhibit CYP2C8 may increase dasabuvir plasma concentrations. Ombitasvir is primarily metabolized via amide hydrolysis while CYP enzymes play a minor role in its metabolism. Ombitasvir, paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Ombitasvir, paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 may increase the plasma concentrations of the various components of VIEKIRA XR.

7.3 Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with VIEKIRA XR, doses should be re-adjusted after administration of VIEKIRA XR is completed. Table 5 provides

the effect of co-administration of VIEKIRA XR on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of VIEKIRA XR. Refer to Contraindications for drugs that are contraindicated with VIEKIRA XR *[see Contraindications (4)]*. Refer to the ritonavir prescribing information for other potentially significant drug interactions with ritonavir.

Table 5. Established Drug Interactions Based on Drug Interaction Trials

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANGIOTENSIN RECEPTOR BLOCKERS		
valsartan* losartan* candesartan*	↑ angiotensin receptor blockers	Decrease the dose of the angiotensin receptor blockers and monitor patients for signs and symptoms of hypotension and/or worsening renal function. If such events occur, consider further dose reduction of the angiotensin receptor blocker or switching to an alternative to the angiotensin receptor blocker.
ANTIARRHYTHMICS		
amiodarone*, bepridil*, disopyramide*, flecainide*, lidocaine (systemic)*, mexiletine*, propafenone*, quinidine*	↑ antiarrhythmics	Contraindicated antiarrhythmics *[see Contraindications (4)]*. Therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with VIEKIRA XR.
ANTIDIABETIC DRUGS		
metformin	↔ metformin	Monitor for signs of onset of lactic acidosis such as respiratory distress, somnolence, and non-specific abdominal distress or worsening renal function. Concomitant metformin use in patients with renal insufficiency or hepatic impairment is not recommended. Refer to the prescribing information of metformin for further guidance.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When VIEKIRA XR is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.

voriconazole*	↓ voriconazole	Co-administration of VIEKIRA XR with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
ANTIPSYCHOTIC		
quetiapine*	↑ quetiapine	Contraindicated antipsychotics *[see Contraindications (4)]*. Quetiapine: • Initiation of VIEKIRA XR in patients taking quetiapine: Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If coadministration is necessary, reduce the quetiapine dose to 1/6th of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for the recommendations on adverse reaction monitoring. • Initiation of quetiapine in patients taking VIEKIRA XR: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
CALCIUM CHANNEL BLOCKERS		
amlodipine nifedipine* diltiazem* verapamil*	↑ calcium channel blockers	Decrease the dose of the calcium channel blocker. The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended for edema and/or signs and symptoms of hypotension. If such events occur, consider further dose reduction of the calcium channel blocker or switching to an alternative to the calcium channel blocker.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone*	↑ fluticasone	Concomitant use of VIEKIRA XR with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long term use.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.

ANTIRETROVIRAL AGENTS: PROTEASE INHIBITORS		
atazanavir/ritonavir once daily	↑ paritaprevir	When coadministered with VIEKIRA XR, atazanavir 300 mg (without ritonavir) should only be given in the morning.
darunavir/ritonavir	↓ darunavir (C_{trough})	Treatment naïve patients or treatment experienced patients with no darunavir associated substitutions: Darunavir 800 mg once daily (without ritonavir) can be co-administered with VIEKIRA XR. Treatment experienced patients with at least one darunavir resistance associated substitution or with no baseline resistance information: Co-administration of darunavir/ritonavir 600/100 mg twice daily with VIEKIRA XR is not recommended.
lopinavir/ritonavir	↑ paritaprevir	Co-administration of VIEKIRA XR with lopinavir/ritonavir is not recommended.
ANTIRETROVIRAL AGENTS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
rilpivirine	↑ rilpivirine	Contraindicated non-nucleoside reverse transcriptase inhibitors *[see Contraindications (4)]*. Rilpivirine: Co-administration of VIEKIRA XR with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS:		
pravastatin rosuvastatin	↑ pravastatin ↑ rosuvastatin	Contraindicated HMG CoA Reductase Inhibitors *[see Contraindications (4)]*. Rosuvastatin: Dose of rosuvastatin should not exceed 10 mg per day. Pravastatin: Dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		

cyclosporine	↑ cyclosporine	For contraindicated immunosuppressants *[see Contraindications (4)]*. When initiating therapy with VIEKIRA XR, reduce cyclosporine dose to 1/5th of the patient's current cyclosporine dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Upon completion of VIEKIRA XR therapy, the appropriate time to resume pre-VIEKIRA XR dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol*	↑ salmeterol	Concurrent administration of VIEKIRA XR and salmeterol is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
MUSCLE RELAXANTS		
carisoprodol	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)	Increase dose if clinically indicated.
cyclobenzaprine	↓cyclobenzaprine ↓norcyclobenzaprine (metabolite of cyclobenzaprine)	Increase dose if clinically indicated.
NARCOTIC ANALGESICS		
acetaminophen/hydrocodone	↑ hydrocodone ↔ acetaminophen	Reduce the dose of hydrocodone by 50% and monitor patients for respiratory depression and sedation at frequent intervals. Upon completion of VIEKIRA XR therapy, adjust the hydrocodone dose and monitor for signs of opioid withdrawal.
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine (metabolite of buprenorphine)	Patients should be closely monitored for sedation and cognitive effects.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Monitor patients for decreased efficacy of

		omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Contraindicated Sedatives/Hypnotics *[see Contraindications (4)]*. Alprazolam: Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)	Increase dose if clinically indicated.
See Clinical Pharmacology, Tables 7 and 8. The direction of the arrow indicates the direction of the change in exposures (C_{max} and AUC) (↑ *= increase of more than 20%,* ↓ *= decrease of more than 20%,* ↔ *= no change or change less than 20%).* *not studied.		

7.4 Drugs without Clinically Significant Interactions with VIEKIRA XR

No dosage adjustments are recommended when VIEKIRA XR is co-administered with the following medications: abacavir, dolutegravir, digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, lamivudine, methadone, progestin only contraceptives, raltegravir, sofosbuvir, sulfamethoxazole, trimethoprim, warfarin and zolpidem.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

If VIEKIRA XR is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in pregnancy.

No adequate human data are available to establish whether or not VIEKIRA XR poses a risk to pregnancy outcomes. In animal reproduction studies, no adverse developmental effects were observed when the components of VIEKIRA XR were administered separately during organogenesis and lactation. During organogenesis, the exposures were up to 28 and 4 times (mice and rabbits, respectively; ombitasvir), 8 and 98 times (mice and rats, respectively; paritaprevir, ritonavir), and 24 and 6 times (rats and rabbits, respectively; dasabuvir) exposures at the recommended clinical dose of VIEKIRA XR. In rodent pre/postnatal developmental studies,

maternal systemic exposures (AUC) to ombitasvir, paritaprevir and dasabuvir were approximately 25, 17 and 44 times, respectively, the exposure in humans at the recommended clinical dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

Dasabuvir

Dasabuvir was administered orally to pregnant rats (0, 60, 300 and 800 mg/kg/day) and rabbits (0, 100, 200 or 400 mg/kg/day) during the period of organogenesis (on GD 6 to 17 and GD 7 to 20, respectively). There were no test article-related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The highest systemic exposure of dasabuvir was 24-times higher (rats) and 6-times higher (rabbits) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in rats, dasabuvir was administered orally at 0, 50, 200, or 800 mg/kg/day from GD 7 to lactation day 21. There were no treatment-related effects at maternal exposures 44-times higher than exposures in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir was administered orally to pregnant mice (0, 15, 50, or 150 mg/kg/day) and rabbits (0, 10 or 60 mg/kg/day) during the period of organogenesis (on gestation days (GD) 6 to 15, and GD 7 to 19, respectively). There were no ombitasvir-related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The systemic exposures at the highest doses were 28-times higher (mice) and 4-times higher (rabbits) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in mice, ombitasvir was administered orally at 0, 10, 40, or 200 mg/kg/day from GD 6 to lactation day 20. There were no ombitasvir-related effects at maternal exposures 25-times higher than exposures in humans at the recommended clinical dose.

The major human metabolites of ombitasvir, M29 and M36, were tested in pregnant mice during the period of organogenesis from GD 6 to 15. M29 was administered orally at doses of 0, 1, 2.5 or 4.5 mg/kg/day. M36 was dosed orally at doses 1.5, 3, or 6 mg/kg/day. In both cases, there were no treatment related embryofetal effects (malformations or fetal toxicity) at any dose level. The highest doses produced exposures approximately 26-times higher than the exposures in humans at the recommended clinical dose.

