PRODUCT INFORMATION

VIEKIRA PAK COMBINATION THERAPY PACK

NAME OF THE MEDICINE

VIEKIRA PAK is a composite pack containing paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets, and dasabuvir 250 mg tablets.

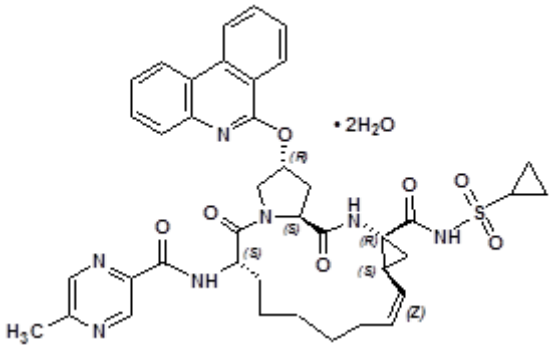
Chemical Structure and Description of each Active Pharmaceutical Ingredient

Paritaprevir

Paritaprevir drug substance is manufactured as a dihydrate, however it is dehydrated during the drug product manufacturing process and is amorphous and anhydrous in the final product. Paritaprevir dihydrate is chemically designated (2*R*,6*S*,12*Z*,13a*S*,14a*R*,16a*S*)-*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,14,15,16,16atetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4] diazacyclopentadecine-14a(5*H*)-carboxamide dihydrate.

The molecular formula is $C_{40}H_{43}N_7O_7S \bullet 2H_2O$ (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate).

Paritaprevir dihydrate has the following structural formula:



CAS Number: 1456607-71-8

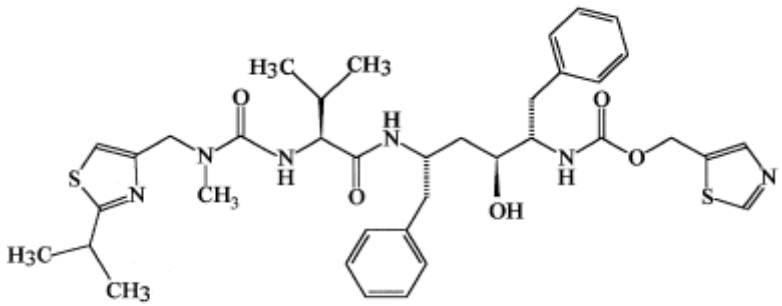
Paritaprevir dihydrate is a white to off-white powder with very low water solubility. Paritaprevir dihydrate has a pKa of 4.6 at 25°C.

Ritonavir

Ritonavir is chemically designated as [5*S*-(5*R**,8*R**,10*R**,11*R**)]10-Hydroxy-2-methyl-5-(1-methyethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmehyl)-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 is 720.95.

Ritonavir has the following structural formula:



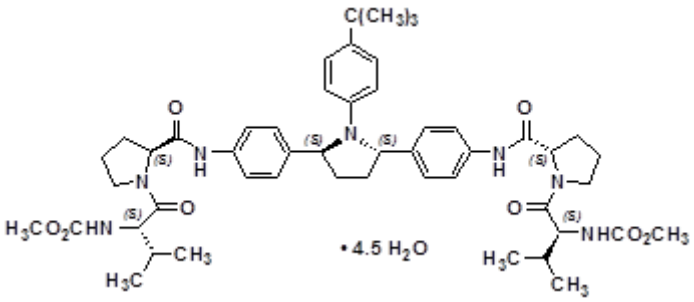
CAS Number: 155213-67-5

Ritonavir is a white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has a pKa of 2.8.

Ombitasvir

Ombitasvir drug substance is manufactured as a hydrate, however it is dehydrated during the drug product manufacturing process and is amorphous and anhydrous in the final product. Ombitasvir hydrate is chemically designated as 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). Ombitasvir hydrate has the following structural formula:



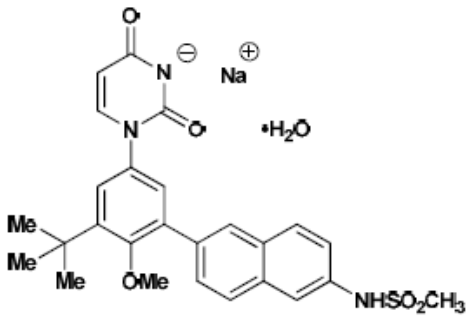
CAS Number: 1456607-70-7

Ombitasvir hydrate is a white to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir hydrate has a pKa of 2.5 at 25°C.

Dasabuvir

Dasabuvir drug substance is manufactured as a sodium salt monohydrate, and is present in the product as the sodium salt monohydrate. Dasabuvir sodium monohydrate is chemically designated as Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalen-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)The molecular formula is $C_{26}H_{26}N_3O_5S$•Na•H_2O (salt, hydrate) and the molecular weight of the drug substance is 533.57 (salt, hydrate).

Dasabuvir hydrate has the following molecular structure:



CAS Number: 1456607-55-8

Dasabuvir sodium monohydrate is a white to off-white to pink powder, slightly soluble in water and very slightly soluble in methanol and isopropyl alcohol. The pKa values of dasabuvir are 8.2 (pK_1) and 9.2 (pK_2).

DESCRIPTION

Paritaprevir, ritonavir, and ombitasvir are co-formulated as film-coated immediate release tablets. The tablets also contain copovidone, tocofersolan, propylene glycol monolaurate, sorbitan monolaurate, silicon dioxide, sodium stearyl fumarate and Opadry II pink 85F140088 (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and iron oxide red). The tablets do not contain gluten. The strength for the fixed dose combination tablet is 75 mg paritaprevir/50 mg ritonavir/12.5 mg ombitasvir.

Dasabuvir is formulated as a 250 mg film-coated, immediate release tablet containing microcrystalline cellulose, lactose, copovidone, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and Opadry II Beige 85F97497 (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and iron oxide yellow, iron oxide red and iron oxide black.). The tablets do not contain gluten.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Direct-acting antiviral, ATC code: J05AX66

Mechanism of Action

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

Paritaprevir

Paritaprevir is an inhibitor of HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyproteins (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication.

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

Ombitasvir

Ombitasvir is an inhibitor of HCV NS5A which is necessary for viral replication.

Dasabuvir

Dasabuvir is a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase encoded by the NS5B gene.

Activity in Cell Culture and/or Biochemical Studies

Paritaprevir

In a biochemical assay, paritaprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a and 1b NS3/4A protease enzymes with IC_{50} values of 0.18 nM and 0.43 nM, respectively. The EC_{50} of paritaprevir against genotype 1a-H77 and 1b-Con1 strains in the HCV replicon cell culture assay was 1.0 and 0.21 nM, respectively. The activity of paritaprevir was attenuated 24- to 27-fold in the presence of 40% human plasma. The mean EC_{50} of paritaprevir against replicons containing NS3 from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.86 nM (range 0.43 to 1.87 nM; n = 11) and 0.06 nM (range 0.03 to 0.09 nM; n = 9), respectively. Paritaprevir had an EC_{50} value of 5.3 nM against the 2a-JFH-1 replicon cell line, and EC_{50} values of 19, 0.09, and 0.68 nM against replicon cell lines containing NS3 from a single isolate each of genotype 3a, 4a, and 6a, respectively. In a biochemical assay, paritaprevir inhibited the activity of NS3/4A enzymes from single isolates of genotypes 2a, 2b, 3a, and 4a with IC_{50} values of 2.4, 6.3, 14.5, and 0.16 nM, respectively.

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

Ombitasvir

In replicon cell culture assays, ombitasvir has EC_{50} values of 14.1 pM and 5.0 pM against HCV genotypes 1a-H77 and 1b-Con1, respectively. The activity of ombitasvir was attenuated 11- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of ombitasvir against replicons containing NS5A from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.66 pM (range 0.35 to 0.88 pM; n = 11) and 1.0 pM (range 0.74 to 1.5 pM; n = 11), respectively. Ombitasvir has EC_{50} values of 12, 4.3, 19, 1.7, 3.2, and 366 pM against replicon cell lines constructed with NS5A from single isolates representing genotypes 2a, 2b, 3a, 4a, 5a, and 6a, respectively. Negligible anti-viral activity against genotypes 1a-H77 and 1b-Con1 was noted by the human major metabolites of ombitasvir, M29 and M36 in the HCV replicon assay; M29 and M36 do not contribute to antiviral activity of ombitasvir.

Dasabuvir

In a biochemical assay, dasabuvir inhibited the polymerase activity of the recombinant HCV genotype 1a and 1b HCV NS5B enzymes with IC_{50} values of 2.8 nM and 10.7 nM, respectively. The EC_{50} of dasabuvir against genotype 1a-H77 and 1b-Con1 strains in HCV replicon cell culture assays was 7.7 and 1.8 nM, respectively. The replicon activity of dasabuvir was attenuated 12- to 13-fold in the presence of 40% human plasma. The mean EC_{50} of dasabuvir against replicons containing NS5B from a panel of treatment-naïve genotype 1a and 1b isolates in the HCV replicon cell culture assay was 0.77 nM (range 0.4 to 2.1 nM; n = 11) and 0.46 nM (range 0.2 to 2 nM; n = 10), respectively. In biochemical assays, dasabuvir inhibited a panel of genotype 1a and 1b polymerases with a mean IC_{50} value of 4.2 nM (range 2.2 to 10.7 nM; n = 7). Dasabuvir had lower potency (>200 times) against polymerases from other HCV genotypes (2a, 2b, 3a and 4a). The M1 metabolite of dasabuvir had 30–40% lower potency than dasabuvir against genotypes 1a-H77 and 1b-Con1 in the HCV replicon assay.

Combination Activity *in vitro*

All two-drug combinations of paritaprevir, ombitasvir, dasabuvir and ribavirin demonstrated additive to synergistic inhibition of HCV genotype 1 replicon at the majority of drug concentrations studied in short term cell culture assays. In long term replicon survival assays, the ability of drug-resistant cells to form colonies in the presence of a single drug or drugs in combination was evaluated. In pair-wise combinations of paritaprevir, ombitasvir, and dasabuvir at concentrations 10-fold over their respective EC_{50}, colony survival was reduced by more than 100-fold by two drugs as compared to each drug alone. When all three drugs were combined at concentrations of 5-fold above their respective EC_{50}, no drug-resistant colonies survived.

Resistance in Cell Culture

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

In genotype 1a, substitutions F43L, R155 G/K/S, A156T, and D168A/E/F/H/N/V/Y in HCV NS3 reduced susceptibility to paritaprevir by 7- to 219-fold. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions V23A (in NS4A), V36A/M, V55I, Y56H, Q80K or E357K. Double variants including combinations of V36M, F43L, Y56H, or E357K with R155K or with a D168 substitution reduced the activity of paritaprevir by an additional 2- to 7-fold relative to the single R155K or D168 substitution. In genotype 1b, substitutions A156T, D168A/H/V/Y, and Y56H in combination with D168A/V/Y in HCV NS3 reduced susceptibility to paritaprevir. In the genotype 1b replicon, the activity of paritaprevir was reduced 27- to 337-fold by D168A/H/V/Y substitutions. The combination of Y56H and D168A, D168V or D168Y reduced the activity of paritaprevir by an additional 12- to 26-fold relative to the single D168 substitution in genotype 1b replicons.

