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

VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Indications and Usage, Removed-Limitations of Use (1)	10/2015
Dosage and Administration, Testing Prior to Initiation of VIEKIRA PAK (2.1)	10/2015
Dosage and Administration, Recommended Dosage in Adults (2.2)	10/2015
Dosage and Administration, Hepatic Impairment (2.4)	10/2015
Contraindications (4)	10/2015
Warnings and Precautions (5.1)	10/2015

INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. VIEKIRA PAK includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor. (1)

DOSAGE AND ADMINISTRATION

Testing Prior to Initiation - Assess for laboratory and clinical evidence of hepatic decompensation. (2.1)
Recommended dosage: Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening) with a meal without regard to fat or calorie content. (2.1)

Treatment Regimen and Duration by Patient Population

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

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA PAK 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. (2.1)
- Liver Transplant Recipients: In liver transplant recipients with normal hepatic function and mild fibrosis (Metavir fibrosis score ≤2), the recommended duration of VIEKIRA PAK with ribavirin is 24 weeks. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets:
- Ombitasvir, paritaprevir, ritonavir: 12.5/75/50 mg (3)
- Dasabuvir: 250 mg (3)

CONTRAINDICATIONS

- If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. (4)
- Patients with moderate to severe hepatic impairment. (4, 5.1, 8.6, 12.3)
- Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate or strong inducers of CYP3A and 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

- 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. (5.1)
- ALT Elevations: Discontinue ethinyl estradiol-containing medications prior to starting VIEKIRA PAK (alternative contraceptive methods are recommended). Perform hepatic laboratory testing on all patients during the first 4 weeks of treatment. For ALT elevations on VIEKIRA PAK, monitor closely and follow recommendations in full prescribing information. (5.2)
- Risks Associated With Ribavirin Combination Treatment: If VIEKIRA PAK is administered with ribavirin, the warnings and precautions for ribavirin also apply to this combination regimen. (5.3)
- Drug Interactions: The concomitant use of VIEKIRA PAK 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 PAK. (5.4)

ADVERSE REACTIONS

In subjects receiving VIEKIRA PAK 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 VIEKIRA PAK 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 PAK can alter the plasma concentrations of some drugs and some drugs may alter the plasma concentrations of VIEKIRA PAK. 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, 5.4, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of VIEKIRA PAK

Prior to initiation of VIEKIRA PAK, assess for laboratory and clinical evidence of hepatic decompensation *[see Warnings and Precautions (5.1 and 5.2)]*.

2.2 Recommended Dosage in Adults

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

The recommended oral dosage of VIEKIRA PAK is two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Take VIEKIRA PAK with a meal without regard to fat or calorie content *[see Clinical Pharmacology (12.3)]*.

VIEKIRA PAK is used in combination with ribavirin (RBV) in certain patient populations (see Table 1). When administered with VIEKIRA PAK, 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. 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 PAK 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 PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks

Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. **VIEKIRA PAK 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 PAK with ribavirin is 24 weeks, irrespective of HCV genotype 1 subtype *[see Clinical Studies (14.6)]*. When VIEKIRA PAK 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 PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

- Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with “AV1” on one side.
- Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with “AV2” on one side. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

4 CONTRAINDICATIONS

- VIEKIRA PAK 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 (5.1), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.
- If VIEKIRA PAK 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 PAK 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.
  - Drugs that are moderate or strong inducers of CYP3A and strong inducers of CYP2C8 and may lead to reduced efficacy of VIEKIRA PAK.
  - Drugs that are strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation.

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

Table 2. Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anti-gout	Colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, 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 (5.2)]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase	Lovastatin,	Potential for myopathy including

Inhibitors	simvastatin	rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
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 PAK 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.

- VIEKIRA PAK is contraindicated in patients with known hypersensitivity (e.g. toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome) to ritonavir.

5 WARNINGS AND PRECAUTIONS

5.1 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 VIEKIRA PAK. Most patients with these severe outcomes had evidence of advanced cirrhosis prior to initiating therapy with VIEKIRA PAK. 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 PAK 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 PAK in patients who develop evidence of hepatic decompensation.

5.2 Increased Risk of ALT Elevations

During clinical trials with VIEKIRA PAK 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 of VIEKIRA PAK with or without ribavirin.

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 PAK *[see Contraindications (4)]*. Alternative methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.

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 PAK *[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 PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or INR.

5.3 Risks Associated With Ribavirin Combination Treatment

If VIEKIRA PAK 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.

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

The concomitant use of VIEKIRA PAK 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 PAK and possible development of resistance
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

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 PAK therapy; review concomitant medications during VIEKIRA PAK therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

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

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

6 ADVERSE REACTIONS

If VIEKIRA PAK is administered with ribavirin (RBV), refer to the prescribing information for ribavirin for a list of ribavirin-associated 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 (5.1)]*
- Increased Risk of ALT Elevations *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

The safety assessment was based on data from six Phase 3 clinical trials in more than 2,000 subjects who received VIEKIRA PAK with or without ribavirin for 12 or 24 weeks.

<u>VIEKIRA PAK with Ribavirin in Placebo-Controlled Trials</u>

The safety of VIEKIRA PAK in combination with ribavirin was assessed in 770 subjects with chronic HCV infection 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 VIEKIRA PAK in combination 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 Treated with VIEKIRA PAK in Combination with Ribavirin Compared to Placebo for 12 Weeks

	SAPPHIRE-I and -II	
	VIEKIRA PAK + 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.

VIEKIRA PAK with and without Ribavirin in Regimen-Controlled Trials

VIEKIRA PAK with and without ribavirin was assessed in 401 and 509 subjects with chronic HCV infection, 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 VIEKIRA PAK in combination 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 both VIEKIRA PAK in combination with ribavirin and VIEKIRA PAK alone.