Paritaprevir/ritonavir

Paritaprevir/ritonavir was administered orally to pregnant rats (0/0, 30/15, 100/15, 450/45 mg/kg/day) and mice (0/0, 30/30, 100/30, or 300/30 mg/kg/day) during the period of organogenesis (on GD 6 to 17, and GD 6 to 15, respectively). There were no test article-

related embryofetal effects (malformations or fetal toxicity) at any dose level in either species. The highest systemic exposure of paritaprevir was 8-times higher (rats) and 98-times higher (mice) than the exposures in humans at the recommended clinical dose.

In a pre- and postnatal developmental study in rats, paritaprevir/ritonavir were administered orally at 0/0, 6/30, 30/30, or 300/30 mg/kg/day from GD 7 to lactation day 20. There were no treatment related effects at maternal exposures 17-times higher than exposures in humans at the recommended clinical dose.

8.2 Lactation

Risk Summary

It is not known whether VIEKIRA XR and its metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. Unchanged ombitasvir, paritaprevir and its hydrolysis product M13, and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIEKIRA XR and any potential adverse effects on the breastfed child from VIEKIRA XR or from the underlying maternal condition.

If VIEKIRA XR is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.

Data

Animal Data

Dasabuvir

No effects of dasabuvir on growth and postnatal development were observed in nursing pups at the highest dose tested (800 mg/kg/day) in rats. Maternal systemic exposure (AUC) to dasabuvir was approximately 44 times the exposure in humans at the recommended clinical dose. Although not measured directly, dasabuvir was likely present in the milk of lactating rats in this study, since systemic exposure was observed in nursing pups on post-natal day 14 (approximately 14% of maternal exposure).

When dasabuvir was administered to lactating rats (5 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was 2 times higher than that in plasma, with unchanged parent drug (78%) accounting for the majority of drug-related material in milk.

Ombitasvir

No effects of ombitasvir on growth and postnatal development were observed in nursing pups at the highest dose tested (200 mg/kg/day) in mice. Maternal systemic exposure (AUC) to ombitasvir was approximately 25 times the exposure in humans at the recommended clinical dose. Although not measured directly, ombitasvir was likely present in the milk of lactating mice in this study, since systemic exposure was observed in nursing pups on post-natal day 21 (approximately 16% of maternal exposure).

When ombitasvir was administered to lactating rats (5 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was 4 times higher than that in plasma, with unchanged parent drug (91%) accounting for the majority of drug-related material in milk.

Paritaprevir/ritonavir

No effects of paritaprevir/ritonavir on growth and postnatal development were observed in nursing pups at the highest dose tested (300/30 mg/kg/day) in rats. Maternal systemic exposure (AUC) to paritaprevir was approximately 17 times the exposure in humans at the recommended clinical dose. Although not measured directly, paritaprevir was likely present in the milk of lactating rats at the high dose in this study, since systemic exposure was observed in nursing pups on post-natal day 15 (approximately 0.3 % of maternal exposure).

When paritaprevir/ritonavir was administered to lactating rats (30/15 mg/kg on post-partum day 10 to 11), milk exposure (AUC) was half that in plasma, with the hydrolysis product M13 (84%) and unchanged parent drug (16%) accounting for all paritaprevir-related material in milk.

8.3 Females and Males of Reproductive Potential

If VIEKIRA XR is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to ribavirin prescribing information for additional information.

8.4 Pediatric Use

Safety and effectiveness of VIEKIRA XR in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

No dosage adjustment of VIEKIRA XR is warranted in geriatric patients. Of the total number of subjects in clinical studies of the components of VIEKIRA XR, 8.5% (174/2053) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No dosage adjustment of VIEKIRA XR is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA XR is contraindicated in patients with moderate to severe (Child-Pugh B and C) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment of VIEKIRA XR is required in patients with mild, moderate or severe renal impairment, including those on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

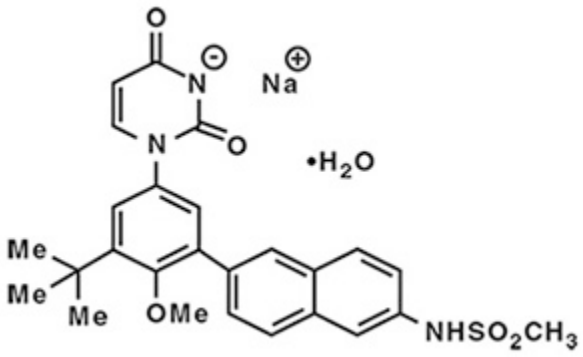
In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

VIEKIRA XR fixed dose combination, extended-release tablet includes a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor (dasabuvir), a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir. The tablets are for oral administration.

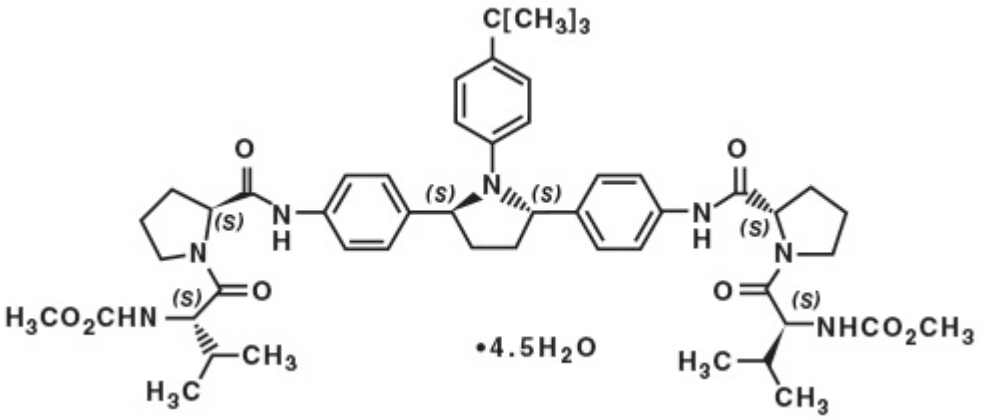
Dasabuvir

The chemical name of dasabuvir is 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). The molecular formula is $C_{26}H_{26}N_3O_5S•Na•H_2O$ (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate). The drug substance is white to pale yellow to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. Dasabuvir has the following molecular structure:



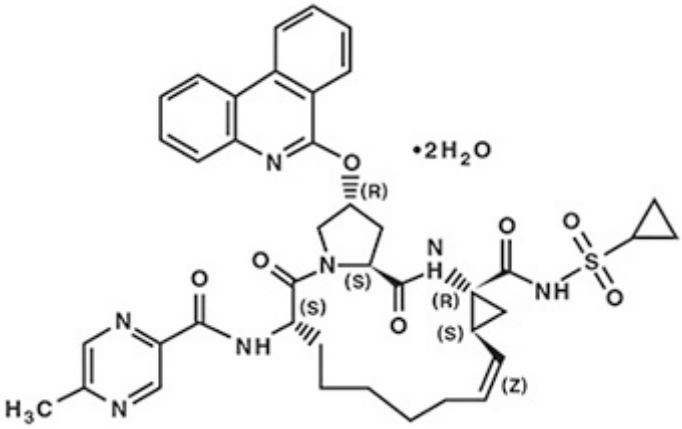
Ombitasvir

The chemical name of ombitasvir is 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. The molecular formula is $C_{50}H_{67}N_7O_8•4.5H_2O$ (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:



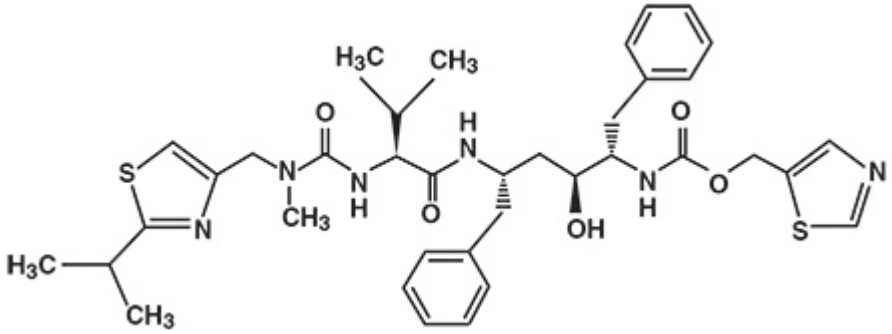
Paritaprevir

The chemical name of paritaprevir is (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. The molecular formula is $C_{40}H_{43}N_7O_7S \bullet 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



Ritonavir

The chemical name of ritonavir is [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. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:



Dasabuvir, Ombitasvir, Paritaprevir, Ritonavir Film-Coated Bilayer Tablets

Dasabuvir, ombitasvir, paritaprevir, and ritonavir film-coated bilayer tablets consist of an extended release (ER) layer and an immediate release (IR) layer. The ER layer contains 200 mg dasabuvir (equivalent to 216.2 mg of dasabuvir sodium monohydrate). The ER layer of the tablet also contains copovidone, K value 28, hypromellose 2208, 17,700 (mPa*s), colloidal silicon dioxide/colloidal anhydrous silica and magnesium stearate. The IR layer contains 8.33 mg ombitasvir, 50 mg paritaprevir and 33.33 mg ritonavir. Strength of ombitasvir and paritaprevir in the drug product are expressed on the anhydrous basis. The IR layer of the tablet also contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica. The tablet coating contains hypromellose (6 mPa*s), hypromellose (15 mPa*s), polyethylene glycol 400, hydroxypropyl cellulose, polysorbate 80, polyethylene glycol 3350/macrogol 4000, talc, titanium dioxide, colloidal silicon dioxide/colloidal anhydrous silica and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIEKIRA XR combines three direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action *[see Microbiology (12.4)]*.