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

In genotype 1a, substitutions C316Y, M4141/T, N444K, E446K/Q, Y448C/H, A553T, G554S, S556G/R, and Y561H in HCV NS5B reduced susceptibility to dasabuvir by 5- to 1472 fold. G558R and D559G/N were observed as treatment-emergent substitutions but the activity of dasabuvir against these variants could not be evaluated due to poor replication capacity. In genotype 1b, substitutions C316H/N/Y, S368T, N411S, M414I/T/V, Y448C/H, A553V, S556G and D559G in HCV NS5B reduced susceptibility to dasabuvir by 5- to 1569 fold. Dasabuvir retained full activity against replicons containing substitutions S282T in the nucleoside binding site, M423T in the lower thumb site, and P495A/S, P496S or V499A in the upper thumb site.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

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

In the greater than 500 genotype 1a baseline samples in this analysis, the most frequently observed resistance-associated variants were M28V (7.4%) in NS5A and S556G (2.9%) in NS5B. Q80K, although a highly prevalent polymorphism in NS3 (41.2% of samples), confers minimal resistance to paritaprevir. Resistance-associated variants at amino acid positions R155 and D168 in NS3 were

rarely observed (less than 1%) at baseline. In the greater than 200 genotype 1b baseline samples in this analysis, the most frequently observed resistance-associated variants observed were Y93H (7.5%) in NS5A, and C316N (17.0%) and S556G (15%) in NS5B. Given the low virologic failure rates observed with recommended treatment regimens for HCV genotype 1a- and 1b-infected subjects, the presence of baseline variants appears to have little impact on the likelihood of achieving sustained virologic response (SVR, virologic cure).

Resistance in Clinical Studies

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

Table 1. Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of VIEKIRA PAK with and without Ribavirin Regimens in Phase 2b and Phase 3 Clinical Trials (N = 2510)

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

a. Observed in at least 2 patients of the same subtype.
b. N = 66 for the NS5B target.
c. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.
d. Observed in combination in genotype 1b-infected patients.
e. Observed in combination in 6% (4/67) of the patients.
Note: The following variants were selected in cell culture but were not treatment-emergent: NS3 variants A156T in genotype 1a, and R155Q and D168H in genotype 1b; NS5A variants Y93C/H in genotype 1a, and L31F/V or Y93H in combination with L28M, L31F/V or P58S in genotype 1b; and NS5B variants Y448H in genotype 1a, and M414T and Y448H in genotype 1b.

Persistence of Resistance-Associated Substitutions

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

NS3 variants V36A/M and R155K and NS5B variants M414T and S556G remained detectable at post-treatment Week 48, whereas NS3 variant D168V and all other NS5B variants were not observed at post-treatment Week 48. All treatment-emergent variants in NS5A remained detectable at post-treatment Week 48. Due to high SVR rates in genotype 1b, trends in persistence of treatment-emergent variants in this genotype could not be established.

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

Cross-resistance

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

Pharmacodynamic interactions

Co-administration with enzyme inducers may increase the risk of adverse events and ALT elevations. Co-administration with ethinylestradiol may increase the risk of ALT elevations (see INTERACTIONS WITH OTHER MEDICINES).

Pharmacokinetics

The pharmacokinetic properties of the combination of paritaprevir, ombitasvir, ritonavir, and dasabuvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Table 2 shows geometric mean C_{max} and AUC_{0-24} of paritaprevir/ritonavir/ombitasvir 150/100/25 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy volunteers.

Table 2: Geometric Mean C_{max} and AUC_{0-24} of Multiple Doses of paritaprevir/ritonavir/ombitasvir 150/100/25 mg Once Daily with dasabuvir 250 mg Twice Daily with Food in Healthy Volunteers

	C_{max} (ng/mL)	**AUC_{0-24} (ng*hr/mL)**
paritaprevir	1470	6990
ombitasvir	127	1420
dasabuvir	1030	13680
ritonavir	1600	9470

Absorption

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

Effects of Food on Oral Absorption

Paritaprevir, ritonavir, ombitasvir and dasabuvir should be administered with food. All clinical trials with paritaprevir, ritonavir, ombitasvir and dasabuvir have been conducted following administration with food.

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

Distribution

Paritaprevir, ombitasvir, ritonavir and dasabuvir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood to plasma concentration ratios in humans ranged from 0.5 to 0.7, indicating that paritaprevir, ombitasvir, and dasabuvir were preferentially distributed in the plasma compartment of whole blood. Paritaprevir was approximately 97 to 98.6% bound to human plasma proteins over a concentration range of 0.08 to 8 microgram/mL. Ritonavir was greater than 99% bound to human plasma proteins over a concentration range of 0.007 to 22 microgram/mL. Ombitasvir was approximately 99.9% bound to human plasma proteins over a concentration range of 0.09 to 9 microgram /mL. Dasabuvir was > 99.5% bound to human plasma proteins over a concentration range of 0.15 to 5 microgram/mL.

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

Metabolism

Paritaprevir

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

Ombitasvir

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

Dasabuvir

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

Ritonavir

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

Elimination

Paritaprevir

Following dosing of paritaprevir/ritonavir/ombitasvir with or without dasabuvir, mean plasma half-life of paritaprevir was approximately 5.5 hours. Following a 200 mg ^{14}C-paritaprevir dose with 100 mg ritonavir, approximately 88% of the radioactivity was recovered in faeces with limited radioactivity (8.8%) in urine. Unchanged paritaprevir accounted for 1.1% of the radioactivity in the faeces and 0.05% in the urine. Unchanged parent drug and M29, the product of faecal hydrolysis, accounted for 61% of total radioactivity recovered in faeces, indicating that biliary excretion of parent drug is a major elimination pathway for paritaprevir.

Ombitasvir

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

Dasabuvir

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

Ritonavir

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

Implications for Drug Interactions

Potential for VIEKIRA PAK to affect the pharmacokinetics of other medicinal products

In vivo drug interaction studies evaluated the net effect of the combination treatment, including ritonavir.

The following section describes the specific transporters and metabolizing enzymes that are affected by VIEKIRA PAK. See INTERACTIONS WITH OTHER MEDICINES for guidance regarding potential interactions with other medicinal products and dosing recommendations.

Medicinal products metabolised by CYP3A4

Ritonavir is a strong inhibitor of CYP3A. Co-administration of VIEKIRA PAK with medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of these medicinal products. Medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious events are contraindicated (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES).

CYP3A substrates evaluated in drug interaction studies which may require dose adjustment and/or clinical monitoring include (see Table 15) ciclosporin, tacrolimus, amlodipine, rilpivirine and alprazolam. Examples of other CYP3A4 substrates which may require dose adjustment and/or clinical monitoring include calcium channel blockers (e.g. nifedipine), and trazodone. Although buprenorphine and zolpidem are also metabolised by CYP3A, drug interaction studies indicate that no dose adjustment is needed when co-administering these medicinal products with VIEKIRA PAK (see Table 15).

Medicinal products transported by the OATP family and OCT1

Paritaprevir is an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, and paritaprevir and ritonavir are inhibitors of OATP2B1. Ritonavir is an *in vitro* inhibitor of OCT1, but the clinical relevance is unknown. Co-administration of VIEKIRA PAK with medicinal products that are substrates of OATP1B1, OATP1B3, OATP2B1 or OCT1 may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include some statins (see Table 15), fexofenadine, repaglinide and angiotensin II receptor antagonists (e.g., valsartan).

OATP1B1/3 substrates evaluated in drug interaction studies include pravastatin and rosuvastatin (see Table 15).

Medicinal products transported by BCRP

Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP *in vivo*. Co-administration of VIEKIRA PAK together with medicinal products that are substrates of BCRP may increase plasma concentrations of these transporter substrates, potentially requiring dose adjustment/clinical monitoring. Such medicinal products include sulfasalazine, imatinib and some of the statins (see Table 15).

BCRP substrates evaluated in drug interaction studies include rosuvastatin (see Table 15).

Medicinal products transported by P-gp in the intestine

While paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, no significant change was observed in the exposure of the P-gp substrate digoxin when administered with VIEKIRA PAK (see Table 15). VIEKIRA PAK may increase the plasma exposure to medicinal products that are sensitive for changed intestinal P-gp activity (such as dabigatran etexilate).

Medicinal products metabolised by glucuronidation (UGT1A1)

Paritaprevir, ombitasvir and dasabuvir are inhibitors of UGT1A1. Co-administration of VIEKIRA PAK with medicinal products that are primarily metabolised by UGT1A1 result in increased plasma concentrations of such medicinal products; routine clinical monitoring is recommended for narrow therapeutic index medicinal products (i.e. levothyroxine). See also INTERACTIONS WITH OTHER

MEDICINES for specific advice on raltegravir and buprenorphine, which have been evaluated in drug interaction studies.

Medicinal products metabolised by CYP2C19

Co-administration of VIEKIRA PAK can decrease exposures of medicinal products that are metabolised by CYP2C19 (e.g. lansoprazole, esomeprazole, s-mephenytoin), which may require dose adjustment/clinical monitoring. CYP2C19 substrates evaluated in drug interaction studies include omeprazole and escitalopram (see Table 15).

Medicinal products metabolised by CYP2C9

VIEKIRA PAK did not affect the exposures of the CYP2C9 substrate, warfarin. Other CYP2C9 substrates (NSAIDs (e.g. ibuprofen), antidiabetics (e.g. glimepiride, glipizide) are not expected to require dose adjustments.

Medicinal products metabolised by CYP2D6 or CYP1A2

VIEKIRA PAK did not affect the exposures of the CYP2D6/CYP1A2 substrate, duloxetine. Other CYP1A2 substrates (e.g. ciprofloxacin, theophylline and caffeine) and CYP2D6 substrates (e.g. desipramine, metoprolol and dextromethorphan) are not expected to require dose adjustments.

Medicinal products renally excreted via transport proteins

Ombitasvir, paritaprevir, and ritonavir do not inhibit organic anion transporter (OAT1) *in vivo* as shown by the lack of interaction with tenofovir (OAT1 substrate). *In vitro* studies show that ombitasvir, paritaprevir, and ritonavir are not inhibitors of organic cation transporters (OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations.

Therefore, VIEKIRA PAK is not expected to affect medicinal products which are primarily excreted by the renal route via these transporters.

Potential for other medicinal products to affect the pharmacokinetics of ombitasvir, paritaprevir, and dasabuvir

Medicinal products that inhibit CYP3A4

Co-administration of VIEKIRA PAK with strong inhibitors of CYP3A may increase paritaprevir concentrations (see Table 15).

Enzyme inducers

Co-administration of VIEKIRA PAK with medicinal products that are moderate or strong enzyme inducers is expected to decrease ombitasvir, paritaprevir, ritonavir and dasabuvir plasma concentrations and reduce their therapeutic effect. Contraindicated enzyme inducers are provided under CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES.

Medicinal products that inhibit CYP3A4 and transport proteins

Paritaprevir is eliminated via CYP3A4 mediated metabolism and biliary excretion (substrate of the hepatic transporters OATP1B1, P-gp and BCRP). Caution is advised if co-administering VIEKIRA PAK with medicinal products that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters (P-gp, BCRP and/or OATP1B1/ OATP1B3). These medicinal products may show clinically relevant increases in exposures of paritaprevir (e.g., ritonavir with atazanavir, erythromycin, diltiazem or verapamil).