Table 4. Adverse Events with ≥5% Greater Frequency Reported in Subjects with Chronic HCV GT1 Infection Treated with VIEKIRA PAK in Combination with Ribavirin Compared to VIEKIRA PAK for 12 Weeks

	PEARL-II, -III and -IV	
	VIEKIRA PAK + RBV **12 Weeks** **N = 401** **%**	**VIEKIRA PAK** **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.

VIEKIRA PAK with Ribavirin in Subjects with Compensated Cirrhosis

VIEKIRA PAK with ribavirin was assessed in 380 subjects with compensated cirrhosis who were treated 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 VIEKIRA PAK for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Skin Reactions

In PEARL-II, -III and -IV, 7% of subjects receiving VIEKIRA PAK alone and 10% of subjects receiving VIEKIRA PAK with ribavirin reported rash-related events. In SAPPHIRE-I and -II 16% of subjects receiving VIEKIRA PAK with ribavirin and 9% of subjects receiving placebo reported skin reactions. In TURQUOISE-II, 18% and 24% of subjects receiving VIEKIRA PAK 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 VIEKIRA PAK 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 (5.2)]*. 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 (5.2)]*.

Serum Bilirubin Elevations

Post-baseline elevations in bilirubin at least 2 x ULN were observed in 15% of subjects receiving VIEKIRA PAK with ribavirin compared to 2% in those receiving VIEKIRA PAK alone. 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 VIEKIRA PAK in combination with ribavirin was -2.4 g/dL and the mean change in subjects treated with VIEKIRA PAK alone 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 VIEKIRA PAK with ribavirin had hemoglobin levels decrease to less than 8.0 g/dL during treatment. Seven percent of subjects treated with VIEKIRA PAK in combination 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 VIEKIRA PAK alone had a hemoglobin level less than 10 g/dL.

VIEKIRA PAK in HCV/HIV-1 Co-infected Subjects

VIEKIRA PAK with ribavirin was 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 (5.5), 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.

VIEKIRA PAK in Selected Liver Transplant Recipients

VIEKIRA PAK with ribavirin was 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 Post-Marketing Adverse Reactions

The following adverse reactions have been identified during post approval use of VIEKIRA PAK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity reactions (including angioedema).

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

See also Contraindications (4), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3).

7.1 Potential for VIEKIRA PAK to Affect Other Drugs

Ombitasvir, paritaprevir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Paritaprevir is an inhibitor of OATP1B1 and OATP1B3 and paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Co-administration of VIEKIRA PAK with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of such drugs.

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

Paritaprevir and ritonavir are primarily metabolized by CYP3A enzymes. Co-administration of VIEKIRA PAK with strong inhibitors of CYP3A may increase paritaprevir and ritonavir concentrations. Dasabuvir is primarily metabolized by CYP2C8 enzymes. Co-administration of VIEKIRA PAK 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 PAK.

7.3 Established and Other Potential Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with VIEKIRA PAK, doses should be re-adjusted after administration of VIEKIRA PAK is completed. Dose adjustment is not required for VIEKIRA PAK.

Table 5 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant drugs and the effect of concomitant drugs on the various components of VIEKIRA PAK. See *Contraindications (4)* for drugs that are contraindicated with VIEKIRA PAK. 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
ANTIPSYCHOTIC		
quetiapine*	↑ quetiapine	• Initiation of VIEKIRA PAK 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 PAK: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
ANTIARRHYTHMICS		
amiodarone*, bepridil*, disopyramide*, flecainide*, lidocaine (systemic)*, mexiletine*, propafenone*, quinidine*	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with VIEKIRA PAK.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	When VIEKIRA PAK 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 PAK with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
CALCIUM CHANNEL BLOCKERS		
amlodipine	↑ amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
CORTICOSTEROIDS (INHALED/NASAL)		
fluticasone*	↑ fluticasone	Concomitant use of VIEKIRA PAK 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.
HIV-ANTIVIRAL AGENTS		
atazanavir/ritonavir once daily	↑ paritaprevir	When coadministered with VIEKIRA PAK, atazanavir 300 mg (without ritonavir) should only be given in the morning.
darunavir/ritonavir	↓ darunavir (C_{trough})	Co-administration of VIEKIRA PAK with darunavir/ritonavir is not recommended.
lopinavir/ritonavir	↑ paritaprevir	Co-administration of VIEKIRA PAK with lopinavir/ritonavir is not recommended.
rilpivirine	↑ rilpivirine	Co-administration of VIEKIRA PAK with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
rosuvastatin	↑ rosuvastatin	When VIEKIRA PAK is co-administered with rosuvastatin, the dose of rosuvastatin should not exceed 10 mg per day.
pravastatin	↑ pravastatin	When VIEKIRA PAK is co-administered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	When initiating therapy with VIEKIRA PAK, 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 PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
tacrolimus	↑ tacrolimus	When initiating therapy with VIEKIRA PAK, the dose of tacrolimus needs to be reduced. Do not administer tacrolimus on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated; reinitiate tacrolimus at a reduced dose based on

		tacrolimus blood concentrations. Typical tacrolimus dosing is 0.5 mg every 7 days. Measure tacrolimus blood concentrations and adjust dose or dosing frequency to determine subsequent dose modifications. Upon completion of VIEKIRA PAK therapy, the appropriate time to resume pre-VIEKIRA PAK dose of tacrolimus should be guided by assessment of tacrolimus blood concentrations. Frequent assessment of renal function and tacrolimus related side effects is recommended.
LONG ACTING BETA-ADRENOCEPTOR AGONIST		
salmeterol*	↑ salmeterol	Concurrent administration of VIEKIRA PAK 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.
NARCOTIC ANALGESICS		
buprenorphine/naloxone	↑ buprenorphine ↑ norbuprenorphine	No dose adjustment of buprenorphine/naloxone is required upon co-administration with VIEKIRA PAK. 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	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
See Clinical Pharmacology, Tables 6 and 7. 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 PAK

No dose adjustments are recommended when VIEKIRA PAK is co-administered with the following medications: digoxin, duloxetine, emtricitabine/tenofovir disoproxil fumarate, escitalopram, methadone, progestin only contraceptives, raltegravir, warfarin and zolpidem.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Pregnancy Exposure Registry

There is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals. Physicians are encouraged to register patients by calling 1-800-258-4263.