Ritonavir is not active against HCV. Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (i.e., area under the curve).

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of a combination of ombitasvir, paritaprevir, ritonavir, and dasabuvir on QTc interval was evaluated in a randomized, double blind, placebo and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 60 healthy subjects. At concentrations approximately 6, 1.8 and 2 times the therapeutic concentrations of paritaprevir, ombitasvir, and dasabuvir, the combination did not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Dasabuvir, ombitasvir, paritaprevir, and ritonavir film-coated bilayer tablets consist of an extended-release (ER) layer of dasabuvir and an immediate-release (IR) layer of ombitasvir, paritaprevir and ritonavir.

The pharmacokinetic properties of the components of VIEKIRA XR are provided in Table 6.

Table 6. Pharmacokinetic Properties of the Components of VIEKIRA XR

	Ombitasvir	Paritaprevir	Ritonavir	Dasabuvir
Absorption				
T_{max} (hr) median values	5	5	4	8
Absolute bioavailability (%)	48	53	NA	70
Effect of high fat meal relative to fasting[a,b]	1.96 (1.83-2.15)	4.60 (3.8-5.57)	2.13 (1.86-2.43)	5.92 (5.06-6.92)
Accumulation[c]	0.90- to 1.03-fold	1.5- to 2-fold		0.96-fold
Distribution				
% Bound to human plasma proteins	99.9	97-98.6	>99	>99.5
Blood-to-plasma ratio	0.49	0.7	0.6	0.7
Volume of distribution at steady state (Vss) (L)	173	103	21.5[d]	149
Metabolism				
Metabolism	amide hydrolysis followed by oxidative metabolism	CYP3A4 (major), CYP3A5	CYP3A (major), CYP2D6	CYP2C8 (major), CYP3A
Elimination[e]				
Major route of elimination	biliary excretion	metabolism	metabolism	metabolism
$t_{1/2}$ (hr)[f]	21-25	5.5	4	5.5-6
% of dose excreted in feces[g]	90.2	88	86.4	94.4
% of dose excreted unchanged in feces[g]	87.8	1.1	33.8	26.2
% of dose excreted in urine[g]	1.91	8.8	11.3	~ 2
% of dose excreted unchanged in urine[g]	0.03	0.05	3.5	0.03

NA - data not available

a. High fat meal of 753 Kcal; 55.3% calories from fat, 27.8% calories from carbohydrates, and

16.9% calories from protein.
b. Similar results are expected for ombitasvir, paritaprevir and dasabuvir under moderate fat meal conditions.
c. Steady state exposures are achieved after approximately 12 days of dosing.
d. It is apparent volume of distribution (V/F) for ritonavir.
e. Ombitasvir, paritaprevir, ritonavir, and dasabuvir do not inhibit organic anion transporter (OAT1) *in vivo* and based on *in vitro* data, are not expected to inhibit organic cation transporter (OCT2), organic anion transporter (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.
f. $t_{1/2}$ values refer to the mean elimination half-life.
g. Dosing in mass balance studies: single dose administration of [^{14}C] ombitasvir; single dose administration of [^{14}C] paritaprevir co-dosed with 100 mg ritonavir; single dose administration of [^{14}C] dasabuvir.

Specific Populations

There are no clinically relevant changes in the pharmacokinetics of the components of VIEKIRA XR in relation to sex, race/ethnicity, or geriatric age *[see Use in Specific Populations (8.5)]*. The pharmacokinetics of VIEKIRA XR in pediatric patients less than 18 years of age have not been established *[see Use in Specific Populations (8.4)]*.

Hepatic Impairment

The single dose pharmacokinetics of the combination of dasabuvir, ombitasvir, paritaprevir, and ritonavir were evaluated in non-HCV infected subjects with mild hepatic impairment (Child-Pugh Category A; score of 5-6), moderate hepatic impairment (Child-Pugh Category B, score of 7-9) and severe hepatic impairment (Child-Pugh Category C, score of 10-15).

Relative to subjects with normal hepatic function, dasabuvir AUC values increased by 17%, and ombitasvir, paritaprevir and ritonavir AUC values decreased by 8%, 29% and 34%, respectively, in subjects with mild hepatic impairment.

Relative to subjects with normal hepatic function, dasabuvir, ombitasvir, and ritonavir AUC values decreased by 16%, 30%, and 30% respectively, and paritaprevir AUC values increased by 62% in subjects with moderate hepatic impairment.

Relative to subjects with normal hepatic function, dasabuvir, paritaprevir, and ritonavir AUC values increased by 325%, 945%, and 13%, respectively, and ombitasvir AUC values decreased by 54% in subjects with severe hepatic impairment.

Renal Impairment

The single dose pharmacokinetics of the combination of dasabuvir, ombitasvir, paritaprevir, and ritonavir were evaluated in non-HCV infected subjects with mild (CL_{cr}: 60 to 89 mL/min), moderate (CL_{cr}: 30 to 59 mL/min), and severe (CL_{cr}: 15 to 29 mL/min) renal impairment.

Pharmacokinetic data are not available on the use of VIEKIRA XR in non-HCV infected subjects with End Stage Renal Disease (ESRD).

Relative to subjects with normal renal function, dasabuvir, paritaprevir, and ritonavir AUC values increased by 21%, 19%, and 42% respectively, while ombitasvir AUC values were unchanged in subjects with mild renal impairment.

Relative to subjects with normal renal function, dasabuvir, paritaprevir, and ritonavir AUC values increased by 37%, 33%, and 80% respectively, while ombitasvir AUC values were unchanged in subjects with moderate renal impairment.

Relative to subjects with normal renal function, dasabuvir, paritaprevir, and ritonavir AUC values increased by 50%, 45%, and 114% respectively, while ombitasvir AUC values were unchanged in subjects with severe renal impairment *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

See also Contraindications (4), Warnings and Precautions (5.5), Drug Interactions (7)

All drug-drug interaction trials were conducted with VIEKIRA PAK. The effects of some drugs discussed in Table 5 on the exposures of dasabuvir, ombitasvir, paritaprevir, and ritonavir are shown in Table 7. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 7. Drug Interactions: Change in Pharmacokinetic Parameters of Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir 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}
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)
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)
Atazanavir/ ritonavir[a]	Atazanavir 300	11	dasabuvir	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)

	and ritonavir 100 once daily in the evening		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)
			ritonavir	1.60 (1.38, 1.86)	3.18 (2.74, 3.69)	24.65 (18.64, 32.60)
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
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)
Cyclosporine	30 single dose[b]	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)
Darunavir[c]	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	1.29	1.30

				(1.14, 2.09)	(1.04, 1.61)	(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[d]	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[e]	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)
Diazepam	2 single dose	13	dasabuvir	1.05 (0.98, 1.13)	1.01 (0.94, 1.08)	1.05 (0.98, 1.12)
			ombitasvir	1.00 (0.93, 1.08)	0.98 (0.93, 1.03)	0.93 (0.88, 0.98)
			paritaprevir	0.95 (0.77, 1.18)	0.91 (0.78, 1.07)	0.92 (0.82, 1.03)
			ritonavir	1.10 (1.02, 1.19)	1.06 (0.98, 1.14)	0.98 (0.92, 1.03)
Ethinyl estradiol/ Norgestimate	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	7[f]	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)
Everolimus	0.75 single dose	12	ombitasvir	0.99 (0.95, 1.03)	1.02 (0.99, 1.05)	1.02 (0.99, 1.06)
			paritaprevir	1.22 (1.03, 1.43)	1.26 (1.07, 1.49)	1.06 (0.97, 1.16)
			ritonavir	1.07 (0.99, 1.16)	1.05 (1.00, 1.10)	1.07 (1.02, 1.13)
			dasabuvir	1.03 (0.90, 1.18)	1.08 (0.98, 1.20)	1.14 (1.05, 1.23)