Medicinal products that inhibit transport proteins

Potent inhibitors of P-gp, BCRP, OATP1B1 and/or OATP1B3 have the potential to increase the exposure to paritaprevir. Inhibition of these transporters is not expected to show clinically relevant increases in exposures of ombitasvir and dasabuvir.

Special Populations

Renal Impairment

Paritaprevir/ritonavir/ombitasvir and dasabuvir

Based on the pharmacokinetic data in HCV uninfected subjects (n=24), no dose adjustment of VIEKIRA PAK is recommended in patients with mild, moderate or severe renal impairment. The efficacy and safety of VIEKIRA PAK have not been evaluated in HCV-infected patients with moderate or severe renal impairment. Pharmacokinetics of the combination of paritaprevir 150 mg, ombitasvir 25 mg, and ritonavir 100 mg, with or without dasabuvir 400 mg were evaluated in patients with mild (CrCl: 60 to 89 mL/min), moderate (CrCl: 30 to 59 mL/min) and severe (CrCl: 15 to 29 mL/min) renal impairment.

In patients with mild renal impairment (n=6), paritaprevir mean C_{max} and AUC values were comparable (up to 19% higher), ombitasvir mean C_{max} and AUC values were comparable (up to 7% lower), and ritonavir mean C_{max} and AUC values were 26% to 42% higher and dasabuvir mean C_{max} and AUC values were 5% to 21% higher compared to subjects with normal renal function.

In patients with moderate renal impairment (n=6), paritaprevir mean C_{max} values were comparable (< 1% increase) and AUC values were 33% higher, ombitasvir mean C_{max} and AUC values were comparable (up to 12% lower), and ritonavir mean C_{max} and AUC value were 48% to 80% and dasabuvir mean C_{max} and AUC values were 9% to 37% higher compared to subjects with normal renal function.

In patients with severe renal impairment (n=6), paritaprevir mean C_{max} values were comparable (< 1% increase) and AUC values were 45% higher, ombitasvir mean C_{max} and AUC values were comparable (up to 15% lower), and ritonavir mean C_{max} and AUC value were 66% to 114% higher and dasabuvir mean C_{max} and AUC values were 12% to 50% higher compared to subjects with normal renal function.

Hepatic Impairment

The changes in paritaprevir, ombitasvir, dasabuvir and ritonavir exposures in patients with mild and moderate hepatic impairment are not considered clinically significant. 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 hepatic impairment (Child-Pugh B and C) (see CONTRAINDICATIONS and PRECAUTIONS).

Pharmacokinetics of the combination of paritaprevir 200 mg, and ritonavir 100 mg, ombitasvir 25 mg, and dasabuvir 400 mg were evaluated in patients (n=17) with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

In patients with mild hepatic impairment (n=6), paritaprevir, ritonavir and ombitasvir mean C_{max} and AUC values decreased by 29% to 48%, 34% to 40% and up to 8%, respectively, and dasabuvir mean C_{max} and AUC values were 17% to 24% higher compared to subjects with normal hepatic function.

In patients with moderate hepatic impairment (n=6), paritaprevir mean C_{max} and AUC value increased by 26% to 62%, ombitasvir and ritonavir mean C_{max} and AUC values decreased by 29% to 30% and 30 to 33%, respectively, and dasabuvir mean C_{max} and AUC values were 16% to 39% lower

compared to subjects with normal hepatic function. The safety and efficacy of VIEKIRA PAK have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B).

In patients with severe hepatic impairment (n=5), paritaprevir and dasabuvir mean C_{max} and AUC values increased by 3.2 to 9.5-fold and 0.3- to 3.3-fold respectively; ritonavir mean C_{max} values were 35% lower and AUC values were 13% higher and ombitasvir mean C_{max} and AUC values decreased by 68% and 54% respectively compared to subjects with normal hepatic function.

Elderly

No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir or dasabuvir in elderly patients.

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, a 10 year increase or decrease in age from 54 years (median age in the Phase 3 studies) would result in approximately 10% change in ombitasvir exposures, less than 10% change in dasabuvir exposures and ≤20% change in paritaprevir exposures. There is no pharmacokinetic information in patients >75 years.

Paediatric Population (<18 years)

The pharmacokinetics, safety and efficacy of VIEKIRA PAK in paediatric patients have not been established.

Race or Ethnicity

No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir or dasabuvir based on race or ethnicity. Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, Asian patients had 18% to 21%, 37% to 39% and 29% to 39% higher ombitasvir, paritaprevir and dasabuvir exposures, respectively, than non-Asian patients. The ritonavir exposures were comparable between Asians and non-Asians. However, patient numbers in the clinical trials were not sufficient to definitively address possible differences in pharmacokinetics and toxicity profiles in specific ethnic groups such as Asian patients.

Sex or Body weight

No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir or dasabuvir based on gender or body weight.

Based on population pharmacokinetic analysis of data from Phase 3 clinical studies, female patients would have approximately 55%, 100%, 15% and 21% higher ombitasvir, paritaprevir, ritonavir and dasabuvir exposures (AUC), respectively, than male patients. A 10 kg change in body weight from 76 kg (median weight in the Phase 3 studies) would results in <10% change in ombitasvir and dasabuvir exposures, and no change in paritaprevir exposures. Body weight is not a significant predictor of ritonavir exposures.

CLINICAL TRIALS

The efficacy and safety of VIEKIRA PAK were evaluated in seven randomised Phase 3 clinical trials, in over 2, 600 patients with genotype 1 chronic hepatitis C infection. Included in the Phase 3 program were two trials exclusively in patients with cirrhosis (Child-Pugh A). Phase 3 trials are summarised in Table 3.

Table 3: Phase 3 Randomised, Global Multicentre Trials Conducted with VIEKIRA PAK with or without ribavirin (RBV).

Trial[1]	Number of patients (treated[2])	HCV Genotype (GT)	Summary of Study Design[3]
Treatment-naïve[4], without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: VIEKIRA PAK + RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: VIEKIRA PAK+ RBV Arm B: VIEKIRA PAK
PEARL IV	305	GT1a	Arm A: VIEKIRA PAK+ RBV Arm B: VIEKIRA PAK
Treatment-experienced[5], without cirrhosis			
SAPPHIRE II	394	GT1	Arm A: VIEKIRA PAK + RBV Arm B: Placebo
PEARL II (open-label)	180	GT1b	Arm A: VIEKIRA PAK+ RBV Arm B: VIEKIRA PAK
Treatment-naïve and treatment-experienced[5], with compensated cirrhosis			
TURQUOISE II (open-label)	380	GT1	Arm A: VIEKIRA PAK + RBV (12 weeks) Arm B: VIEKIRA PAK + RBV (24 weeks)
TURQUOISE-III (open-label)	60	GT1b	VIEKIRA PAK (12 weeks)

1 Double-blind unless otherwise noted

2 Treated is defined as patients who were randomised and received at least one dose of VIEKIRA PAK.

3 Treatment duration was 12 weeks for all arms, except for TURQUOISE II which included a 24 week arm.

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

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

In all seven trials, the paritaprevir/ritonavir/ombitasvir dose was 150/100/25 mg once daily and the dasabuvir dose was 250 mg twice daily. For patients who received ribavirin, the ribavirin dose was 1000 mg per day for patients weighing less than 75 kg or 1200 mg per day for patients weighing greater than or equal to 75 kg.

Sustained virologic response (virologic cure) was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12) in the Phase 3 trials. Treatment duration was fixed in

each trial and was not guided by patients' HCV RNA levels (no response-guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System. The assay had a lower limit of quantification (LLOQ) of 25 IU per mL.

Pooled Analyses of Clinical Trials

Durability of Response

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

Pooled Efficacy Analyses

In phase 3 clinical trials, 1088 patients (including 194 with cirrhosis) received the recommended regimen for their HCV subtype, cirrhosis status and previous treatment. Table 4 shows SVR rates for these patients.

Among patients who received the recommended regimen, 97% achieved SVR (95% with cirrhosis and 97% without cirrhosis), while 0.6% demonstrated virologic breakthrough and 1.5% experienced post-treatment relapse.

Table 4: SVR12 rates for recommended treatment regimens

	Genotype 1a		**Genotype 1b**	
	No Cirrhosis VIEKIRA PAK-RBV	**With Cirrhosis VIEKIRA PAK-RBV**	**No cirrhosis VIEKIRA PAK**	**With cirrhosis VIEKIRA PAK**
	12 weeks	**12 weeks***	**12 weeks**	**12 weeks**
Treatment-naïve	96% (403/420)	92% (61/66)	100% (210/210)	100% (27/27)
Treatment-experienced	96% (166/173)	94% (64/68)*	100% (91/91)	100% (33/33)
Prior pegIFN/RBV relapser	94% (47/50)	93% (14/15)	100% (33/33)	100% (3/3)
Prior pegIFN/RBV partial responder	100% (36/36)	100% (11/11)	100% (26/26)	100% (5/5)
Prior pegIFN/RBV null responder	95% (83/87)	93% (39/42) (24 weeks)	100% (32/32)	100% (7/7)
Other pegIFN/RBV failures	0	0	0	100% (18/18)+
TOTAL	96% (569/593)	93% (125/134)*	100% (301/301)	100% (60/60)

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

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

Impact of Ribavirin Dose Adjustment on Probability of SVR

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

Clinical Trials in Treatment-Naïve Adults

SAPPHIRE-I (M11-646) - Genotype 1, Treatment-Naïve

SAPPHIRE-I was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 631 treatment-naïve adults with genotype 1 chronic hepatitis C virus infection without cirrhosis. VIEKIRA PAK was given for 12 weeks of treatment. Patients randomised to the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK with ribavirin for 12 weeks.

Treated patients (N=631) had a median age of 52 years (range: 18 to 70); 64.8% were born between 1945 – 1965; 54.5% were male; 5.4% were Black and 5.1% were Hispanic or Latino; 16.2% had a body mass index of at least 30 kg/m^2; 15.2% had a history of depression or bipolar disorder; 69.3% had IL28B non-CC genotype; 79.1% had baseline HCV RNA levels at least 800,000 IU/mL; 15.4% had portal fibrosis (F2) and 8.7% had bridging fibrosis (F3); 67.7% had HCV genotype 1a infection; 32.3% had HCV genotype 1b infection.

Table 5 shows the SVR12 rates for genotype 1-infected, treatment-naïve patients receiving VIEKIRA PAK-RBV for 12 weeks in SAPPHIRE-I.

Table 5: SVR12 for Genotype 1-Infected Treatment-Naïve Patients in SAPPHIRE-I

	VIEKIRA PAK –RBV for 12 Weeks		
Treatment Outcome	**n/N**	**%**	**95% CI**
Overall SVR12	456/473	96.4	94.7, 98.1
HCV genotype 1a	308/322	95.7	93.4, 97.9
HCV genotype 1b	148/151	98.0	95.8, 100.0
Outcome for patients without SVR12			
On-treatment VF[a]	1/473	0.2	
Relapse[b]	7/463	1.5	
Other[c]	9/473	1.9	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 log10 IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.

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

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

In the primary efficacy analysis, VIEKIRA PAK-RBV demonstrated superiority to the historical control SVR rate of 78% {95% CI of 75%, 80%} (based upon telaprevir plus peginterferon (pegIFN/RBV) for patients with genotype 1 HCV infection who were treatment-naïve without cirrhosis. Refer to the telaprevir prescribing information.