Risk Summary

Adequate and well controlled studies with VIEKIRA PAK have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir, ritonavir (mice and rats), or dasabuvir (rats and rabbits) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, VIEKIRA PAK should be used during pregnancy only if clearly needed.

If VIEKIRA PAK 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.

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir, ritonavir, or dasabuvir. For ombitasvir, the highest dose tested produced exposures approximately 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses tested produced exposures approximately 98-fold (mouse) or 8-fold (rat) the exposures in humans at the recommended clinical dose. For dasabuvir, the highest dose tested produced exposures approximately 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the recommended clinical dose.

8.3 Nursing Mothers

It is not known whether any of the components of VIEKIRA PAK or their metabolites are present in human milk. 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.

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

If VIEKIRA PAK is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

8.4 Pediatric Use

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

8.5 Geriatric Use

No dosage adjustment of VIEKIRA PAK is warranted in geriatric patients. Of the total number of subjects in clinical studies of VIEKIRA PAK, 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 PAK is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is contraindicated in patients with moderate to severe (Child-Pugh B and C) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment of VIEKIRA PAK is required in patients with mild, moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients 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)]*.

8.8 Other HCV Genotypes

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

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

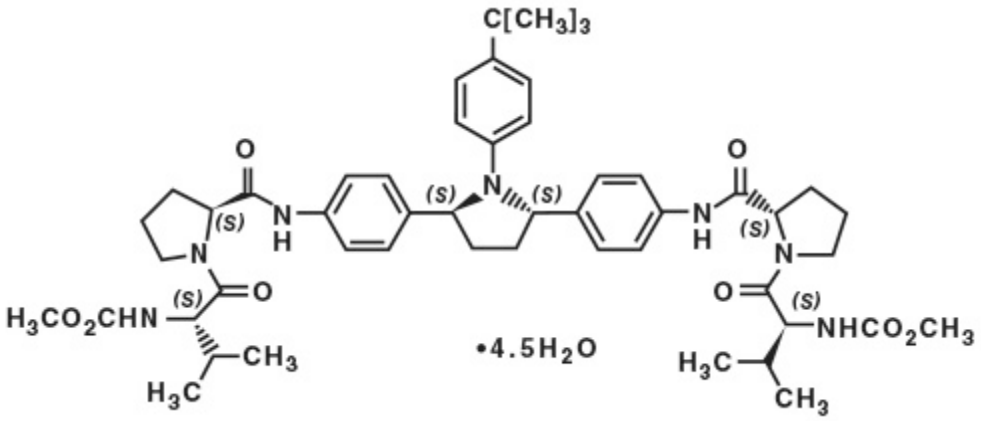
VIEKIRA PAK is ombitasvir, paritaprevir, ritonavir fixed dose combination tablets copackaged with dasabuvir tablets.

Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes 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. Dasabuvir is a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor, which is supplied as separate tablets in the copackage. Both tablets are for oral administration.

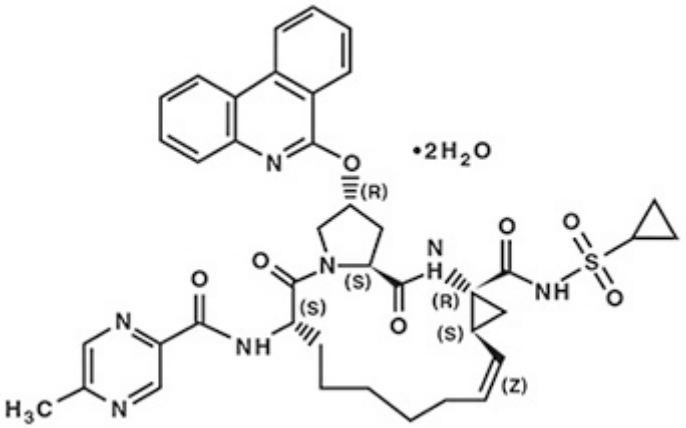
Ombitasvir

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:



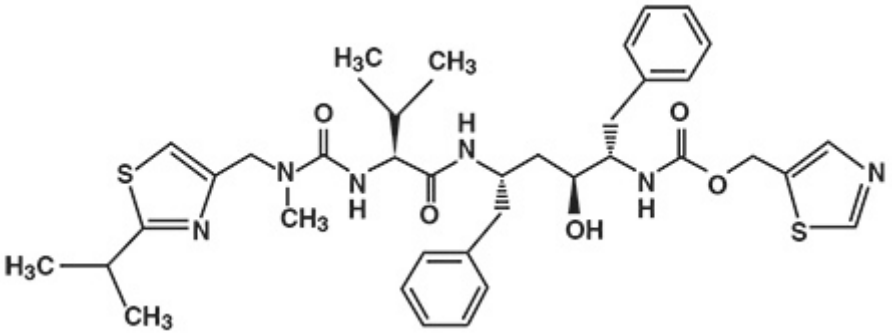
Paritaprevir

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 $C_{40}H_{43}N_7O_7S$•$2H_2O$ (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:

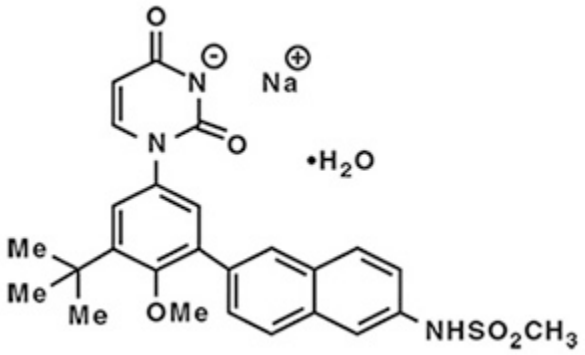


Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir, and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

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 $C_{26}H_{26}N_3O_5S{\bullet}Na{\bullet}H_2O$ (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:



Dasabuvir is formulated as a 250 mg film-coated, immediate release tablet containing microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc, and iron oxide yellow, iron oxide red and iron oxide black. Each tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VIEKIRA PAK 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

Absorption

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

The absolute bioavailability of dasabuvir estimated to be approximately 70%. The absolute bioavailability of ombitasvir, paritaprevir, and ritonavir was not evaluated.