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)
Gemfibrozil[g]	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
			ritonavir	0.84 (0.69, 1.03)	0.90 (0.78, 1.04)	NA
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)
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
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[h]	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)
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)
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)	0.94 (0.89, 0.99)	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)
Rilpivirine	25 once daily (morning)[i]	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)
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)
Sirolimus	0.5 single dose[j]	11	ombitasvir	1.03 (0.93, 1.15)	1.02 (0.96, 1.09)	1.05 (0.98, 1.12)
			paritaprevir	1.18 (0.91, 1.54)	1.19 (0.97, 1.46)	1.16 (1.00, 1.34)
			ritonavir	1.00 (0.85, 1.17)	1.04 (0.94, 1.15)	1.10 (1.04, 1.17)
			dasabuvir	1.04	1.07	1.13

				(0.89, 1.22)	(0.95, 1.22)	(1.01, 1.25)
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)

a. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of the components of VIEKIRA XR.
b. 30 mg cyclosporine was administered with the components of VIEKIRA XR in the test arm and 100 mg cyclosporine was administered in the reference arm without the components of VIEKIRA XR.
c. Darunavir administered with the components of VIEKIRA XR in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.
d. Darunavir administered with the components of VIEKIRA XR 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.
e. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after the morning dose of the components of VIEKIRA XR compared to darunavir administered with 100 mg ritonavir in the evening.
f. N=3 for dasabuvir.
g. Study was conducted with paritaprevir, ritonavir and dasabuvir.
h. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of the components of VIEKIRA XR.
i. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
j. 0.5 mg sirolimus was administered with the components of VIEKIRA XR in the test arm and 2 mg sirolimus was administered in the reference arm without the components of VIEKIRA XR.

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 8 summarizes the effects of dasabuvir, ombitasvir, paritaprevir, and ritonavir on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 8. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of VIEKIRA XR

Co-administered	Dose of Co-	n	Ratio (with/without the Components

Drug	administered Drug (mg)		of VIEKIRA XR) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			C_{max}	AUC	C_{min}
Alprazolam	0.5 single dose	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
Amlodipine	5 single dose	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
Atazanavir/ ritonavir[a]	Atazanavir 300 and ritonavir 100 once daily in the evening	12	1.02 (0.92, 1.13)[b]	1.19 (1.11, 1.28)[b]	1.68 (1.44, 1.95)[b]
Buprenorphine	Buprenorphine: 4 to 24 once daily and Naloxone 1 to 6 once daily	10	2.18 (1.78, 2.68)[c]	2.07 (1.78, 2.40)[c]	3.12 (2.29, 4.27)[c]
Norbuprenorphine			2.07 (1.42, 3.01)[c]	1.84 (1.30, 2.60)[c]	2.10 (1.49, 2.97)[c]
Naloxone			1.18 (0.81, 1.73)	1.28 (0.92, 1.79)[c]	NA
Carbamazepine	200 once daily followed by 200 twice daily	12	1.10 (1.07, 1.14)	1.17 (1.13, 1.22)	1.35 (1.27, 1.45)
Carbamazepine's metabolite, carbamazepine-10,11-epoxide (CBZE)			0.84 (0.82, 0.87)	0.75 (0.73, 0.77)	0.57 (0.54, 0.61)
Carisoprodol	250 single dose	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 single dose	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 single dose[d]	10	1.01 (0.85, 1.20)[c]	5.82 (4.73, 7.14)[c]	15.80 (13.81, 18.09)[c]
Darunavir[e]	800 once daily	8	0.92 (0.87, 0.98)[b]	0.76 (0.71, 0.82)[b]	0.52 (0.47, 0.58)[b]
Darunavir/ ritonavir[f]	Darunavir 600 twice daily and ritonavir 100	7	0.87 (0.79, 0.96)[b]	0.80 (0.74, 0.86)[b]	0.57 (0.48, 0.67)[b]

	once daily in the evening				
Darunavir/ ritonavir[g]	Darunavir 800 and ritonavir 100 once daily in the evening	10	0.79 (0.70, 0.90)[b]	1.34 (1.25, 1.43)[b]	0.54 (0.48, 0.62)[b]
Diazepam	2 single dose	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
Ethinyl Estradiol	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)
Norelgestromin		9	2.01 (1.77, 2.29)	2.60 (2.30, 2.95)	3.11 (2.51, 3.85)
Norgestrel		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
Everolimus	0.75 single dose	12	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)
Furosemide	20 single dose	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
Hydrocodone	5 single dose	15	1.27 (1.14, 1.40)	1.90 (1.72, 2.10)	NA
Ketoconazole	400 once daily	12	1.15 (1.09, 1.21)	2.17 (2.05, 2.29)	NA
Lopinavir/ ritonavir	400/100 twice daily	6	0.87 (0.76, 0.99)[b]	0.94 (0.81, 1.10)[b]	1.15 (0.93, 1.42)[b]
Lopinavir/ ritonavir[h]	800/200 once daily	12	0.86 (0.80, 0.93)[b]	0.94 (0.87, 1.01)[b]	3.18 (2.49, 4.06)[b]
Omeprazole	40 once daily	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
Pravastatin	10 once daily	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
Rilpivirine	25 once daily (morning)[i]	8	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
Rosuvastatin	5 once daily	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)
Sirolimus	0.5 single dose[j]	11	6.40 (5.34, 7.68)[c]	37.99 (31.5, 45.8)[c]	19.55 (16.7, 22.9)[c]
Tacrolimus	2 single dose	12	3.99 (3.21, 4.97)[c]	57.13 (45.53,	16.56 (12.97,

				71.69)[c]	21.16)[c]

a. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of the components of VIEKIRA XR.
b. Atazanavir or darunavir or lopinavir parameters are reported.
c. Dose normalized parameters reported.
d. 30 mg cyclosporine was administered with the components of VIEKIRA XR in the test arm and 100 mg cyclosporine was administered in the reference arm without the components of VIEKIRA XR.
e. Darunavir administered with the components of VIEKIRA XR in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.
f. Darunavir administered with the components of VIEKIRA XR 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.
g. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of the components of VIEKIRA XR compared to darunavir administered with 100 mg ritonavir in the evening.
h. Lopinavir/ritonavir administered in the evening, 12 hours after morning dose of the components of VIEKIRA XR.
i. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.
j. 0.5 mg sirolimus was administered with the components of VIEKIRA XR in the test arm and 2 mg sirolimus was administered in the reference arm without the components of VIEKIRA XR.

NA: not available/not applicable; 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 ketoconazole and carbamazepine that used single doses.

12.4 Microbiology

Mechanism of Action

VIEKIRA XR 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.

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 a panel of genotype 1a and 1b NS5B polymerases with median IC_{50} values of 2.8 nM (range 2.4 nM to 4.2 nM; n = 3) and 3.7 nM (range 2.2 nM to 10.7 nM; n = 4), respectively. Based on drug resistance mapping studies of HCV genotypes 1a and 1b, dasabuvir targets the palm domain of the NS5B polymerase, and is therefore referred to as a non-nucleoside NS5B-palm polymerase inhibitor.

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of ombitasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Paritaprevir

Paritaprevir is an inhibitor of the 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 recombinant HCV genotype 1a and 1b NS3/4A protease enzymes with IC_{50} values of 0.18 nM and 0.43 nM, respectively.

Antiviral Activity

Dasabuvir

The EC_{50} values of dasabuvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays were 7.7 nM and 1.8 nM, respectively. The median EC_{50} values of dasabuvir against HCV replicons containing NS5B genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.6 nM (range 0.4 nM to 2.1 nM; n = 11) and 0.3 nM (range 0.2 nM to 2 nM; n = 10), respectively.

Ombitasvir

The EC_{50} values of ombitasvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays were 14.1 pM and 5 pM, respectively. The median EC_{50} values of ombitasvir against HCV replicons containing NS5A genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.68 pM (range 0.35 to 0.88 pM; n = 11) and 0.94 pM (range 0.74 to 1.5 pM; n = 11), respectively.

Paritaprevir

The EC_{50} values of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay were 1.0 nM and 0.21 nM, respectively. The median EC_{50} values of paritaprevir against HCV replicons containing NS3 genes from a panel of genotype 1a and 1b isolates from treatment-naïve subjects were 0.68 nM (range 0.43 nM to 1.87 nM; n = 11) and 0.06 nM (range 0.03 nM to 0.09 nM; n = 9), respectively.

Ritonavir

In HCV replicon cell culture assays, ritonavir did not exhibit a direct antiviral effect and the presence of ritonavir did not affect the antiviral activity of paritaprevir.

Combination Antiviral Activity

Evaluation of pairwise combinations of ombitasvir, paritaprevir, dasabuvir and ribavirin in HCV genotype 1 replicon cell culture assays showed no evidence of antagonism in antiviral activity.