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

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 70%):

- *Viral factors:* genotype 1 subtype, baseline viral load
- *Host factors:* Gender, race, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage

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

Significantly more patients (352/363 = 97.0%) who received VIEKIRA PAK with ribavirin had normalised ALT by the end of treatment than those who received placebo (18/114 = 15.8%); *p* value < 0.001.

PEARL-III (M13-961) – Genotype 1b, Treatment-Naïve

PEARL-III was a randomised, global multi-centre, double-blind, controlled trial conducted in 419 treatment-naïve adults with genotype 1b chronic hepatitis C virus infection without cirrhosis. Patients were randomised in a 1:1 ratio to receive VIEKIRA PAK or VIEKIRA-PAK-RBV for 12 weeks of treatment.

Treated patients (N=419) had a median age of 50 years (range: 19 to 70); 54.9% were born between 1945 – 1965, 45.8% were male; 4.8% were Black; 1.7% were Hispanic or Latino; 16.5% had a body mass index of at least 30 kg/m^2; 9.3% had a history of depression or bipolar disorder; 79.0% had IL28B non-CC genotype; 73.3% had baseline HCV RNA of at least 800,000 IU/mL; 20.3% had portal fibrosis (F2) and 10.0% had bridging fibrosis (F3).

Table 6 shows the SVR12 rates for genotype 1b-infected, treatment-naïve patients who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL III. In this study, VIEKIRA PAK had similar SVR12 rates (100%) compared to VIEKIRA PAK with ribavirin (99.5%).

Table 6: SVR12 for Genotype 1b-Infected Treatment-Naïve Patients in PEARL III

	VIEKIRA PAK-RBV for 12 weeks			**VIEKIRA PAK for 12 weeks**		
	n/N	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall SVR12	209/210	99.5	98.6, 100.0	209/209	99	98.2, 100.0
Outcome for patients without SVR12	1/210	0.5		2/209	1.0	
On-treatment VF[a]	1/210	0.5		0/209	0	
Relapse[b]	0/210	0		0/209	0	
Other[c]	0/210	0		2/209	0	

CI = confidence interval, VF = virologic failure

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

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

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

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK with ribavirin demonstrated superiority to the historical control SVR rate of 80% {95% CI of 75%, 84%} (based upon telaprevir plus pegIFN/RBV) for patients with genotype 1b HCV infection who were treatment-naïve without cirrhosis. Refer to the telaprevir prescribing information.

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 73%):

- *Viral factors:* baseline viral load
- *Host factors:* Gender, race, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage

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

PEARL-IV (M14-002) – Genotype 1a, Treatment-Naïve

PEARL-IV was a randomised, global multicentre, double-blind, controlled trial conducted in 305 treatment-naïve adults with genotype 1a chronic hepatitis C virus infection without cirrhosis. Patients were randomised in a 1:2 ratio to receive VIEKIRA PAK or VIEKIRA PAK with ribavirin for 12 weeks of treatment.

Treated patients (N=305) had a median age of 54 years (range: 19 to 70); 72.5% were born between 1945 – 1965, 65.2% were male; 11.8% were Black; 9.2% were Hispanic or Latino; 19.7% had a body mass index of at least 30 kg/m^2; 20.7% had a history of depression or bipolar disorder; 69.2% had IL28B non-CC genotype; 86.6% had baseline HCV RNA levels of at least 800,000 IU/mL; 18.4% had portal fibrosis (F2) and 17.7% had bridging fibrosis (F3).

Table 7 shows the SVR12 rates for genotype 1a-infected, treatment-naïve patients who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL IV. VIEKIRA PAK was not non-inferior to VIEKIRA PAK with ribavirin.

Table 7: SVR12 for Genotype 1a-Infected Treatment-Naïve Patients in PEARL IV

	VIEKIRA PAK RBV for 12 weeks			**VIEKIRA PAK for 12 weeks**		
	n/N	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall SVR12	97/100	97.0	93.7, 100.0	185/205	90.2	86.2, 94.3
Outcome for patients without SVR12						
On-treatment VF[a]	1/100	1.0		6/205	2.9	
Relapse[b]	1/98	1.0		10/194	5.2	
Other[c]	1/100	1.0		1/205	0.5	

CI = confidence interval, VF = virologic failure

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

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

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

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK with ribavirin demonstrated superiority to the historical control SVR rate of 72% {95% CI of 68%, 75%} (based upon telaprevir plus pegIFN/RBV) for patients with genotype 1a HCV infection who were treatment-naïve without cirrhosis. Refer to the telaprevir prescribing information.

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 65%):

- *Viral factors:* baseline viral load
- *Host factors:* Gender, race, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage

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

Clinical Trials in Treatment-Experienced Adults

SAPPHIRE-II (M13-098) Genotype 1 – Treatment-experienced

SAPPHIRE-II was a randomised, global multicentre, double-blind, placebo-controlled trial conducted in 394 patients with genotype 1 chronic hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. VIEKIRA PAK-RBV was given for 12 weeks of treatment. Patients randomised to the placebo arm received placebo for 12 weeks, after which they received VIEKIRA PAK-RBV for 12 weeks.

Treated patients (N=394) had a median age of 54 years (range: 19 to 71); 49.0% were prior pegIFN/RBV null responders; 21.8% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers; 73.9% were born between 1945 – 1965; 57.6% were male; 8.1% were Black and 6.3% were Hispanic or Latino; 19.8% had a body mass index of at least 30 kg/m^2; 20.6% had a history of depression or bipolar disorder; 89.6% had IL28B non-CC genotype; 87.1% had baseline HCV RNA levels at least 800,000 IU per mL; 17.8% had portal fibrosis (F2) and 14.5% had bridging fibrosis (F3); 58.4% had HCV genotype 1a infection; 41.4% had HCV genotype 1b infection.

Table 8 shows the SVR12 rates for treatment-experienced patients with genotype 1-infection receiving VIEKIRA PAK with ribavirin for 12 weeks in SAPPHIRE-II.

Table 8: SVR12 for Genotype 1-infected Treatment-Experienced Patients in SAPPHIRE-II

	VIEKIRA PAK -RBVfor 12 weeks		
Treatment Outcome	**n/N**	**%**	**95% CI**
Overall SVR12	286/297	96.3	94.1, 98.4
HCV Genotype 1a	166/173	96.0	93.0, 98.9
Prior pegIFN/RBV null responder	83/87	95.4	91.0, 99.8
Prior pegIFN/RBV partial responder	36/36	100	100.0, 100.0
Prior pegIFN/RBV relapser	47/50	94.0	87.4, 100.0
HCV Genotype 1b	119/123	96.7	93.6, 99.9
Prior pegIFN/RBV null responder	56/59	94.9	89.3, 100.0
Prior pegIFN/RBV partial responder	28/28	100	100.0, 100.0
Prior pegIFN/RBV relapser	35/36	97.2	91.9, 100.0
Outcome for patients without SVR12			
On-treatment VF[a]	0/297	0	
Relapse[b]	7/293	2.4	
Other[c]	4/297	1.3	

CI = confidence interval, VF = virologic failure

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

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

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

No patients with HCV genotype 1b infection experienced on-treatment virologic failure and 2 patients with HCV genotype 1b infection experienced relapse.

In the primary efficacy analysis, VIEKIRA PAK with ribavirin demonstrated superiority to the historical control SVR rate of 65% {95% CI of 60%, 70%} (based upon telaprevir plus pegIFN/RBV) for patients with genotype 1 HCV infection who were treatment-experienced without cirrhosis. Refer to the telaprevir prescribing information.

Significantly more patients (217/224 = 96.9%) who received VIEKIRA PAK with ribavirin had normalised ALT by the end of treatment than those who received placebo (Arm B, 10/78=12.8%); *P* value < 0.001.

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 60%):

- *Viral factors:* genotype 1 subtype, baseline viral load
- *Host factors:* prior pegIFN/RBV response, gender, race, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage

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

PEARL-II (M13-389) – Genotype 1b, Treatment-Experienced

PEARL-II was a randomised, global multicentre, open-label trial conducted in 180 adults with chronic genotype 1b hepatitis C virus infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Patients were randomised, in a 1:1 ratio, to receive VIEKIRA PAK or VIEKIRA PAK-RBVfor 12 weeks of treatment.

Treated patients (N=179) had a median age of 57 years (range: 26 to 70); 35.2% were prior pegIFN/RBV null responders; 28.5% were prior pegIFN/RBV partial responders, and 36.3% were prior pegIFN/RBV relapsers; 70.9% were born between 1945 – 1965; 54.2% were male; 3.9% were Black; 1.7% were Hispanic or Latino; 21.8% had a body mass index of at least 30 kg/m^2; 12.8% had a history of depression or bipolar disorder; 90.5% had IL28B non-CC genotype; 87.7% had baseline HCV RNA levels of at least 800,000 IU/mL; 17.9% had portal fibrosis (F2) and 14.0% had bridging fibrosis (F3).

Table 9 shows the SVR12 rates for genotype 1b-infected, treatment-experienced patients who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL II. In this study, VIEKIRA PAK had a similar SVR12 rate (100%) compared to VIEKIRA PAK with ribavirin (97.7%).

Table 9: SVR12 for Genotype 1b-infected Treatment-Experienced Patients in PEARL II

	VIEKIRA PAK-RBV for 12 weeks			**VIEKIRAPAK for 12 weeks**		
	n/N	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall SVR12	86/88	97.7	94.6, 100.0	91/91	100	95.9, 100.0
Prior pegIFN/RBV null responder	30/31	96.8	90.6, 100.0	32/32	100	89.3, 100.0
Prior pegIFN/RBV partial responder	24/25	96.0	88.3, 100.0	26/26	100	87.1, 100.0
Prior pegIFN/RBV relapser	32/32	100	89.3, 100.0	33/33	100	89.6, 100.0
Outcome for patients without SVR12						
On-treatment VF[a]	0/88	0		0/91	0	
Relapse[b]	0/88	0		0/91	0	
Other[c]	2/88	2.3		0/91	0	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 log_{10} IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA greater than 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK with ribavirin demonstrated superiority to the historical control SVR rate of 69% {95% CI of 62%, 75%} (based upon telaprevir plus pegIFN/RBV) for patients with genotype 1b HCV infection who were treatment- experienced without cirrhosis. Refer to the telaprevir prescribing information.

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 64%):

- *Viral factors:* baseline viral load
- *Host factors:* prior pegIFN/RBV response, gender, race, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage

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

Clinical Trial in Patients with Cirrhosis

TURQUOISE-II (M13-099) – Genotype 1, Treatment-naïve or treatment-experienced patients with cirrhosis

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

Treated patients (N=380) had a median age of 58 years (range: 21 to 71); 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders; 8.2% were prior pegIFN/RBV partial responders, 13.7% were prior pegIFN/RBV relapsers; 85.5% were born between 1945 – 1965; 70.3% were male; 3.2% were Black; 11.8% were Hispanic or Latino; 28.4% had a body mass index of at least 30 kg/m^2; 14.7% had platelet counts of < 90 x 10^9/L; 11.3% had albumin (< 35 g/L); 86.1% had baseline HCV RNA levels of at least 800,000 IU/mL; 81.8% had IL28B non-CC genotype; 24.7% had a history of depression or bipolar disorder; 68.7% had HCV genotype 1a infection, 31.3% had HCV genotype 1b infection.