Based on the population pharmacokinetic analysis, the median steady-state AUC_{0-24} for ombitasvir, paritaprevir and ritonavir were 1000, 2220 and 6180 ng•hr/mL, respectively, and the median steady-state AUC_{0-12} for dasabuvir was 3240 ng•hr/mL when VIEKIRA PAK was administered to HCV-infected subjects. Median steady-state C_{max} for ombitasvir, paritaprevir, ritonavir and dasabuvir were 68, 262, 682 and 667 ng/mL, respectively, when VIEKIRA PAK was administered to HCV-infected subjects.

Effects of Food on Oral Absorption

Relative to fasting conditions, administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir with a moderate fat meal (approximately 600 Kcal, 20-30% calories from fat) increased the mean AUC by 82%, 211%, 49%, and 30%, respectively.

Relative to fasting conditions, administration of ombitasvir, paritaprevir, ritonavir, and dasabuvir with a high fat meal (approximately 900 Kcal, 60% calories from fat) increased the mean AUC by 76%, 180%, 44%, and 22%, respectively.

Ombitasvir, paritaprevir, ritonavir, and dasabuvir should always be administered with a meal.

Distribution

Ombitasvir: Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 µg per mL. The mean blood-to-plasma concentration ratio was 0.49. The apparent volume of distribution (V/F) was 50.1 L.

Paritaprevir: Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 µg per mL. The mean blood-to-plasma concentration ratio was 0.7. The apparent volume of distribution (V/F) was 16.7 L.

Ritonavir: Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 µg per mL. The mean blood-to-plasma concentration ratio was 0.6. The apparent volume of distribution (V/F) was 21.5 L.

Dasabuvir: Dasabuvir was greater than 99.5% bound to human plasma proteins over a concentration range of 0.05 to 5 µg per mL. The mean blood-to-plasma concentration ratio was 0.7. The apparent volume of distribution (V/F) was 396 L.

Metabolism

Ombitasvir: Ombitasvir is predominantly metabolized by amide hydrolysis followed by oxidative metabolism.

Paritaprevir: Paritaprevir is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

Ritonavir: Ritonavir is predominantly metabolized by CYP3A, and to a lesser extent, by CYP2D6.

Dasabuvir: Dasabuvir is predominantly metabolized by CYP2C8, and to a lesser extent by CYP3A.

Elimination

Ombitasvir: Following a single dose administration of ^{14}C-ombitasvir, approximately 90.2% of the radioactivity was recovered in feces with limited radioactivity (1.91%) in urine; unchanged ombitasvir accounted for 87.8% of the radioactivity in the feces and 0.03% in the urine. The mean elimination half-life of ombitasvir was approximately 21 to 25 hours.

Paritaprevir: Following a single dose administration of ^{14}C-paritaprevir co-dosed with 100 mg of ritonavir, approximately 88% of the radioactivity was recovered in feces with limited radioactivity (8.8%) in urine; unchanged paritaprevir accounted for 1.1% of the radioactivity in the feces and 0.05% in the urine. The mean plasma half-life of paritaprevir was approximately 5.5 hours.

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

Dasabuvir: Following a single dose administration of ^{14}C-dasabuvir, approximately 94.4% of the radioactivity was recovered in feces with limited radioactivity (approximately 2%) in urine; unchanged dasabuvir accounted for 26% of the radioactivity in the feces and 0.03% in the urine. The mean plasma half-life of dasabuvir was approximately 5.5 to 6 hours.

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.

Specific Populations

Hepatic Impairment

The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir 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, ombitasvir, paritaprevir and ritonavir AUC values decreased by 8%, 29% and 34%, respectively, and dasabuvir AUC values increased by 17% in subjects with mild hepatic impairment.

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

Relative to subjects with normal hepatic function, paritaprevir, ritonavir and dasabuvir AUC values increased by 945%, 13%, and 325% respectively, and ombitasvir AUC values decreased by 54% in subjects with severe hepatic impairment *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

Renal Impairment

The single dose pharmacokinetics of ombitasvir, paritaprevir, ritonavir and dasabuvir 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.

Overall, changes in exposure of ombitasvir, paritaprevir, ritonavir and dasabuvir in non-HCV infected subjects with mild-, moderate- and severe renal impairment are not expected to be clinically relevant. Pharmacokinetic data are not available on the use of VIEKIRA PAK in non-HCV infected subjects with End Stage Renal Disease (ESRD).

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

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

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

Pediatric Population

The pharmacokinetics of VIEKIRA PAK in pediatric patients less than 18 years of age has not been established *[see Use in Specific Populations (8.4)]*.

Sex

No dose adjustment is recommended based on sex or body weight.

Race/Ethnicity

No dose adjustment is recommended based on race or ethnicity.

Age

No dose adjustment is recommended in geriatric patients *[see Use in Specific Populations (8.5)]*.