Resistance

In Cell Culture

Exposure of HCV genotype 1a and 1b replicons to ombitasvir, paritaprevir or dasabuvir resulted in the emergence of drug resistant replicons carrying amino acid substitutions in

NS5A, NS3, or NS5B, respectively. Amino acid substitutions in NS5A, NS3, or NS5B selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a or 1b replicons.

For dasabuvir, in HCV genotype 1a replicons single NS5B substitutions C316Y, M414I/T, E446K/Q, Y448C/H, A553T, G554S, S556G/R, and Y561H reduced dasabuvir antiviral activity by 8- to 1,472-fold. In genotype 1b replicons, single NS5B substitutions C316H/N/Y, S368T, N411S, M414I/T, Y448C/H, A553V, S556G and D559G reduced dasabuvir antiviral activity by 5- to 1,569-fold.

For ombitasvir, in HCV genotype 1a replicons single NS5A substitutions M28T/V, Q30E/R, L31V, H58D, and Y93C/H/L/N reduced ombitasvir antiviral activity by 58- to 67,000-fold. In genotype 1b replicons, single NS5A substitutions L28T, L31F/V, and Y93H reduced ombitasvir antiviral activity by 8- to 661-fold. In general, combinations of ombitasvir resistance-associated substitutions in HCV genotype 1a or 1b replicons further reduced ombitasvir antiviral activity.

For paritaprevir, in HCV genotype 1a replicons single NS3 substitutions F43L, R155G/K/S, A156T, and D168A/E/F/H/N/V/Y reduced paritaprevir antiviral activity by 7- to 219-fold. An NS3 Q80K substitution in a genotype 1a replicon reduced paritaprevir antiviral activity by 3-fold. Combinations of V36M, Y56H, or E357K with R155K or D168 substitutions reduced the activity of paritaprevir by an additional 2- to 7-fold relative to the single R155K or D168 substitutions in genotype 1a replicons. In genotype 1b replicons single NS3 substitutions A156T and D168A/H/V reduced paritaprevir antiviral activity by 7- to 159-fold. The combination of Y56H with D168 substitutions reduced the activity of paritaprevir by an additional 16- to 26-fold relative to the single D168 substitutions in genotype 1b replicons.

In Clinical Studies

In a pooled analysis of subjects treated with regimens containing dasabuvir, ombitasvir, paritaprevir, and ritonavir with or without ribavirin (for 12 or 24 weeks) in Phase 2b and Phase 3 clinical trials, resistance analyses were conducted for 64 subjects who experienced virologic failure (20 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent substitutions observed in the viral populations of these subjects are shown in Table 9. Treatment-emergent substitutions were detected in all 3 HCV drug targets in 30/57 (53%) HCV genotype 1a infected subjects, and 1/6 (17%) HCV genotype 1b infected subjects.

Table 9. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of the Components of VIEKIRA XR with and without Ribavirin Regimens (12- or 24-week durations) in Phase 2b and Phase 3 Clinical Trials

Target	Emergent Amino Acid Substitutions	Genotype 1a N = 58[a] % (n)	Genotype 1b N = 6 % (n)
NS3	Any of the following NS3 substitutions: V36A/M/T, F43L, V55I, Y56H, Q80L, I132V, R155K, A156G, D168(any), P334S, S342P, E357K, V406A/I, T449I,	88 (51)	67 (4)

	P470S, V23A (NS4A)		
	V36A/M/T[b]	7 (4)	--
	V55I[b]	7 (4)	--
	Y56H[b]	10 (6)	50 (3)
	I132V[b]	7 (4)	--
	R155K	16 (9)	--
	D168 (any)[d]	72 (42)	67 (4)
	D168V	59 (34)	50 (3)
	P334S[b,c]	7 (4)	--
	E357K[b,c]	5 (3)	17 (1)
	V406A/I[b,c]	5 (3)	--
	T449I[b,c]	5 (3)	--
	P470S[b,c]	5 (3)	--
	NS4A V23A[b]	--	17 (1)
	F43L[b], Q80L[b], A156G, S342P[b,c]	<5%	--
NS5A	Any of the following NS5A substitutions: K24R, M28A/T/V, Q30E/K/R, H/Q54Y, H58D/P/R, Y93C/H/N	78 (45)	33 (2)
	K24R	5 (3)	--
	M28A/T/V	33 (19)	--
	Q30E/K/R	47 (27)	--
	H/Q54Y	--	17 (1)
	H58D/P/R	7 (4)	--
	Y93C/N	5 (3)	--
	Y93H	--	33 (2)
NS5B	Any of the following NS5B substitutions: G307R, C316Y, M414I/T, E446K/Q, A450V, A553I/T/V, G554S, S556G/R, G558R, D559G/I/N/V, Y561H	67 (38)	33 (2)
	C316Y	4 (2)	17 (1)
	M414I	--	17 (1)
	M414T	5 (3)	17 (1)
	A553I/T/V	7 (4)	--
	S556G/R	39 (22)	17 (1)
	D559G/I/N/V	7 (4)	--
	Y561H	5 (3)	--
	G307R, E446K/Q, A450V, G554S, G558R	<5%	--

a. N = 57 for the NS5B target.
b. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.
c. Position located in NS3 helicase domain.
d. D168A/F/H/I/L/N/T/V/Y.

Persistence of Resistance-Associated Substitutions

The persistence of dasabuvir, ombitasvir, and paritaprevir treatment-emergent amino acid substitutions in NS5B, NS5A, and NS3, respectively, was assessed in HCV genotype 1a-infected subjects in Phase 2 trials whose virus had at least 1 treatment-emergent resistance-associated substitution in the drug target, and with available data through at least 24 weeks post-treatment. Population and clonal nucleotide sequence analyses (assay sensitivity approximately 5-10%) were conducted to detect the persistence of viral populations with treatment-emergent substitutions.

For dasabuvir, viral populations with 1 or more treatment-emergent substitutions in NS5B persisted at detectable levels through at least Post-Treatment Week 24 in 11/16 (69%) subjects, and through Post-Treatment Week 48 in 8/15 (53%) subjects with available data. Treatment-emergent S556G persisted through Post-Treatment Week 48 in 6/9 (67%) subjects.

For ombitasvir, viral populations with 1 or more resistance-associated treatment-emergent substitutions in NS5A persisted at detectable levels through at least Post-Treatment Week 24 in 24/24 (100%) subjects, and through Post-Treatment Week 48 in 18/18 (100%) subjects with available data.

For paritaprevir, viral populations with 1 or more treatment-emergent substitutions in NS3 persisted at detectable levels through at least Post-Treatment Week 24 in 17/29 (59%) subjects, and through Post-Treatment Week 48 in 5/22 (23%) subjects with available data. Resistance-associated variant R155K remained detectable in 5/8 (63%) subjects through Post-Treatment Week 24, and in 1/5 (20%) subjects through Post-Treatment Week 48. Resistance-associated D168 substitutions remained detectable in 6/22 (27%) subjects through Post-Treatment Week 24, and were no longer detectable through Post-Treatment Week 48.

Among HCV genotype 1b infected subjects who experienced virologic failure with a regimen including ombitasvir and paritaprevir, a treatment-emergent NS5A Y93H substitution persisted through at least Post-Treatment Week 48 in 2/2 subjects, and a NS3 D168V treatment-emergent substitution persisted through Post-Treatment Week 24 in 2/4 subjects, but was no longer detectable through Post-Treatment Week 48 (0/4 subjects).

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 VIEKIRA XR-resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

A pooled analysis of subjects in the Phase 3 clinical trials of dasabuvir, ombitasvir, and paritaprevir with or without ribavirin was conducted to explore the association between baseline HCV NS5B, NS5A, or NS3 resistance-associated polymorphisms and treatment outcome. Baseline samples from HCV genotype 1a infected subjects who experienced virologic failure (n=47), as well as samples from a subset of demographically matched subjects who achieved SVR (n=94), were analyzed to compare the frequencies of resistance-associated polymorphisms in these two populations. The NS3 Q80K polymorphism was detected in approximately 38% of subjects in this analysis and was enriched approximately 2-fold in virologic failure subjects compared to SVR-achieving subjects. Ombitasvir resistance-associated polymorphisms in NS5A (pooling data from all resistance-associated amino acid positions) were detected in approximately 22% of subjects in this analysis and similarly were enriched approximately 2-fold in virologic failure subjects. Dasabuvir resistance-associated polymorphisms in NS5B were detected in approximately 5% of subjects in this analysis and were not enriched in virologic failure subjects.