Table 10 shows the SVR12 rates for genotype 1-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 10: SVR12 for Genotype 1-Infected Patients with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV

Treatment Outcome	VIEKIRA PAK -RBV					
	12 Weeks			24 Weeks		
	n/N	%	CI[a]	n/N	%	CI[a]
Overall SVR12	191/208	91.8	87.6, 96.1	166/172	96.5	93.4, 99.6
HCV Genotype 1a	124/140	88.6	83.3, 93.8	115/121	95.0	91.2, 98.9
Treatment naïve	59/64	92.2		53/56	94.6	
Prior pegIFN/RBV null responders	40/50	80.0		39/42	92.9	
Prior pegIFN/RBV partial responders	11/11	100		10/10	100	
Prior pegIFN/RBV Prior relapsers	14/15	93.3		13/13	100	
HCV Genotype 1b	67/68	98.5	95.7, 100	51/51	100	93.0, 100
Treatment naïve	22/22	100		18/18	100	
Prior pegIFN/RBV null responders	25/25	100		20/20	100	
Prior pegIFN/RBV partial responders	6/7	85.7		3/3	100	
Prior pegIFN/RBV Prior relapsers	14/14	100		10/10	100	
Outcome for patients without SVR12						
On-treatment VF[b]	1/208	0.5		3/172	1.7	
Relapse[c]	12/203	5.9		1/164	0.6	
Other[d]	4/208	1.9		2/172	1.2	

CI = confidence interval, VF = virologic failure, NA = data not yet available

a. 97.5% confidence intervals are used for the primary efficacy endpoints (overall SVR12 rate); 95% confidence intervals are used for additional efficacy endpoints (SVR12 rates in HCV genotype 1a and 1b patients).

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

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

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

In the primary efficacy analysis, VIEKIRA PAK-RBV administered for 12 or 24 weeks demonstrated superiority to the historical control SVR rate of 47% {95% CI of 41%, 54%} (based upon telaprevir plus pegIFN/RBV) for patients with genotype 1 HCV infection with cirrhosis that were treatment-naïve or previously treated with pegIFN/RBV. Refer to the telaprevir prescribing information.

Based on subgroup analyses, the following baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound > 43%):

- *Viral factors:* genotype 1 subtype, baseline viral load
- *Host factors:* prior pegIFN/RBV response, gender, ethnicity, age, birth year (1945 – 1965), IL28B allele, baseline body mass index, history of depression or bipolar disorder, fibrosis stage, baseline platelet count, baseline albumin

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

TURQUOISE-III: Clinical Trial of GT1b-Infected Patients with Compensated Cirrhosis not receiving RBV

TURQUOISE-III is a Phase 3b, open-label, single-arm, multicentre study evaluating the efficacy and safety of VIEKIRA PAK without ribavirin administered for 12 weeks in HCV GT1b-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. Treated patients (N = 60) had a median age of 60.5 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment experienced (includes 12 null and partial responders and 6 other patients with less well-characterised nonresponse); 25.0% were ≥65 years; 61.7% were male; 11.7% were Black; 5.0% were Hispanic or Latino; 28% had a body mass index of at least 30 kg per m^2; 21.7% had platelet counts of less than 90 x 10^9 per L; 16.7% had albumin less than 35 g/L; 91.7% had baseline HCV RNA levels of at least 800,000 IU per mL; 83.3% had IL28B non-CC genotype; 28.3% had a history of depression or bipolar disorder.

Table 11 shows the SVR12 rates for genotype 1b-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV. There were no relapses during the SVR24 window or beyond SVR24 in this study.

Table 11. SVR12 for Genotype 1b-infected patients with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV

Treatment Outcome	**VIEKIRA PAK without RBV for 12 weeks**
	% (n/N)
Overall SVR12	100% (60/60)
SVR12 for Naïve	100% (27/27)
SVR12 by Prior pegIFN Experience	100% (33/33)
Outcome for patients without SVR12	
On-treatment VF[a]	0
Relapse[b]	0
Other[c]	0

CORAL I: Clinical Trial in Liver Transplant Recipients

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

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

TURQUOISE I: Clinical Trial in Patients with HCV Genotype 1 Infection/HIV-1 Co-infection

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

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

Table 12 shows the SVR12 rates for patients with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

Table 12 SVR12 for HIV-1 Co-infected Patients in TURQUOISE-I

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

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected patients were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected patients. Seven out of 7 patients with genotype 1b infection and 51 of 56 patients with genotype 1a infection achieved SVR12. 5 of 6 patients with compensated cirrhosis in each arm achieved SVR12.

Clinical Trial in Patients Receiving Opioid Substitution Therapy

In a phase 2, multicentre, open-label, single arm study, 38 treatment-naïve or pegIFN/RBV treatment experienced, non-cirrhotic patients with genotype 1 infection who were on stable doses of methadone (N=19) or buprenorphine +/- naloxone (N=19) received 12 weeks of VIEKIRA PAK-RBV. Treated patients had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had genotype 1a infection; 68.4% had IL28B non-CC genotype; 15.8% had portal fibrosis (F2) and 5.3% had bridging fibrosis (F3); and 94.7% were naïve to prior HCV treatment.

Overall, 37 (97.4%) of 38 patients achieved SVR12. No patients experienced on-treatment virologic failure or relapse.

INDICATIONS

VIEKIRA PAK is indicated for the treatment of genotype 1 chronic hepatitis C infection, including patients with compensated cirrhosis. Duration of therapy and addition of ribavirin are dependent on patient population (see DOSAGE AND ADMINISTRATION, PRECAUTIONS, CLINICAL TRIALS).

CONTRAINDICATIONS

Hypersensitivity to components of VIEKIRA PAK, or to any of the excipients.

Patients with moderate to severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity.

Use of ethinylestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings

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 therefore may increase dasabuvir plasma concentrations and the risk of QT prolongations.

The following drugs are contraindicated with VIEKIRA PAK.

Table 13: 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.
Antianginal	Ranolazine	Potential for serious and/or life threatening reactions
Antiarrhythmics	Amiodarone, quinidine	Potential for cardiac arrhythmias.
	Dronedarone	Potential for serious and/or life threatening reactions
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihistamines (for systemic use)	Astemizole, terfenadine	Potential for cardiac arrhythmias.
GI motility agent	Cisapride	Potential for cardiac arrhythmias.
Antigout medications	Colchicine (in patients with renal or hepatic impairment)	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.

Antimycobacterial	Rifampicin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antipsychotic	Blonanserin	No information on potential effects is currently available
	Lurasidone	Potential for serious and/or life threatening reactions
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterised by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinylestradiol- containing products	Ethinylestradiol- containing medications such as combined oral contraceptives	Potential for ALT elevations (see PRECAUTIONS).
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 Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Long Acting Beta-Adrenoceptor agonist	Salmeterol	The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
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 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.
Platelet aggregation inhibitors excluding heparin	Ticagrelor	Increased potential for ticagrelor associated adverse events.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolised by CYP3A4. Co-administration 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.
Steroid antibacterials	Fusidic acid	Increased potential for fusidic acid associated adverse events.

Anticancer agents	Mitotane Enzalutamide	Increased potential for mitotane and enzalutamide associated adverse events.

PRECAUTIONS

VIEKIRA PAK efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VIEKIRA PAK or other direct-acting antiviral agents.

Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis

Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported from postmarketing sources in patients treated with paritaprevir/ritonavir/ombitasvir with and without dasabuvir and with and without ribavirin. Most patients with these severe outcomes had evidence of advanced or decompensated cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were characterised 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.

Paritaprevir/ombitasvir/ritonavir with or without dasabuvir is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C) (see CONTRAINDICATIONS).

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal haemorrhage).
- Hepatic laboratory testing including direct bilirubin levels should be performed at baseline, during the first 4 weeks of starting treatment and as clinically indicated thereafter.
- Discontinue treatment in patients who develop evidence of hepatic decompensation.

ALT Elevations

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

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

Patients using estrogens other than ethinylestradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any

estrogens (1%). No additional monitoring of ALT is required outside of local recommendations and routine clinical practice guidelines.

If ALT is found to be elevated above baseline levels, it should be 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 discoloured urine or faeces (see Serum Bilirubin Elevations under PRECAUTIONS).

- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ration (INR).

Co-administration with Drugs Metabolised by CYP3A

Also refer to CONTRAINDICATIONS, INTERACTIONS WITH OTHER MEDICINES, Table 15 and PHARMACOKINETICS-Implications for Drug Interactions.

Use with Fluticasone (glucocorticoids metabolised by CYP3A)

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

Use with Quetiapine

The use of VIEKIRA PAK with quetiapine is not recommended due to increases in quetiapine exposure. If co-administration 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.

Use with colchicine

A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with VIEKIRA PAK is required. In patients with renal or hepatic impairment, use of colchicine with VIEKIRA PAK is contraindicated (see CONTRAINDICATIONS).

Use with statins

Simvastatin and lovastatin are contraindicated (see CONTRAINDICATIONS).

Atorvastatin, Pitavastatin and fluvastatin

The interactions between atorvastatin, pitavastatin and fluvastatin and VIEKIRA PAK have not been investigated. Theoretically, VIEKIRA PAK is expected to increase the exposure to atorvastatin, pitavastatin and fluvastatin. A temporary suspension of atorvastatin, pitavastatin, fluvastatin is recommended for the duration of treatment with VIEKIRA PAK. If statin treatment is required during the treatment period, a switch to a reduced dose of pravastatin or rosuvastatin is possible (see Table 15).

Use with tacrolimus

Co-administration of VIEKIRA PAK with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see **PHARMACOLOGY**). Serious and/or life threatening events have been observed with co-administration of VIEKIRA PAK with systemic tacrolimus.

Avoid concomitant use of tacrolimus with VIEKIRA PAK unless the benefits outweigh the risks. If tacrolimus and VIEKIRA PAK are used concomitantly, tacrolimus should not be administered on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood concentrations. The recommended tacrolimus dose is 0.5 mg every 7 days.

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

Hepatic Impairment

No dose 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 hepatic impairment (Child-Pugh B and C) (see CONTRAINDICATIONS and Pharmacokinetics).

Treatment of Patients with Other HCV Genotypes

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

HCV/HIV-1 co-infected Patients

Low dose ritonavir, which is part of the fixed dose combination VIEKIRA PAK, may select for PI resistance in HIV co-infected patients without ongoing antiretroviral therapy. HIV co-infected patients without suppressive antiretroviral therapy should not be treated with VIEKIRA PAKRBV.

Drug interactions need to be carefully taken into account in the setting of HIV co-infection. For extensive details on Drug Interactions with antiretroviral therapy, refer to INTERACTIONS WITH OTHER MEDICINES.

Hepatitis B Virus (HBV) Reactivation

Cases of Hepatitis B virus (HBV) reactivation, including fatal cases, have been reported during and after treatment of HCV with direct-acting antiviral agents in HCV/HBV co-infected patients. Screening for current or past HBV infection, including testing for HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc), should be performed in all patients before initiation of treatment with VIEKIRA PAK

Patients with serologic evidence of current or past HBV infection should be monitored and treated according to current clinical practice guidelines to manage potential HBV reactivation. Consider initiation of HBV antiviral therapy, if indicated.

Effects on Fertility

Paritaprevir/ritonavir

Paritaprevir/ritonavir had no effects on embryofoetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg/kg/day. Paritaprevir and ritonavir AUC exposures at this dosage were approximately 2 and 3-fold the exposure in humans at the recommended clinical dose.