Drug Interaction Studies

See also Contraindications (4), Warnings and Precautions (5.4), Drug Interactions (7)

The effects of drugs discussed in Table 5 on the exposures of the individual components of VIEKIRA PAK are shown in Table 6. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 6. Drug Interactions: Change in Pharmacokinetic Parameters of the Individual Components of VIEKIRA PAK in the Presence of Co-administered Drug

Co-administered Drug	Dose of Co-administered Drug (mg)	n	DAA	Ratio (with/without co-administered drug) of DAA Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{min}
Alprazolam	0.5 single dose	12	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)
			dasabuvir	0.93	0.98	1.00

				(0.83, 1.04)	(0.87, 1.11)	(0.87, 1.15)
Amlodipine	5 single dose	14	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)
			dasabuvir	1.05 (0.97, 1.14)	1.01 (0.96, 1.06)	0.95 (0.89, 1.01)
Atazanavir/ ritonavir[a]	Atazanavir 300 and ritonavir 100 once daily in the evening	11	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)
			dasabuvir	0.81 (0.73, 0.91)	0.81 (0.71, 0.92)	0.80 (0.65, 0.98)
Carbamazepine	200 once daily followed by 200 twice daily	12	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
			dasabuvir	0.45 (0.41, 0.50)	0.30 (0.28, 0.33)	NA
Cyclosporine	30 single dose[b]	10	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)
			dasabuvir	0.66 (0.58, 0.75)	0.70 (0.65, 0.76)	0.76 (0.71, 0.82)
Darunavir[c]	800 once daily	9	ombitasvir	0.86 (0.77, 0.95)	0.86 (0.79, 0.94)	0.87 (0.82, 0.92)
			paritaprevir	1.54 (1.14, 2.09)	1.29 (1.04, 1.61)	1.30 (1.09, 1.54)
			ritonavir	0.84 (0.72, 0.98)	0.85 (0.78, 0.93)	1.07 (0.93, 1.23)
			dasabuvir	1.10 (0.88, 1.37)	0.94 (0.78, 1.14)	0.90 (0.76, 1.06)
Darunavir/ ritonavir[d]	Darunavir 600 twice	7	ombitasvir	0.76 (0.65, 0.88)	0.73 (0.66, 0.80)	0.73 (0.64, 0.83)

	daily and ritonavir 100 once daily in the evening		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)
			dasabuvir	0.84 (0.67, 1.05)	0.73 (0.62, 0.86)	0.54 (0.49, 0.61)
Darunavir/ ritonavir[e]	Darunavir 800 and ritonavir 100 once daily in the evening	12	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)
			dasabuvir	0.75 (0.64, 0.88)	0.72 (0.64, 0.82)	0.65 (0.58, 0.72)
Ethinyl estradiol/ Norgestimate	Ethinyl estradiol 0.035 and Norgestimate 0.25 once daily	7[f]	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)
			dasabuvir	0.51 (0.22, 1.18)	0.48 (0.23, 1.02)	0.53 (0.30, 0.95)
Furosemide	20 single dose	12	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)
			dasabuvir	1.12 (0.96, 1.31)	1.09 (0.96, 1.23)	1.06 (0.98, 1.14)
Gemfibrozil[g]	600 twice daily	11	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
			dasabuvir	2.01 (1.71, 2.38)	11.25 (9.05, 13.99)	NA
Ketoconazole	400 once daily	12	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

			dasabuvir	1.16 (1.03, 1.32)	1.42 (1.26, 1.59)	NA
Lopinavir/ ritonavir	400/100 twice daily	6	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)
			dasabuvir	0.99 (0.75, 1.31)	0.93 (0.75, 1.15)	0.68 (0.57, 0.80)
Lopinavir/ ritonavir[h]	800/200 once daily	12	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)
			dasabuvir	0.56 (0.47, 0.66)	0.54 (0.46, 0.65)	0.47 (0.39, 0.58)
Omeprazole	40 once daily	11	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)
			dasabuvir	1.13 (1.03, 1.25)	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)
Pravastatin	10 once daily	12	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)
			dasabuvir	1.00 (0.87, 1.14)	0.96 (0.85, 1.09)	1.03 (0.91, 1.15)
Rosuvastatin	5 once daily	11	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)
			dasabuvir	1.07 (0.92, 1.24)	1.08 (0.92, 1.26)	1.15 (1.05, 1.25)
Rilpivirine	25 once daily	10	ombitasvir	1.11	1.09	1.05

	(morning)[i]			(1.02, 1.20)	(1.04, 1.14)	(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)
			dasabuvir	1.18 (1.02, 1.37)	1.17 (0.99, 1.38)	1.10 (0.89, 1.37)
Tacrolimus	2 single dose	12	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)
			dasabuvir	0.85 (0.73, 0.98)	0.90 (0.80, 1.02)	1.01 (0.91, 1.11)

a. Atazanavir plus 100 mg ritonavir administered in the evening, 12 hours after morning dose of VIEKIRA PAK.
b. 30 mg cyclosporine was administered with VIEKIRA PAK in the test arm and 100 mg cyclosporine was administered in the reference arm without VIEKIRA PAK.
c. Darunavir administered with VIEKIRA PAK in the morning was compared to darunavir administered with 100 mg ritonavir in the morning.
d. Darunavir administered with VIEKIRA PAK in the morning and with 100 mg ritonavir in the evening was compared to darunavir administered with 100 mg ritonavir in the morning and evening.
e. Darunavir plus 100 mg ritonavir administered in the evening, 12 hours after the morning dose of VIEKIRA PAK 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 VIEKIRA PAK.
i. Similar increases were observed when rilpivirine was dosed in the evening with food or 4 hours after food.

NA: not available/not applicable; DAA: Direct-acting antiviral agent; CI: Confidence interval
Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg. Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily and dasabuvir was dosed twice daily in all the above studies except studies with gemfibrozil, ketoconazole and carbamazepine that used single doses.