In contrast to the Phase 3 subset analysis, no association of NS3 or NS5A polymorphisms and treatment outcome was seen in an analysis of noncirrhotic HCV genotype 1a-infected subjects (n=174 for NS3 and n=183 for NS5A) who received dasabuvir, ombitasvir, and paritaprevir with or without ribavirin (for 12 or 24 weeks) in a Phase 2b trial.

Baseline HCV polymorphisms are not expected to have a substantial impact on the likelihood of achieving SVR when VIEKIRA XR is used as recommended for HCV genotype 1a and 1b infected patients, based on the low virologic failure rates observed in clinical trials.

Cross-resistance

Cross-resistance is expected among NS5A inhibitors, NS3/4A protease inhibitors, and non-nucleoside NS5B-palm inhibitors by class. Dasabuvir retained full activity against HCV replicons containing a single NS5B L159F, S282T, or V321A substitution, which are associated with resistance or prior exposure to nucleot(s)ide analogue NS5B polymerase inhibitors. In clinical trials of the components of VIEKIRA XR, no subjects who experienced virologic failure had treatment-emergent substitutions potentially associated with resistance to nucleot(s)ide analogue NS5B polymerase inhibitors.

The impact of prior dasabuvir, ombitasvir, or paritaprevir treatment experience on the efficacy of other NS5B inhibitors, NS5A inhibitors, or NS3/4A protease inhibitors has not been studied. Similarly, the efficacy of VIEKIRA XR has not been studied in subjects who have failed prior treatment with another NS5B inhibitor, NS5A inhibitor, or NS3/4A protease inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Dasabuvir

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (2000 mg per kg per day). Similarly, dasabuvir was not carcinogenic in a 2-year rat study up to the highest dose tested (800 mg per kg per day), resulting in dasabuvir exposures approximately 19-fold higher than those in humans at 500 mg.

Dasabuvir was not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* rat micronucleus assays.

Ombitasvir

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (150 mg per kg per day). Similarly, ombitasvir was not carcinogenic in a 2-year rat study up to the highest dose tested (30 mg per kg per day), resulting in ombitasvir exposures approximately 16-fold higher than those in humans at 25 mg.

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of *in vitro* or *in vivo* assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and *in vivo* mouse micronucleus assays.

Paritaprevir, ritonavir

Paritaprevir, ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (300/30 mg per kg per day). Similarly, paritaprevir, ritonavir was not carcinogenic in a 2-year rat study up to the highest dose tested (300/30 mg per kg per day), resulting in paritaprevir exposures approximately 9-fold higher than those in humans at 150 mg.

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

If VIEKIRA XR is administered with ribavirin, refer to the prescribing information for ribavirin for information on carcinogenesis, and mutagenesis.

Impairment of Fertility

Dasabuvir

Dasabuvir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 800 mg per kg per day. Dasabuvir exposures at this dose were approximately 16-fold the exposure in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir had no effects on embryo-fetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg per kg per day. Ombitasvir exposures at this dose were approximately 25-fold the exposure in humans at the recommended clinical dose.

Paritaprevir, ritonavir

Paritaprevir, ritonavir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg per kg per day. Paritaprevir exposures at this dose were approximately 2- to 5-fold the exposure in humans at the recommended clinical dose.

If VIEKIRA XR is administered with ribavirin, refer to the prescribing information for ribavirin for information on Impairment of Fertility.

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

Table 10 presents the clinical trial design including different treatment arms that were conducted with the components of VIEKIRA XR with or without ribavirin in subjects with chronic hepatitis C (HCV) genotype 1 (GT1) infection. For detailed description of trial design and recommended regimen and duration *[see Dosage and Administration (2) and Clinical Studies (14)]*.

Table 10. Clinical Trials Conducted with the Components of VIEKIRA XR With or Without Ribavirin (RBV) in Subjects with Chronic HCV GT1 Infection

Trial	Population	Study Arms and Duration (Number of Subjects Treated)
SAPPHIRE-I (double-blind)	GT1 (a and b) TN[a] without cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (473) • Placebo for 12 weeks (158)
SAPPHIRE-II (double-blind)	GT1 (a and b) TE[b] without cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (297) • Placebo for 12 weeks (97)
PEARL-II (open-label)	GT1b TE without cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (88) • Components of VIEKIRA XR for 12 weeks (91)
PEARL-III (double-blind)	GT1b TN without cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (210) • Components of VIEKIRA XR for 12 weeks (209)
PEARL-IV (double-blind)	GT1a TN without cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (100) • Components of VIEKIRA XR for 12 weeks (205)
TURQUOISE-II (open-label)	GT1 (a and b) TN & TE with compensated cirrhosis	• Components of VIEKIRA XR + RBV for 12 weeks (208) • Components of VIEKIRA XR + RBV for 24 weeks (172)

TURQUOISE-III (open-label)	GT1b TN & TE with compensated cirrhosis	• Components of VIEKIRA XR for 12 weeks (60)

a. TN, treatment-naïve was defined as not having received any prior therapy for HCV infection.
b. TE, treatment-experienced subjects were defined as having failed to respond to prior treatment with pegIFN/RBV.

The components of VIEKIRA XR with RBV were also evaluated in the following two studies:

- HCV GT1-infected liver transplant recipients (CORAL-I) *[see Clinical Studies (14.5)]*.
- Subjects with HCV GT1 co-infected with HIV-1 (TURQUOISE-I) *[see Clinical Studies (14.6)]*.

In all clinical trials, the ombitasvir, paritaprevir, ritonavir dose was 25/150/100 mg once daily and the dasabuvir dose was 250 mg twice daily and doses were not adjusted. For subjects who received RBV, the RBV dose was 1000 mg per day for subjects weighing less than 75 kg or 1200 mg per day for subjects weighing greater than or equal to 75 kg. RBV dose adjustments were performed according to the RBV labeling.

In all clinical trials, sustained virologic response was defined as HCV RNA below the lower limit of quantification (<LLOQ) 12 weeks after the end of treatment (SVR12). Plasma HCV RNA levels were measured using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System, which has an LLOQ of 25 IU per mL. Outcomes for subjects not achieving an SVR12 were recorded as on-treatment virologic failure (VF), post-treatment virologic relapse through post-treatment Week 12 or failure due to other non-virologic reasons (e.g., premature discontinuation, adverse event, lost to follow-up, consent withdrawn).

14.2 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection without Cirrhosis

Subjects with Chronic HCV GT1a Infection without Cirrhosis

Subjects with HCV GT1a infection without cirrhosis treated with the components of VIEKIRA XR with RBV for 12 weeks in SAPPHIRE-I and -II and in PEARL-IV *[see Clinical Studies (14.1)]* had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 19% had a body mass index of at least 30 kg per m^2; 55% of patients were enrolled in US sites; 72% had IL28B (rs12979860) non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU per mL.

Table 11 presents treatment outcomes for HCV GT1a treatment-naïve and treatment-experienced subjects treated with the components of VIEKIRA XR with RBV for 12 weeks in SAPPHIRE-I, PEARL-IV and SAPPHIRE-II.

Treatment-naïve, HCV GT1a-infected subjects without cirrhosis treated with the components of VIEKIRA XR with RBV for 12 weeks in PEARL-IV had a significantly higher SVR12 rate than subjects treated with the components of VIEKIRA XR without RBV (97% and 90% respectively; difference +7% with 95% confidence interval, +1% to +12%). The components of

VIEKIRA XR without RBV were not studied in treatment-experienced subjects with GT1a infection.

In SAPPHIRE-I and SAPPHIRE-II, no placebo subject achieved a HCV RNA <25 IU/mL during treatment.

Table 11. SVR12 for HCV Genotype 1a-Infected Subjects without Cirrhosis Who Were Treatment-Naïve or Previously Treated with PegIFN/RBV

	Components of VIEKIRA XR + RBV for 12 Weeks % (n/N)
GT1a treatment-naïve	
SAPPHIRE-I SVR12	96% (308/322)
Outcome for subjects without SVR12	
On-treatment VF	<1% (1/322)
Relapse	2% (6/314)
Other	2% (7/322)
PEARL-IV SVR12	97% (97/100)
Outcome for subjects without SVR12	
On-treatment VF	1% (1/100)
Relapse	1% (1/98)
Other	1% (1/100)
GT1a treatment-experienced	
SAPPHIRE-II SVR12	96% (166/173)
Outcome for subjects without SVR12	
On-treatment VF	0% (0/173)
Relapse	3% (5/172)
Other	1% (2/173)
SVR12 by Prior pegIFN Experience	
Null Responder	95% (83/87)
Partial Responder	100% (36/36)
Relapser	94% (47/50)

Subjects with Chronic HCV GT1b Infection without Cirrhosis

Subjects with HCV GT1b infection without cirrhosis were treated with the components of VIEKIRA XR with or without RBV for 12 weeks in PEARL-II and -III *[see Clinical Studies (14.1)]*. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were Hispanic or Latino; 21% had a body mass index of at least 30 kg per m^2; 21% of patients were enrolled in US sites; 83% had IL28B (rs12979860) non-CC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU per mL.