Ombitasvir

Ombitasvir had no effects on embryofoetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg/kg/day. Ombitasvir AUC exposures at this dosage were approximately 23-fold (female) or 29-fold (male) the exposure in humans at the recommended clinical dose.

Dasabuvir

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

Use in Pregnancy

Pregnancy Category B3: VIEKIRA PAK

Since there are no adequate and well-controlled studies with VIEKIRA PAK in pregnant women, it should be used during pregnancy only if the benefits outweigh the risks.

No effects on embryofoetal development have been noted in studies in animals with paritaprevir/ritonavir (in combination), ombitasvir and its major inactive human metabolites (M29, M36) or dasabuvir. For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 98-fold (mouse) or 8-fold (rat) (for paritaprevir and 8-fold (mouse) or 3-fold (rat) for ritonavir) the exposures in humans at the recommended clinical doses. For ombitasvir, the highest dose tested produced exposures equal to 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 times higher in mice than in humans at the recommended clinical dose.

Developmental toxicity has been observed in embryofoetal development studies with ritonavir alone. In rats, early resorptions, decreased foetal body weight and ossification delays and developmental variations occurred at a maternally toxic dosage of 75 mg/kg/day (5-fold the exposure in humans at the recommended clinical dose). A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day (4-fold the exposure in humans at the recommended clinical dose). Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased foetal weights) also occurred at a maternally toxic dosage of 110 mg/kg/day. For dasabuvir, the highest dose tested produced exposures equal to 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the recommended clinical dose. Developmental effects have not been identified in humans exposed to ritonavir during pregnancy nor has there been an association with cryptorchidism.

Use in Lactation

It is not known whether paritaprevir/ritonavir, ombitasvir, dasabuvir and their metabolites or ribavirin are excreted in human breast milk. Paritaprevir and its hydrolysis product M13, unchanged ombitasvir and dasabuvir were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

Because of the potential for adverse reactions in nursing infants, breast feeding must be discontinued prior to initiation of treatment.

Paediatric Use

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

Use in the Elderly

No dose adjustment of VIEKIRA PAK is warranted in elderly patients. In Phase 3 clinical trials, 8.5% (174/2053) of patients were age 65 or over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. The safety and effectiveness of VIEKIRA PAK has not been established in patients aged 70 years or over.

Genotoxicity

Paritaprevir

Paritaprevir was positive in an *in vitro* human chromosome aberration test. 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).

Ombitasvir

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.

Dasabuvir

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.

Ritonavir

Ritonavir showed no mutagenic potential in a series of assays for gene mutations (S. typhimurium, E. coli and mouse lymphoma cells) and chromosomal damage (mouse micronucleus assay in-vivo and human lymphocytes *in-vitro*).

Carcinogenicity

Paritaprevir/ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (300/30 mg/kg/day), resulting in paritaprevir and ritonavir AUC exposures approximately 38 and 5-fold higher, respectively than those in humans at the recommended dose of 150/50 mg. Similarly, paritaprevir/ritonavir was not carcinogenic in a 2-year rat study up to the highest dosage tested (300/30 mg/kg/day), resulting in paritaprevir/ritonavir AUC exposures approximately 8/5-fold higher than those in humans at 150/50 mg.

Two-year carcinogenicity studies have been conducted in rodents with ritonavir alone at dietary levels of 50, 100 and 200 mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose-dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance only at the high-dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumorigenic effects.

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (150 mg/kg/day), resulting in ombitasvir AUC exposures approximately 26-fold higher than those in humans at the recommended clinical dose of 25 mg. The carcinogenicity study of ombitasvir in rats is ongoing.

Dasabuvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dosage tested (2000 mg per kg per day), resulting in dasabuvir AUC exposures approximately 19-fold higher

than those in humans at the recommended dose of 500 mg (250 mg twice daily).The carcinogenicity study of dasabuvir in rats is ongoing.

Effect on Laboratory Tests

Changes in selected laboratory parameters are described in Table 14. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in study design.

Table 14: Selected Treatment Emergent Laboratory Abnormalities

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

Serum ALT elevations

During clinical trials with VIEKIRA PAK and VIEKIRA PAK-RBV, less than 1% of patients who were not on systemic ethinylestradiol-containing medications experienced transient serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. These elevations were asymptomatic, generally occurred during the first 4 weeks of treatment and resolved with ongoing therapy. Elevations in ALT were generally not associated with bilirubin elevations. Cirrhosis was not a risk factor for elevated ALT (see PRECAUTIONS).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in patients receiving VIEKIRA PAK, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-induced haemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Elevations in bilirubin in patients with HCV/HIV-1 co-infection who are on treatment with atazanavir have been observed (Refer to the Adverse Effects section). Bilirubin elevations were not associated with aminotransferase elevations.

The frequency of indirect bilirubin elevations was lower among patients who did not receive ribavirin.

Liver Transplant Recipients

Ten patients (29.4%) had at least one postbaseline haemoglobin value of less than 10 g/dL. Ten of 34 patients (29.4%) underwent ribavirin dose modification due to decrease in haemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. Five patients required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No patient received a blood transfusion. Refer to *Dosage and Administration*, *Dosage Modification Guidelines of RBV for Adverse Reactions* for instructions on dosage modification.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and operate machinery have been performed. Patients should be informed that fatigue has been reported during treatment with VIEKIRA PAK.

INTERACTIONS WITH OTHER MEDICINES

Also refer to the CONTRAINDICATIONS, PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES SECTION, Table 15 and PHARMACOKINETICS-Implications for Drug Interactions sections.

Recommendations for co-administration of VIEKIRA PAK for a number of medicinal products are provided in Table 15.

If a patient is already taking medicinal product(s) or initiating a medicinal product while receiving VIEKIRA PAK for which potential for drug interaction is expected, dose adjustment of the concomitant medicinal product(s) or appropriate clinical monitoring should be considered (Table 15).

A change of 0.5- to 2.0-fold in the exposures (C_{max} and AUC) of paritaprevir, ombitasvir and dasabuvir is not considered clinically relevant and does not require dose adjustment for VIEKIRA PAK.

If dose adjustments of concomitant medicinal products are made due to treatment with VIEKIRA PAK, doses should be re-adjusted after administration of VIEKIRA PAK is completed.

Table 15 provides the Least Squares Means Ratio (90% Confidence Interval) effect on concentration of VIEKIRA PAK and concomitant medicinal products. Dose adjustment is not required for VIEKIRA PAK when administered with the concomitant medications listed in Table 15 unless otherwise noted.

Table 15: Interactions between VIEKIRA PAK and other medicinal products

<table>
<tr><th>Drug Class
Drug Name</th><th>Effect</th><th>Clinical Comment</th></tr>
<tr><td colspan="3">Aminosalicylate</td></tr>
<tr><td>Sulfasalazine*</td><td>↑ sulfasalazine</td><td>Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.
Caution should be used when sulfasalazine is co-administered with VIEKIRA PAK.</td></tr>
<tr><td colspan="3">Analgesic</td></tr>
<tr><td>paracetamol</td><td colspan="2">No dose adjustments are required when co-administering with VIEKIRA PAK.</td></tr>
<tr><td colspan="3">Angiotensin receptor blocker</td></tr>
<tr><td>Valsartan *
Losartan *
Candesartan *</td><td>↑ angiotensin receptor blockers</td><td>Mechanism: OATP1B inhibition by paritaprevir.
Decrease the dose of the angiotensin receptor blockers and monitor patients for signs and symptoms of hypotension and/or worsening renal function.</td></tr>
<tr><td colspan="3">Antiarrhythmics</td></tr>
<tr><td rowspan="5">Digoxin</td><td></td><td>C_{max}</td><td>AUC</td><td>C_{min}</td><td rowspan="5">Mechanism: P-gp inhibition by paritaprevir, ritonavir and dasabuvir.
While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.</td></tr>
<tr><td>↔ digoxin</td><td>1.15 (1.04-1.27)</td><td>1.16 (1.09-1.23)</td><td>1.01 (0.97-1.05)</td></tr>
<tr><td>↔ ombitasvir</td><td>1.03 (0.97-1.10)</td><td>1.00 (0.98-1.03)</td><td>0.99 (0.96-1.02)</td></tr>
<tr><td>↔ paritaprevir</td><td>0.92 (0.80-1.06)</td><td>0.94 (0.81-1.08)</td><td>0.92 (0.82-1.02)</td></tr>
<tr><td>↔ dasabuvir</td><td>0.99 (0.92-1.07)</td><td>0.97 (0.91-1.02)</td><td>0.99 (0.92-1.07)</td></tr>
<tr><td>Bepridil*, Lidocaine (systemic) *, Disopyramide*, Propafenone*</td><td colspan="2">↑ antiarrhythmic agents
Decrease in the dose and therapeutic concentration monitoring (if available) is recommended for the antiarrhythmic agents when co-administered with VIEKIRA PAK.</td></tr>
<tr><td colspan="3">Antibiotics</td></tr>
<tr><td>Erythromycin*</td><td>↑ erythromycin</td><td>Mechanism: CYP3A4/P-gp inhibition by paritaprevir, ritonavir and dasabuvir.
Caution is advised when erythromycin is administered with VIEKIRA PAK.</td></tr>
<tr><td>Sulfamethoxazole</td><td colspan="2">No dose adjustments are required when co-administering with VIEKIRA PAK.</td></tr>
<tr><td>Trimethoprim</td><td colspan="2">No dose adjustments are required when co-administering with VIEKIRA PAK.</td></tr>
<tr><td colspan="3">Anticancer agents</td></tr>
<tr><td>Imatinib*</td><td>↑ imatinib</td><td>Mechanism: BCRP inhibition by paritaprevir, ritonavir and dasabuvir.
Clinical monitoring and lower doses of imatinib are recommended.</td></tr>
</table>

Anticoagulants					
Warfarin 5 mg single dose		C_{max}	AUC	C_{min}	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
	↔ R-warfarin	1.05 (0.95-1.17)	0.88 (0.81-0.95)	0.94 (0.84-1.05)	
	↔ S-warfarin	0.96 (0.85-1.08)	0.88 (0.81-0.96)	0.95 (0.88-1.02)	
	↔ ombitasvir	0.94 (0.89-1.00)	0.96 (0.93-1.00)	0.98 (0.95-1.02)	
	↔ paritaprevir	0.98 (0.82-1.18)	1.07 (0.89-1.27)	0.96 (0.85-1.09)	
	↔ dasabuvir	0.97 (0.89-1.06)	0.98 (0.91-1.06)	1.03 (0.94-1.13)	
Fluindione	↑ fluindione				Appropriate monitoring of international normalised ration (INR) is recommended
Dabigatran* etexilate	↑ dabigatran				Mechanism: Intestinal P-gp inhibition by paritaprevir, dasabuvir and ritonavir. VIEKIRA PAK may increase the plasma concentrations of dabigatran etexilate. Use with caution.
S-mephenytoin*	↓ S-mephenytoin				Mechanism: CYP2C19 induction by ritonavir. Clinical monitoring and dose adjustment maybe needed for s-mephenytoin.
Antidepressants					
Escitalopram 10 mg single dose		C_{max}	AUC	C_{min}	No dose adjustment is necessary for escitalopram.
	↔ es-citalopram	1.00 (0.96-1.05)	0.87 (0.80-0.95)	NA	
	↑ S-Desmethyl citalopram	1.15 (1.10-1.21)	1.36 (1.03-1.80)	NA	
	↔ ombitasvir	1.09 (1.01-1.18)	1.02 (1.00-1.05)	0.97 (0.92-1.02)	
	↔ paritaprevir	1.12 (0.88-1.43)	0.98 (0.85-1.14)	0.71 (0.56-0.89)	
	↔ dasabuvir	1.10 (0.95-1.27)	1.01 (0.93-1.10)	0.89 (0.79-1.00)	
Duloxetine 60 mg single dose		C_{max}	AUC	C_{min}	No dose adjustment is necessary for duloxetine.
	↓ duloxetine	0.79 (0.67-0.94)	0.75 (0.67-0.83)	NA	
	↔ ombitasvir	0.98 (0.88-1.08)	1.00 (0.95-1.06)	1.01 (0.96-1.06)	
	↓ paritaprevir	0.79 (0.53-1.16)	0.83 (0.62-1.10)	0.77 (0.65-0.91)	
	↔ dasabuvir	0.94 (0.81-1.09)	0.92 (0.81-1.04)	0.88 (0.76-1.01)	
Trazodone*	↑ Trazodone				Mechanism: CYP3A4 inhibition by ritonavir. Trazodone should be used with caution and a lower dose of trazodone may be considered.