Table 7 summarizes the effects of VIEKIRA PAK on the pharmacokinetics of co-administered drugs which showed clinically relevant changes. For information regarding clinical recommendations, see *Drug Interactions (7)*.

Table 7. Drug Interactions: Change in Pharmacokinetic Parameters for Co-administered Drug in the Presence of VIEKIRA PAK

Co-administered Drug	Dose of Co-administered Drug (mg)	n	Ratio (with/without VIEKIRA PAK) 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)
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 once daily in the evening	7	0.87 (0.79, 0.96)[b]	0.80 (0.74, 0.86)[b]	0.57 (0.48, 0.67)[b]
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]
Ethinyl Estradiol	Ethinyl estradiol 0.035 and	8	1.16 (0.90, 1.50)	1.06 (0.96, 1.17)	1.12 (0.94, 1.33)
Norelgestromin		9	2.01	2.60	3.11

	Norgestimate 0.25 once daily		(1.77, 2.29)	(2.30, 2.95)	(2.51, 3.85)
Norgestrel		9	2.26 (1.91, 2.67)	2.54 (2.09, 3.09)	2.93 (2.39, 3.57)
Furosemide	20 single dose	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	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
Rosuvastatin	5 once daily	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)
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)
Tacrolimus	2 single dose	12	3.99 (3.21, 4.97)[c]	57.13 (45.53, 71.69)[c]	16.56 (12.97, 21.16)[c]

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

NA: not available/not applicable; CI: Confidence interval
Doses of ombitasvir, paritaprevir, and ritonavir were 25 mg, 150 mg and 100 mg. Doses of dasabuvir were 250 mg or 400 mg (both doses showed similar exposures).
Ombitasvir, paritaprevir and ritonavir were dosed once daily and dasabuvir was dosed twice daily in all the above studies except studies with ketoconazole and carbamazepine that used single doses.

12.4 Microbiology

Mechanism of Action

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

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A, which is essential for viral 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. Paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 2a, 2b, 3a, and 4a with IC_{50} values of 2.4 nM, 6.3 nM, 14.5 nM, and 0.16 nM, respectively.

Dasabuvir

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome. In a biochemical assay, dasabuvir inhibited 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. Dasabuvir had reduced activity in biochemical assays against NS5B polymerases from HCV genotypes 2a, 2b, 3a and 4a (IC_{50} values ranging from 900 nM to >20 μM).

Antiviral Activity

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. Ombitasvir had EC_{50} values of 12 pM, 4.3 pM, 19 pM, 1.7 pM, 3.2 pM, and 366 pM against chimeric replicons constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 5a, and 6a, 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. Paritaprevir had an EC_{50} value of 5.3 nM against the HCV genotype 2a-JFH-1 replicon cell line, and EC_{50} values of 19 nM, 0.09 nM, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, and 6a, respectively.

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.

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.

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 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.

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.

In Clinical Studies

In a pooled analysis of subjects treated with regimens containing ombitasvir, paritaprevir, and dasabuvir 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 8. 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 8. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of VIEKIRA PAK 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, P470S, V23A (NS4A)	88 (51)	67 (4)
	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 ombitasvir, paritaprevir, and dasabuvir treatment-emergent amino acid substitutions in NS5A, NS3, and NS5B, 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 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.

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.

Due to virologic failure rates in clinical trials of less than 1% for subjects infected with HCV genotype 1b, trends in persistence of treatment-emergent substitutions in this genotype could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing VIEKIRA PAK-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 ombitasvir, paritaprevir, and dasabuvir with or without ribavirin was conducted to explore the association between baseline HCV NS5A, NS3, or NS5B 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 ombitasvir, paritaprevir, and dasabuvir 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 PAK 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 nucleos(t)ide analogue NS5B polymerase inhibitors. In clinical trials of VIEKIRA PAK, 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 ombitasvir, paritaprevir, or dasabuvir treatment experience on the efficacy of other NS5A inhibitors, NS3/4A protease inhibitors, or NS5B inhibitors has not been studied. Similarly, the efficacy of VIEKIRA PAK has not been studied in subjects who have failed prior treatment with another NS5A inhibitor, NS3/4A protease inhibitor, or NS5B inhibitor.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

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).

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.

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

Impairment of Fertility

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.

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.

If VIEKIRA PAK 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

The efficacy and safety of VIEKIRA PAK was evaluated in six randomized, multicenter, clinical trials in 2,308 subjects with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection, including one trial exclusively in subjects with cirrhosis with mild hepatic impairment (Child-Pugh A), as summarized in Table 9.

Table 9. Randomized, Multicenter Trials Conducted with VIEKIRA PAK With or Without Ribavirin (RBV) in Subjects with Chronic HCV GT1 Infection

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

a. TN, treatment-naïve was defined as not having received any prior therapy for HCV infection.
b. TE, treatment-experienced subjects were defined as either: prior relapsers, prior partial responders, or prior null responders to pegIFN/RBV treatment.

- In SAPPHIRE-I and -II, subjects without cirrhosis were randomized to VIEKIRA PAK in combination with ribavirin for 12 weeks or to placebo. Subjects in the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK in combination with RBV for 12 weeks *[see Clinical Studies (14.2)]*.
- In PEARL-II, -III and -IV, subjects without cirrhosis were randomized to receive VIEKIRA PAK with or without RBV for 12 weeks of treatment *[see Clinical Studies (14.2)]*.
- In the open-label TURQUOISE-II trial, subjects with compensated cirrhosis (Child-Pugh A) who were either treatment-naïve or pegylated interferon/RBV (pegIFN/RBV) treatment-experienced were randomized to receive VIEKIRA PAK in combination with RBV for either 12 or 24 weeks of treatment. Subjects who previously failed therapy with a treatment regimen that included VIEKIRA PAK or other direct-acting antiviral agents were excluded *[see Clinical Studies (14.3)]*.