The SVR rate for HCV GT1b-infected subjects without cirrhosis treated with the components of VIEKIRA XR without RBV for 12 weeks in PEARL-II (treatment-experienced: null responder, n=32; partial responder, n=26; relapser, n=33) and PEARL-III (treatment-naïve, n=209) was 100%.

14.3 Clinical Trial Results in Adults with Chronic HCV Genotype 1a and 1b Infection and Compensated Cirrhosis

The components of VIEKIRA XR with and without ribavirin were evaluated in two clinical trials in patients with compensated cirrhosis.

TURQUOISE-II was an open-label trial that enrolled 380 HCV GT1 subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects were randomized to receive the components of VIEKIRA XR with RBV for either 12 or 24 weeks of treatment.

Treated subjects had a median age of 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 43% of patients were enrolled in US sites; 82% had IL28B (rs12979860) non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU per mL; 69% had HCV GT1a infection, 31% had HCV GT1b infection; 42% were treatment-naïve, 36% were prior pegIFN/RBV null responders; 8% were prior pegIFN/RBV partial responders, 14% were prior pegIFN/RBV relapsers; 15% had platelet counts of less than 90 x 10^9 per L; 50% had albumin less than 4.0 mg per dL.

TURQUOISE-III was an open-label trial that enrolled 60 HCV GT1b-infected subjects with cirrhosis and mild hepatic impairment (Child-Pugh A) who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects received the components of VIEKIRA XR without RBV for 12 weeks. Treated subjects had a median age of 61 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment-experienced; 25% were ≥65 years; 62% were male; 12% were Black; 5% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 40% of patients were enrolled in US sites; 22% had platelet counts of less than 90 x 10^9 per L; 17% had albumin less than 35 g/L; 92% had baseline HCV RNA levels of at least 800,000 IU per mL; 83% had IL28B (rs12979860) non-CC genotype.

Table 12 presents treatment outcomes for GT1a- and GT1b-infected treatment-naïve and treatment-experienced subjects.

In GT1a infected subjects, the overall SVR12 rate difference between 24 and 12 weeks of treatment with the components of VIEKIRA XR with RBV was +6% with 95% confidence interval (-0.1% to +13% with differences varying by pretreatment history).

Table 12. TURQUOISE-II: SVR12 for Chronic HCV Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV

	GT1a (TURQUOISE-II)	GT1b (TURQUOISE-III)

	Components of VIEKIRA XR + RBV for 24 Weeks % (n/N)	Components of VIEKIRA XR + RBV for 12 Weeks % (n/N)	Components of VIEKIRA XR without RBV for 12 Weeks % (n/N)
SVR12	95% (115/121)	89% (124/140)	100% (60/60)
Outcome for subjects without SVR12			
On-treatment VF	2% (3/121)	<1% (1/140)	0
Relapse	1% (1/116)	8% (11/135)	0
Other	2% (2/121)	3% (4/140)	0
SVR12 for Naïve	95% (53/56)	92% (59/64)	100% (27/27)
SVR12 by Prior pegIFN Experience			100% (33/33)
Null Responder	93% (39/42)	80% (40/50)	100% (7/7)
Partial Responder	100% (10/10)	100% (11/11)	100% (5/5)
Relapser	100% (13/13)	93% (14/15)	100% (3/3)

14.4 Effect of Ribavirin Dose Reductions on SVR12

Seven percent of subjects (101/1551) treated with the components of VIEKIRA XR with RBV had a RBV dose adjustment due to a decrease in hemoglobin level; of these, 98% (98/100) achieved an SVR12.

14.5 Clinical Trial of Selected Liver Transplant Recipients (CORAL-I)

The components of VIEKIRA XR with RBV were administered for 24 weeks to 34 HCV GT1-infected liver transplant recipients who were at least 12 months post transplantation at enrollment with normal hepatic function and mild fibrosis (Metavir fibrosis score F2 or lower). The initial dose of RBV 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 the components of VIEKIRA XR and at the end of treatment.

Of the 34 subjects (29 with HCV GT1a infection and 5 with HCV GT1b infection) enrolled, (97%) achieved SVR12 (97% in subjects with GT1a infection and 100% of subjects with GT1b infection). One subject with HCV GT1a infection relapsed post-treatment.

14.6 Clinical Trial in Subjects with HCV/HIV-1 Co-infection (TURQUOISE-I)

In an open-label clinical trial 63 subjects with HCV GT1 infection co-infected with HIV-1 were treated for 12 or 24 weeks with the components of VIEKIRA XR with RBV. Subjects were on a stable HIV-1 antiretroviral therapy (ART) regimen that included tenofovir disoproxil fumarate plus emtricitabine or lamivudine, administered with ritonavir boosted atazanavir or raltegravir. Subjects on atazanavir stopped the ritonavir component of their HIV-1 ART regimen upon initiating treatment with the components of VIEKIRA XR with RBV. Atazanavir was taken with the morning dose. The ritonavir component of the HIV-1 ART regimen was restarted after completion of treatment.

Treated subjects had a median age of 51 years (range: 31 to 69); 24% of subjects were black; 81% of subjects had IL28B (rs12979860) non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection.

The SVR12 rates were 91% (51/56) for subjects with HCV GT1a infection and 100% (7/7) for those with HCV GT1b infection. Of the 5 subjects who were non-responders, 1 experienced virologic breakthrough, 1 discontinued treatment, 1 experienced relapse and 2 subjects had evidence of HCV re-infection post-treatment.

One subject had confirmed HIV-1 RNA >400 copies/mL during the post-treatment period. This subject had no evidence of resistance to the ART regimen. No subjects switched their ART regimen due to loss of plasma HIV-1 RNA suppression.

14.7 Durability of Response

In an open-label clinical trial, 92% of subjects (526/571) who received various combinations of the direct acting antivirals included in VIEKIRA XR with or without RBV achieved SVR12, and 99% of those who achieved SVR12 maintained their response through 48 weeks post-treatment (SVR48).

16 HOW SUPPLIED/STORAGE AND HANDLING

VIEKIRA XR is dispensed in a 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 child-resistant daily dose pack contains three tablets. The NDC number is 0074-0063-28.

Dasabuvir, ombitasvir, paritaprevir, and ritonavir 200 mg/8.33 mg/50 mg/33.33 mg tablets are pale yellow-colored, film-coated, oblong shaped, debossed with “3QD” on one side.

Store at or below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients to review the Medication Guide for ribavirin *[see Warnings and Precautions (5.3)]*.

Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV

Inform patients that HBV reactivation can occur in patients coinfected with HBV during or after treatment of HCV infection. Advise patients to tell their healthcare provider if they have a history of hepatitis B virus infection *[see Warnings and Precautions (5.1)]*.

Risk of ALT Elevations or Hepatic Decompensation and Failure

Inform patients to watch for early warning signs of liver inflammation or failure, such as fatigue, weakness, lack of appetite, nausea and vomiting, as well as later signs such as jaundice, onset of confusion, abdominal swelling, and discolored feces, and to consult their health care professional

without delay if such symptoms occur *[see Warnings and Precautions (5.2 and 5.3) and Adverse Reactions (6)]*.

Pregnancy

Advise patients taking VIEKIRA XR with ribavirin to avoid pregnancy during treatment and within 6 months of stopping ribavirin. Inform patients to notify their health care provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)]*.

Drug Interactions

Inform patients that VIEKIRA XR may interact with some drugs; therefore, patients should be advised to report to their healthcare provider the use of any prescription, non-prescription medication or herbal products *[see Contraindications (4), Warnings and Precautions (5.5) and Drug Interactions (7)]*.

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with VIEKIRA XR *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

Administration

Advise patients to take VIEKIRA XR every day at the regularly scheduled time and that VIEKIRA XR must be taken with a meal because taking it under fasting conditions may result in reduced virologic response and possible development of resistance. Inform patients to swallow tablets whole and not to consume alcohol within 4 hours of taking VIEKIRA XR *[see Dosage and Administration (2.2)]*.

Inform patients that it is important not to miss or skip doses and to take VIEKIRA XR for the duration that is recommended by the healthcare provider.

Manufactured by AbbVie Inc., North Chicago, IL 60064.