Antifungals					
Ketoconazole 400 mg once daily.		C_{max}	AUC	C_{min}	When VIEKIRA PAK is co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg per day.
	↑ keto-conazole	1.15 (1.09-1.21)	2.17 (2.05-2.29)	NA	
	↔ ombitasvir	0.98 (0.90-1.06)	1.17 (1.11-1.24)	NA	
	↑ paritaprevir	1.37 (1.11-1.69)	1.98 (1.63-2.42)	NA	
	↑ dasabuvir	1.16 (1.03-1.32)	1.42 (1.26-1.59)	NA	
Voriconazole*	↓ voriconazole				Mechanism: CYP2C19 induction by ritonavir. Co-administration of VIEKIRA PAK with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
Antidiabetic					
Metformin	No dose adjustments are required when co-administering with VIEKIRA PAK. Concomitant metformin use in patients with renal insufficiency or hepatic impairment is not recommended				
Antigout					
Colchicine	A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with VIEKIRA PAK is required. See also the colchicine Product Information. Use of colchicine is contraindicated with VIEKIRA PAK in patients with renal or hepatic impairment.				
Antihistamines (for systemic use)					
Fexofenadine*	↑ fexofenadine				Mechanism: OATP1B1 inhibition by paritaprevir. Caution should be used when VIEKIRA PAK is co-administered with fexofenadine.
Antihyperlipidemic agent					
Gemfibrozil		C_{max}	AUC	C_{min}	10-fold increase in dasabuvir exposure. Increased risk of QT-prolongation (see CONTRAINDICATIONS).
	↑ paritaprevir	1.21 (0.94-1.57)	1.38 (1.18-1.61)	NA	
	↑ dasabuvir	2.01 (1.71-2.38)	11.25 (9.05-13.99)	NA	
Calcium Channel Blockers					
Amlodipine 5mg single dose		C_{max}	AUC	C_{min}	Mechanism: CYP3A4 inhibition by ritonavir. The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended.
	↑ amlodipine	1.26 (1.11-1.44)	2.57 (2.31-2.86)	NA	
	↔ 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)	
	↔ dasabuvir	1.05 (0.97-1.14)	1.01 (0.96-1.06)	0.95 (0.89-1.01)	
Diltiazem* Verapamil*	↑ diltiazem, verapamil ↑ paritaprevir ↑/↔ dasabuvir				Mechanism: CYP3A4/P-gp inhibition Caution is advised due to the expected increase in paritaprevir exposures. Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with VIEKIRA PAK.
Nifedipine*	↑ nifedipine				Mechanism: CYP3A4 inhibition Dose decrease and clinical monitoring of calcium channel blockers is recommended when co-administered with VIEKIRA PAK.
Contraceptives- Oral					
Norethisterone	No dose adjustments are required when co-administering with VIEKIRA PAK				
Diuretics					
Furosemide		C_{max}	AUC	C_{min}	Mechanism: Possibly due to UGT1A1
	↑	1.42	1.08	NA	

20mg single dose	furosemide	(1.17-1.72)	(1.00-1.17)		inhibition by paritaprevir, ombitasvir and dasabuvir. Patients should be monitored for clinical effects; a decrease in furosemide dose of up to 50% may be required.
	↔ 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)	
	↔ dasabuvir	1.12 (0.96-1.31)	1.09 (0.96-1.23)	1.06 (0.98-1.14)	
HCV Antiviral					
Sofosbuvir	No dose adjustments are required when co-administering with VIEKIRA PAK				
HIV Antivirals: Protease Inhibitors					
Atazanavir 300mg once daily (given at the same time)		C_{max}	AUC	C_{min}	Mechanism: Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir. In combination with ritonavir, the Increase in paritaprevir exposures may be due to inhibition of OATP1B1/B3 and CYP3A by atazanavir and CYP3A by the additional dose of ritonavir.
	↔ atazanavir	0.91 (0.84-0.99)	1.01 (0.93-1.10)	0.90 (0.81-1.01)	
	↓ ombitasvir	0.77 (0.70-0.85)	0.83 (0.74-0.94)	0.89 (0.78-1.02)	
	↑ paritaprevir	1.46 (1.06-1.99)	1.94 (1.34-2.81)	3.26 (2.06-5.16)	
	↔ dasabuvir	0.83 (0.71-0.96)	0.82 (0.71-0.94)	0.79 (0.66-0.94)	
Atazanavir/ Ritonavir 300/100mg once daily (administered 12 hours apart)		C_{max}	AUC	C_{min}	The recommended dose of atazanavir is 300 mg, without ritonavir, in combination with VIEKIRA PAK. Atazanavir must be administered at the same time as VIEKIRA PAK. Ritonavir dose in VIEKIRA PAK will provide atazanavir pharmacokinetic enhancement. Treatment with atazanavir/ritonavir + VIEKIRA PAK is not recommended.
	↔ atazanavir	1.02 (0.92-1.13)	1.19 (1.11-1.28)	1.68 (1.44-1.95)	
	↔ 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)	
	↔ dasabuvir	0.81 (0.73-0.91)	0.81 (0.71-0.92)	0.80 (0.65-0.98)	
Darunavir 800mg once daily (given at the same time)		C_{max}	AUC	C_{min}	The recommended dose of darunavir is 800 mg once daily, without ritonavir, when administered at the same time as VIEKIRA PAK (ritonavir dose in VIEKIRA PAK will provide darunavir pharmacokinetic enhancement). This regimen can be used in the absence of extensive PI resistance (i.e. lack of darunavir associated RAMs). Darunavir combined with VIEKIRA PAK is not recommended in patients with extensive PI resistance.
	↓ darunavir	0.92 (0.87-0.98)	0.76 (0.71-0.82)	0.52 (0.47-0.58)	
	↔ 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)	
	↔ dasabuvir	1.10 (0.88-1.37)	0.94 (0.78-1.14)	0.90 (0.76-1.06)	
Darunavir/ Ritonavir 600/100mg twice daily		C_{max}	AUC	C_{min}	
	↔ darunavir	0.87 (0.79-0.96)	0.80 (0.74-0.86)	0.57 (0.48-0.67)	
	↓ ombitasvir	0.76 (0.65-0.88)	0.73 (0.66-0.80)	0.73 (0.64-0.83)	
	↓ paritaprevir	0.70 (0.43-1.12)	0.59 (0.44-0.79)	0.83 (0.69-1.01)	
	↓ dasabuvir	0.84 (0.67-1.05)	0.73 (0.62-0.86)	0.54 (0.49-0.61)	
Darunavir/ Ritonavir 800/100mg once daily (administered 12 hours apart)		C_{max}	AUC	C_{min}	
	↑ darunavir	0.79 (0.70-0.90)	1.34 (1.25-1.43)	0.54 (0.48-0.62)	
	↔ 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)	
	↓ dasabuvir	0.75 (0.64-0.88)	0.72 (0.64-0.82)	0.65 (0.58-0.72)	

Lopinavir / Ritonavir 400/100mg twice daily[2]		C_{max}	AUC	C_{min}	Mechanism: Increase in paritaprevir exposures may be due to inhibition of CYP3A/efflux transporters by lopinavir and higher dose of ritonavir. Lopinavir/ritonavir 400/100 mg twice daily and 800/200 mg once daily (evening administration) increases paritaprevir concentrations. Lopinavir/ritonavir use is not recommended with VIEKIRA PAK.
	↔ lopinavir	0.87 (0.76-0.99)	0.94 (0.81-1.10)	1.15 (0.93-1.42)	
	↔ 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)	
	↔ dasabuvir	0.99 (0.75-1.31)	0.93 (0.75-1.15)	0.68 (0.57-0.80)	
HIV Antivirals: Non-nucleoside reverse transcriptase inhibitors					
Rilpivirine 25mg once daily administered in the morning, with food [3]		C_{max}	AUC	C_{min}	Mechanism: CYP3A4 inhibition by ritonavir. Co-administration of VIEKIRA PAK with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher concentrations of rilpivirine.
	↑ rilpivirine	2.55 (2.08-3.12)	3.25 (2.80-3.77)	3.62 (3.12-4.21)	
	↔ ombitasvir	1.11 (1.02-1.20)	1.09 (1.04-1.14)	1.05 (1.01-1.08)	
	↑ paritaprevir	1.30 (0.94-1.81)	1.23 (0.93-1.64)	0.95 (0.84-1.07)	
	↔ dasabuvir	1.18 (1.02-1.37)	1.17 (0.99-1.38)	1.10 (0.89-1.37)	
Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate 600/300/200mg once daily	Co-administration of efavirenz (enzyme inducer) based regimens with paritaprevir/ritonavir + dasabuvir resulted in ALT elevations and therefore, early discontinuation of the study.				Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations. (see CONTRAINDICATIONS).
HIV Antivirals: Nucleoside reverse transcriptase inhibitors					
Lamivudine	No dose adjustments are required when co-administering with VIEKIRA PAK				
Abacavir	No dose adjustments are required when co-administering with VIEKIRA PAK				
HIV Antivirals: Integrase strand transfer inhibitor					
Dolutegravir 50mg once daily		C_{max}	AUC	C_{min}	No dose adjustment is necessary for dolutegravir.
	↑dolutegravir	1.22 (1.15-1.29)	1.38 (1.30-1.47)	1.36 (1.19-1.55)	
	↔ ombitasvir	0.96 (0.89-1.03)	0.95 (0.90-1.00)	0.92 (0.87-0.98)	
	↔ paritaprevir	0.89 (0.69-1.14)	0.84 (0.67-1.04)	0.66 (0.59-0.75)	
	↔ dasabuvir	1.01 (0.92-1.11)	0.98 (0.92-1.05)	0.92 (0.85-0.99)	
Raltegravir 400mg twice daily		C_{max}	AUC	C_{min}	No dose adjustment is necessary for raltegravir.
	↑ raltegravir	2.33 (1.66-3.27)	2.34 (1.70-3.24)	2.00 (1.17-3.42)	
	No clinically relevant changes in dasabuvir, paritaprevir and ombitasvir exposures (based on comparison with historical data) were observed during co-administration				
HIV Antivirals: Nucleoside Inhibitors					
Emtricitabine/ tenofovir 200mg once daily/300mg once daily	↔ em-tricitabine	1.05 (1.00-1.12)	1.07 (1.00-1.14)	1.09 (1.01-1.17)	No dose adjustment is necessary for emtricitabine/tenofovir.
	↔ tenofovir	1.07 (0.93-1.24)	1.13 (1.07-1.20)	1.24 (1.13-1.36)	
	↔ ombitasvir	0.89 (0.81-0.97)	0.99 (0.93-1.05)	0.97 (0.90-1.04)	
	↓ paritaprevir	0.68 (0.42-1.11)	0.84 (0.59-1.17)	1.06 (0.83-1.35)	
	↔ dasabuvir	0.85 (0.74-0.98)	0.85 (0.75-0.96)	0.85 (0.73-0.98)	