In these six clinical trials, the ombitasvir, paritaprevir, ritonavir dose was 25/150/100 mg once daily and the dasabuvir dose was 250 mg twice daily. Doses of drugs in VIEKIRA PAK 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.

VIEKIRA PAK with RBV was 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 eight clinical studies, 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 VIEKIRA PAK 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 10 presents treatment outcomes for HCV GT1a treatment-naïve and treatment-experienced subjects treated with VIEKIRA PAK with RBV for 12 weeks in SAPPHIRE-I, PEARL-IV and SAPPHIRE-II.

Treatment-naïve, HCV GT1a-infected subjects without cirrhosis treated with VIEKIRA PAK in combination with RBV for 12 weeks in PEARL-IV had a significantly higher SVR12 rate than subjects treated with VIEKIRA PAK alone (97% and 90% respectively; difference +7% with 95% confidence interval, +1% to +12%). VIEKIRA PAK alone was 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 10. SVR12 for HCV Genotype 1a-Infected Subjects without Cirrhosis Who Were Treatment-Naïve or Previously Treated with PegIFN/RBV

	VIEKIRA PAK with 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 VIEKIRA PAK 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 VIEKIRA PAK 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

TURQUOISE-II was an open-label trial that enrolled 380 HCV GT1a and 1b-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 were randomized to receive VIEKIRA PAK in combination 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.
Table 11 presents treatment outcomes for GT1 treatment-naïve and treatment-experienced subjects with cirrhosis treated with VIEKIRA PAK with RBV for 12 or 24 weeks in TURQUOISE-II. In GT1a infected subjects, the overall SVR12 rate difference between 24 and 12 weeks of treatment with VIEKIRA PAK with RBV was +6% with 95% confidence interval, -0.1% to +13% with differences varying by pretreatment history.

Table 11. TURQUOISE-II: SVR12 for Chronic HCV Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV

	GT1a		**GT1b**
	VIEKIRA PAK with RBV for 24 Weeks % (n/N)	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**
SVR12	95% (115/121)	89% (124/140)	99% (67/68)
Outcome for subjects without SVR12			
On-treatment VF	2% (3/121)	<1% (1/140)	0% (0/68)
Relapse	1% (1/116)	8% (11/135)	1% (1/68)
Other	2% (2/121)	3% (4/140)	0% (0/68)
SVR12 for Naïve	95% (53/56)	92% (59/64)	100% (22/22)
SVR12 by Prior pegIFN Experience			
Null Responder	93% (39/42)	80% (40/50)	100% (25/25)

Partial Responder	100% (10/10)	100% (11/11)	86% (6/7)
Relapser	100% (13/13)	93% (14/15)	100% (14/14)

14.4 Effect of Ribavirin Dose Reductions on SVR12

Seven percent of subjects (101/1551) treated with VIEKIRA PAK 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)

VIEKIRA PAK with RBV was 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 VIEKIRA PAK 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 VIEKIRA PAK in combination 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 VIEKIRA PAK in combination with RBV. Atazanavir was taken with the morning dose of VIEKIRA PAK. The ritonavir component of the HIV-1 ART regimen was restarted after completion of treatment with VIEKIRA PAK and RBV.

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 PAK 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 PAK 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 four tablets: two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening. The NDC number is NDC 0074-3093-28.

Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets are pink-colored, film-coated, oblong biconvex shaped, debossed with “AV1” on one side. Dasabuvir 250 mg tablets are beige-colored, film-coated, oval-shaped, debossed with “AV2” on one side.

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 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 (5.1 and 5.2) and Adverse Reactions (6)]*.

Pregnancy

Advise patients to avoid pregnancy during treatment with VIEKIRA PAK with ribavirin. Inform patients to notify their health care provider immediately in the event of a pregnancy. Inform pregnant patients that there is an Antiretroviral Pregnancy Registry that monitors pregnancy outcomes in women who are HCV/HIV-1 co-infected and taking concomitant antiretrovirals *[see Use in Specific Populations (8.1)]*.

Drug Interactions

Inform patients that VIEKIRA PAK 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 (5.4) and Drug Interactions (7)]*.

Inform patients that contraceptives containing ethinyl estradiol are contraindicated with VIEKIRA PAK *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

Hepatitis C Virus Transmission

Inform patients that the effect of treatment of hepatitis C virus infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment should be taken.

Missed Dose

Inform patients that in case a dose of ombitasvir, paritaprevir, ritonavir is missed, the prescribed dose can be taken within 12 hours.

In case a dose of dasabuvir is missed, the prescribed dose can be taken within 6 hours.

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

Instruct patients not to take more than their prescribed dose of VIEKIRA PAK to make up for a missed dose.

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03-B243

MEDICATION GUIDE

VIEKIRA PAK (vee-KEE-rah-pak)

(ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets)

co-packaged for oral use

Read this Medication Guide before you start taking VIEKIRA PAK and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about your treatment with VIEKIRA PAK before you start taking it and at regular check-ups. You should stay under your healthcare provider's care when taking VIEKIRA PAK.

When taking VIEKIRA PAK 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 PAK?

- VIEKIRA PAK 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 PAK 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 PAK. See the section **"Who should not take VIEKIRA PAK?"** 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 PAK, and for about **2** weeks after you finish treatment with VIEKIRA PAK. 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 PAK.
- Your healthcare provider may tell you to stop taking VIEKIRA PAK 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 PAK:
  - 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

What is VIEKIRA PAK?

VIEKIRA PAK 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, including people who have a certain type of cirrhosis (compensated).

VIEKIRA PAK is not for people with advanced cirrhosis (decompensated). If you have cirrhosis, talk to your healthcare provider before taking VIEKIRA PAK.

VIEKIRA PAK contains 2 different types of tablets. **You must take both types of tablets** exactly as prescribed, to treat your chronic hepatitis C virus (HCV) infection.