03-B505

MEDICATION GUIDE **VIEKIRA XR (vee-KEE-rah-XR)** **(dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets** **for oral use**
Important: When taking VIEKIRA XR in combination with ribavirin, you should also read the Medication Guide that comes with ribavirin.
What is the most important information I should know about VIEKIRA XR? VIEKIRA XR can cause serious side effects, including, **Hepatitis B virus reactivation**: Before starting treatment with VIEKIRA XR, your healthcare provider will do blood tests to check for hepatitis B virus infection. If you have ever had hepatitis B virus infection, the hepatitis B virus could become active again during or after treatment of hepatitis C virus with VIEKIRA XR. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems

including liver failure and death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop taking VIEKIRA XR.

VIEKIRA XR may cause severe liver problems, especially in people with certain types of cirrhosis. These severe liver problems can lead to the need for a liver transplant, or can lead to death.
VIEKIRA XR can cause increases in your liver function blood test results, especially if you use ethinyl estradiol-containing medicines (such as some birth control products).

- You must stop using ethinyl estradiol-containing medicines before you start treatment with VIEKIRA XR. See the section **"Who should not take VIEKIRA XR?"** for a list of these medicines.
- If you use these medicines as a method of birth control, you must use another method of birth control during treatment with VIEKIRA XR, and for about **2** weeks after you finish treatment with VIEKIRA XR. Your healthcare provider will tell you when you may begin taking ethinyl estradiol-containing medicines.
- Your healthcare provider should do blood tests to check your liver function during the first 4 weeks and then as needed, during treatment with VIEKIRA XR.
- Your healthcare provider may tell you to stop taking VIEKIRA XR if you develop signs or symptoms of liver problems.
- Tell your healthcare provider right away if you develop any of the following symptoms, or if they worsen during treatment with VIEKIRA XR:
  - tiredness
  - weakness
  - loss of appetite
  - nausea and vomiting
  - yellowing of your skin or eyes
  - color changes in your stools
  - confusion
  - swelling of the stomach area

For more information about side effects, see the section "What are the possible side effects of VIEKIRA XR?"

What is VIEKIRA XR?

- VIEKIRA XR is a prescription medicine used with or without ribavirin to treat people with genotype 1 chronic (lasting a long time) hepatitis C virus (HCV) infection.
- VIEKIRA XR can be used in people who have compensated cirrhosis.
- VIEKIRA XR is not for people with advanced cirrhosis (decompensated). If you have cirrhosis, talk to your healthcare provider before taking VIEKIRA XR. VIEKIRA XR is not for people with certain types of liver problems.

It is not known if VIEKIRA XR is safe and effective in children under 18 years of age.

Who should not take VIEKIRA XR?

Do not take VIEKIRA XR if you:

- **have certain liver problems**
- **take any of the following medicines:**
  - alfuzosin hydrochloride (Uroxatral®)
  - atorvastatin (Caduet®, Lipitor®, Liptruzet®)
  - carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®, TEGRETOL-XR®, TERIL®)
  - cisapride (Propulsid®)
  - colchicine (Colcrys®) in patients who have certain kidney or liver problems
  - dronedarone (Multaq®)
  - efavirenz (Atripla®, Sustiva®)
  - ergot containing medicines including:
    - ergotamine tartrate (Cafergot®, Ergomar®, Ergostat®, Medihaler®, Migergot®, Wigraine®, Wigrettes®)
    - dihydroergotamine mesylate (D.H.E. 45®, Migranal®)
    - methylergonovine (Ergotrate®, Methergine®)
  - ethinyl estradiol-containing medicines:
    - combination birth control pills or patches, such as Lo Loestrin® FE, Norinyl®, Ortho Tri-Cyclen Lo®, Ortho Evra®
    - hormonal vaginal rings such as NuvaRing®

- the hormone replacement therapy medicine, Fem HRT®
- everolimus (Afinitor®, Zortress®)
- gemfibrozil (Lopid®)
- lovastatin (Advicor®, Altoprev®, Mevacor®)
- lurasidone (Latuda®)
- midazolam, when taken by mouth
- phenytoin (Dilantin®, Phenytek®)
- phenobarbital (Luminal®)
- pimozide (Orap®)
- ranolazine (Ranexa®)
- rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane)
- sildenafil citrate (Revatio®), when taking for pulmonary artery hypertension (PAH)
- simvastatin (Simcor®, Vytorin®, Zocor®)
- sirolimus (Rapamune®)
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
- tacrolimus (Astagraf XL®, Envarsus XR®, Prograf®)
- Triazolam (Halcion®)

- **have had a severe skin rash after taking ritonavir (Norvir®)**

What should I tell my healthcare provider before taking VIEKIRA XR?
Before taking VIEKIRA XR, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had hepatitis B virus infection
- have liver problems other than hepatitis C infection. **See "Who should not take VIEKIRA XR?"**
- have HIV infection
- have had a liver transplant. If you take cyclosporine (Gengraf®, Neoral®, Sandimmune®) to help prevent rejection of your transplanted liver, the amount of this medicine in your blood may increase during treatment with VIEKIRA XR.
  - Your healthcare provider should check the level of cyclosporine in your blood, and if needed may change your dose or how often you take it.
  - When you finish taking VIEKIRA XR or if you have to stop VIEKIRA XR for any reason, your healthcare provider should tell you what dose of cyclosporine to take and how often you should take it.
- are pregnant or plan to become pregnant. It is not known if VIEKIRA XR will harm your unborn baby. **When taking VIEKIRA XR in combination with ribavirin you should also read the ribavirin Medication Guide for important pregnancy information.**
- are breastfeeding or plan to breastfeed. It is not known if VIEKIRA XR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take VIEKIRA XR.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines interact with VIEKIRA XR. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with VIEKIRA XR.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take VIEKIRA XR with other medicines.
- When you finish treatment with VIEKIRA XR:
  - If your healthcare provider changed the dose of one of your usual medicines during treatment with VIEKIRA XR: Ask your healthcare provider about when you should change back to your original dose after you finish treatment with VIEKIRA XR.
  - If your healthcare provider told you to stop taking one of your usual medicines during treatment with VIEKIRA XR: Ask your healthcare provider if you should start taking these medicines again after you finished treatment with VIEKIRA XR.

How should I take VIEKIRA XR?

- Take VIEKIRA XR exactly as your healthcare provider tells you to take it. Do not change your dose.

- Do not stop taking VIEKIRA XR without first talking with your healthcare provider.
- Take VIEKIRA XR tablets one time each day.
- **VIEKIRA XR tablets must be taken with a meal**.
- Swallow VIEKIRA XR tablets whole. Do not split, crush, or chew the tablets.
- Do not drink alcohol within 4 hours of taking VIEKIRA XR.
- VIEKIRA XR comes in **monthly cartons that contain enough medicine for 28 days**.
  - Each monthly carton of VIEKIRA XR contains **4 smaller cartons**.
  - Each of the 4 smaller cartons contains enough child resistant **daily dose packs** of medicine to last for **7 days (1 week)**.
  - Each **daily dose pack** contains all of your VIEKIRA XR medicine for **1 day** (3 tablets). Follow the instructions on each daily dose pack about how to remove the tablets.
- It is important that you do not miss or skip doses of VIEKIRA XR during treatment.
- If you take too much VIEKIRA XR, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of VIEKIRA XR?
VIEKIRA XR can cause serious side effects, including:

- Hepatitis B virus reactivation. See "What is the most important information I should know about VIEKIRA XR?"

Common side effects of VIEKIRA XR when used with ribavirin include:

- tiredness
- nausea
- itching
- skin reactions such as redness or rash
- sleep problems
- feeling weak

Common side effects of VIEKIRA XR when used without ribavirin include:

- nausea
- itching
- sleep problems

These are not all the possible side effects of VIEKIRA XR. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIEKIRA XR?

- Store VIEKIRA XR at or below 86°F (30°C).

Keep VIEKIRA XR and all medicines out of the reach of children.

General information about the safe and effective use of VIEKIRA XR
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIEKIRA XR for a condition for which it was not prescribed. Do not give VIEKIRA XR to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about VIEKIRA XR that is written for health professionals.

What are the ingredients in VIEKIRA XR?
Active ingredients: dasabuvir, ombitasvir, paritaprevir, and ritonavir
Inactive ingredients:

- The extended release layer contains: copovidone, K value 28, hypromellose 2208, 17,700 (mPa*s), colloidal silicon dioxide/colloidal anhydrous silica, and magnesium stearate.
- The immediate release layer contains: copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica.
- The tablet coating contains: hypromellose (6 mPa*s), hypromellose (15 mPa*s), polyethylene glycol 400, hydroxypropyl cellulose, polysorbate 80, polyethylene glycol 3350/macrogol 4000, talc, titanium dioxide, colloidal silicon dioxide/colloidal anhydrous silica and iron oxide yellow.

Manufactured by AbbVie Inc., North Chicago, IL 60064.

For more information go to www.viekira.com or call 1-844-843-5472.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: March 2017
03-B505