- the pink tablet contains: the medicines ombitasvir, paritaprevir, and ritonavir
- the beige tablet contains: the medicine dasabuvir

If you take VIEKIRA PAK with ribavirin, you should also read the Medication Guide for ribavirin.

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

Who should not take VIEKIRA PAK?

Do not take VIEKIRA PAK if you:

- **have certain liver problems**
- **take any of the following medicines:**
  - alfuzosin hydrochloride (Uroxatral®)
  - carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
  - colchicine (Colcrys®)
  - 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®
  - gemfibrozil (Lopid®)
  - lovastatin (Advicor®, Altoprev®, Mevacor®)
  - midazolam, when taken by mouth
  - phenytoin, (Dilantin®, Phenytek®)
  - phenobarbital (Luminal®)
  - pimozide (Orap®)
  - rifampin (Rifadin®, Rifamate®, Rifater® Rimactane®)
  - sildenafil citrate (Revatio®), when taken for pulmonary artery hypertension (PAH)
  - simvastatin (Simcor®, Vytorin®, Zocor®)
  - St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
  - triazolam (Halcion®)
- **have had a severe skin rash after taking ritonavir (Norvir®).**

What should I tell my healthcare provider before taking VIEKIRA PAK?

Tell your healthcare provider about all your medical conditions, including if you:

- have liver problems other than hepatitis C infection. **See "Who should not take VIEKIRA PAK?"**
- have HIV infection
- have had a liver transplant. If you take the medicines tacrolimus (Prograf®) or cyclosporine (Gengraf®, Neoral®, Sandimmune®) to help prevent rejection of your transplanted liver, the amount of these medicines in your blood may increase during treatment with VIEKIRA PAK.
  - Your healthcare provider should check the level of tacrolimus or cyclosporine in your blood, and if needed may change your dose of these medicines or how often you take them.

- When you finish taking VIEKIRA PAK or if you have to stop VIEKIRA PAK for any reason, your healthcare provider should tell you what dose of tacrolimus or cyclosporine you should take and how often you should take it.
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if VIEKIRA PAK will harm your unborn baby. **When taking VIEKIRA PAK in combination with ribavirin you should also read the ribavirin Medication Guide for important pregnancy information.**

  Pregnancy Registry: There is a registry for females who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of the pregnant mother and her baby. If you are a pregnant female and have both HCV and HIV infection, talk with your healthcare provider about enrolling in this registry.
- are breastfeeding or plan to breastfeed. It is not known if VIEKIRA PAK passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take VIEKIRA PAK.

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 PAK. **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 PAK.
- **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 PAK with other medicines.
- When you finish treatment with VIEKIRA PAK:
  - If your healthcare provider changed the dose of any of your usual medicines during treatment with VIEKIRA PAK: Ask your healthcare provider about when you should change back to your original dose after you finish treatment with VIEKIRA PAK.
  - If your healthcare provider told you to stop taking any of your usual medicines during treatment with VIEKIRA PAK: Ask your healthcare provider if you should start taking these medicines again after you finish treatment with VIEKIRA PAK.

How should I take VIEKIRA PAK?

- Take VIEKIRA PAK exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
- Do not stop taking VIEKIRA PAK without first talking with your healthcare provider.
- When you receive your VIEKIRA PAK prescription, you will get a **monthly carton that contains enough medicine for 28 days**.
- Each monthly carton of VIEKIRA PAK 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 PAK medicine for **1 day** (4 tablets). Follow the instructions on each daily dose pack about how to remove the tablets.
- Take VIEKIRA PAK tablets with a meal as follows:
  - take the **2** pink tablets (ombitasvir, paritaprevir, and ritonavir), with **1** of the beige tablets (dasabuvir), at about the same time every morning.
  - take the **second** beige tablet (dasabuvir), at about the same time every evening.
- If you miss a dose of the pink tablets, and it is **less than 12 hours** from the time you usually take your dose, **take the missed dose** with a meal as soon as possible. Then take your next dose at your usual time with a meal.
- If you miss a dose of the pink tablets, and it is **more than 12 hours** from the time you usually take your dose, **do not take the missed dose**. Take your next dose at your usual time with a meal.
- If you miss a dose of the beige tablet, and it is **less than 6 hours** from the time you usually take your dose, **take the missed dose** with a meal as soon as possible. Then take your next dose at your usual time with a meal.
- If you miss a dose of the beige tablet, and it is **more than 6 hours** from the time you usually take your dose, **do not take the missed dose**. Take your next dose at your usual time with a meal.
- Do not take more than your prescribed dose of VIEKIRA PAK to make up for a missed dose.
- If you take too much VIEKIRA PAK, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of VIEKIRA PAK?

See **"What is the most important information I should know about VIEKIRA PAK?"**

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

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

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

- nausea
- itching
- sleep problems

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of VIEKIRA PAK. For more information, ask your healthcare provider or pharmacist.

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 PAK?

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

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

General information about the safe and effective use of VIEKIRA PAK

It is not known if treatment with VIEKIRA PAK will prevent you from infecting another person with the hepatitis C virus during your treatment. Talk with your healthcare provider about ways to prevent spreading the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIEKIRA PAK for a condition for which it was not prescribed. Do not give VIEKIRA PAK to other people, even if they have the same condition you have. It may harm them.

If you would like more information about VIEKIRA PAK, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VIEKIRA PAK that is written for health professionals.

For more information, call 1-800-633-9110 or go to www.viekira.com.

What are the ingredients in VIEKIRA PAK?

Ombitasvir, paritaprevir, and ritonavir tablets:

Active ingredients: ombitasvir, paritaprevir, and ritonavir

Inactive ingredients: copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and red iron oxide.

Dasabuvir tablets:

Active ingredients: dasabuvir

Inactive ingredients: microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc and iron oxide yellow, iron oxide red and iron oxide black.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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