HMG-CoA Reductase Inhibitors					
Rosuvastatin 5mg once daily		C_{max}	AUC	C_{min}	Mechanism: OATP1B inhibition by paritaprevir and BCRP inhibition by paritaprevir, ritonavir or dasabuvir The maximum daily dose of rosuvastatin should be 5 mg
	↑ rosuvastatin	7.13 (5.11-9.96)	2.59 (2.09-3.21)	0.59 (0.51-0.69)	
	↔ 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)	
	↔ dasabuvir	1.07 (0.92-1.24)	1.08 (0.92-1.26)	1.15 (1.05-1.25)	
Pravastatin 10mg once daily		C_{max}	AUC	C_{min}	Mechanism: OATP1B/CYP3A4 inhibition by paritaprevir. Reduce pravastatin dose by 50%.
	↑ pravastatin	1.37 (1.11-1.69)	1.82 (1.60-2.08)	NA	
	↔ ombitasvir	0.95 (0.89-1.02)	0.89 (0.83-0.95)	0.94 (0.89-0.99)	
	↔ dasabuvir	1.00 (0.87-1.14)	0.96 (0.85-1.09)	1.03 (0.91-1.15)	
	↔ paritaprevir	0.96 (0.69-1.32)	1.13 (0.92-1.38)	1.39 (1.21-1.59)	
Immunosuppressants					
Ciclosporin 30mg once daily single dose[4]		C_{max}	AUC	C_{min}	When starting co-administration with VIEKIRA PAK, give one fifth of the total daily dose of ciclosporin once daily with VIEKIRA PAK. Monitor ciclosporin levels and adjust dose and/or dosing frequency as needed.
	↑ cilosporin	1.01 (0.85-1.20)	5.82 (4.73-7.14)	15.8 (13.8-18.09)	
	↔ 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)	
	↓ dasabuvir	0.66 (0.58-0.75)	0.70 (0.65-0.76)	0.76 (0.71-0.82)	
Tacrolimus 2mg single dose		C_{max}	AUC	C_{min}	Mechanism: Effect on tacrolimus is due to CYP3A4 inhibition by ritonavir. Co-administration of VIEKIRA PAK with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition. It is recommended to avoid concomitant use of tacrolimus with VIEKIRA PAK unless the benefits outweigh the risks. If tacrolimus and VIEKIRA PAK are used concomitantly, tacrolimus should not be administered 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. The recommended tacrolimus dosing is 0.5 mg every 7 days (see **PRECAUTIONS**). Tacrolimus whole blood concentrations should be monitored upon initiation and throughout co-administration with VIEKIRA PAK and the dose and/or dosing frequency should be adjusted as needed. Upon completion of VIEKIRA PAK treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
	↑ tacrolimus	3.99 (3.21-4.97)	57.1 (45.5-71.7)	16.6 (13.0-21.2)	
	↔ 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)	
	↔ dasabuvir	0.85 (0.73-0.98)	0.90 (0.80-1.02)	1.01 (0.91-1.11)	

Sirolimus 0.5mg single dose		C_{max}	AUC	C_{min}	When co-administering with VIEKIRA PAK, administer 0.2 mg sirolimus twice a week (every three or four days on the same two days each week. Monitor sirolimus levels and adjust dose and/or dosing frequency as needed. Upon completion of VIEKIRA PAK treatment, the appropriate dose and dosing frequency of sirolimus should be guided by assessment of sirolimus blood concentrations.
	↑ Sirolimus	6.40 (5.34, 7.68)	37.99 (31.5, 45.8)	19.55 (16.7, 22.9)	
Everolimus 0.75mg single dose		C_{max}	AUC	C_{min}	Co-administration of VIEKIRA PAK with everolimus is not recommended due a significant increase in everolimus exposures.
	↑ Everolimus	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)	
Insulin Secretagogues					
Repaglinide*	↑ repaglinide				Mechanism: OATP1B1 inhibition by paritaprevir. Caution should be used and dose decrease maybe needed for repaglinide
Iron Chelators					
Deferasirox*	↑ dasabuvir				Mechanism: CYP2C8 inhibition by deferasirox. Deferasirox may increase dasabuvir exposures and should be used with caution.
Medicinal Products used in Multiple Sclerosis					
Teriflunomide*	↑ dasabuvir				CYP2C8 inhibition by teriflunomide. Teriflunomide may increase dasabuvir exposures and should be used with caution.
Muscle Relaxants					
Carisoprodol	↓ carisoprodol ↔ mepobramate (metabolite of carisoprodol)				No dose adjustment required; increase dose if clinically indicated
Cyclobenzaprine	↓ cyclobenzaprine ↓ norcyclobenzaprine (metabolite of cyclobenzaprine)				No dose adjustment required; increase dose if clinically indicated
Opioids					
Methadone 20-120mg once daily[5]		C_{max}	AUC	C_{min}	No dose adjustment is necessary for methadone.
	↔ R-Methadone	1.04 (0.98-1.11)	1.05 (0.98-1.11)	0.94 (0.87-1.01)	
	↔ S-Methadone	0.99 (0.91-1.08)	0.99 (0.89-1.09)	0.86 (0.76-0.96)	
	↔ paritaprevir/ombitasvir/dasabuvir (based on the cross-study comparison)				
Buprenorphine/ naloxone 4-24mg/1-6mg once daily[5]		C_{max}	AUC	C_{min}	No dose adjustment is necessary for buprenorphine/naloxone.
	↑ bu-prenorphine	2.18 (1.78-2.68)	2.07 (1.78-2.40)	3.12 (2.29-4.27)	
	↑ norbu-prenorphine	2.07 (1.42-3.01)	1.84 (1.30-2.60)	2.10 (1.49-2.97)	
	↑ naloxone	1.18 (0.81-1.73)	1.28 (0.92-1.79)	NA	
	↔ ombitasvir/paritaprevir/dasabuvir (based on the cross-study comparison)				

Hydrocodone		C_{max}	AUC	C_{min}	Reduce the dose of hydrocodone by 50% and monitor patients for respiratory depression and sedation at frequent intervals. Upon completion of VIEKIRA PAK therapy, adjust the hydrocodone dose and monitor for signs of opioid withdrawal.
	↑ hydrocodone	1.27 (1.14-1.40)	1.90 (1.72-2.10)	NA	
	↔ ombitasvir	1.01 (0.93-1.10)	0.97 (0.93-1.02)	0.93 (0.90-0.97)	
	↔ paritaprevir	1.01 (0.80-1.27)	1.03 (0.89-1.18)	1.10 (0.97-1.26)	
	↔ dasabuvir	1.13 (1.01-1.26)	1.12 (1.05-1.19)	1.16 (1.08-1.25)	
Proton Pump Inhibitors					
Omeprazole 40mg once daily		C_{max}	AUC	C_{min}	Mechanism: CYP2C19 induction by ritonavir. If clinically indicated higher doses of omeprazole should be used.
	↓ omeprazole	0.62 (0.48-0.80)	0.62 (0.51-0.75)	NA	
	↔ 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)	
	↔ dasabuvir	1.13 (1.03-1.25)	1.08 (0.98-1.20)	1.05 (0.93-1.19)	
Esomeprazole*, Lansoprazole*	↓ esomeprazole, lansoprazole				Mechanism: CYP2C19 induction by ritonavir. If clinically indicated, higher doses of esomeprazole/lansoprazole may be needed.
Sedatives/hypnotics					
Triazolam, orally administered Midazolam	Large ↑ triazolam, orally administered midazolam				Triazolam and orally administered midazolam are extensively metabolised by CYP3A4. Co-administration 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. (see CONTRAINDICATIONS).
Zolpidem 5mg single dose		C_{max}	AUC	C_{min}	No dose adjustment is necessary for zolpidem.
	↔ zolpidem	0.94 (0.76-1.16)	0.95 (0.74-1.23)	NA	
	↔ ombitasvir	1.07 (1.00-1.15)	1.03 (1.00-1.07)	1.04 (1.00-1.08)	
	↓ paritaprevir	0.63 (0.46-0.86)	0.68 (0.55-0.85)	1.23 (1.10-1.38)	
	↔ dasabuvir	0.93 (0.84-1.03)	0.95 (0.84-1.08)	0.92 (0.83-1.01)	
Alprazolam 0.5mg single dose		C_{max}	AUC	C_{min}	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
	↑ alprazolam	1.09 (1.03-1.15)	1.34 (1.15-1.55)	NA	
	↔ 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)	
	↔ dasabuvir	0.93 (0.83-1.04)	0.98 (0.87-1.11)	1.00 (0.87-1.15)	
Diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)				No dose adjustment required; increase dose if clinically indicated.

Thyroid Hormones		
Levothyroxine*	↑ levothyroxine	Mechanism: UGT1A1 inhibition by paritaprevir, ombitasvir and dasabuvir. Clinical monitoring and dose adjustment may be required for levothyroxine.

∗ Not studied; expected effect.

1. Drug interaction study carried out with paritaprevir/ritonavir + dasabuvir combination.
2. Lopinavir/ritonavir 800/200 mg once daily (administered in the evening) was also administered with VIEKIRA PAK. The effect on C_{max} and AUC of DAAs and lopinavir was similar to that observed when lopinavir/ritonavir 400/100 mg twice daily was administered with VIEKIRA PAK.
3. Rilpivirine was also administered in the evening with food and at night 4 hours after dinner with VIEKIRA PAK in other two arms in the study. The effect on rilpivirine exposures was similar to that observed when rilpivirine was administered in the morning with food with VIEKIRA PAK (shown in the table above).
4. Ciclosporin 100 mg dosed alone and 30 mg administered with VIEKIRA PAK. Dose normalized ciclosporin ratios are shown for interaction with VIEKIRA PAK.
5. Dose normalised parameters reported for methadone, buprenorphine and naloxone.

Note: Doses used for VIEKIRA PAK were: ombitasvir 25mg, paritaprevir 150mg, ritonavir 100mg, once daily and dasabuvir 400mg twice daily or 250mg twice daily. The dasabuvir exposures obtained with the 400 mg formulation and the 250mg tablet are similar. VIEKIRA PAK was administered as multiple doses in all the drug interaction studies except the drug interaction studies with carbamazepine, gemfibrozil and ketoconazole.

ADVERSE EFFECTS

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

<u>VIEKIRA PAK with Ribavirin in Patients with Genotype 1 Hepatitis C Infection (including patients with cirrhosis)</u>

In patients receiving VIEKIRA PAK, the most commonly reported adverse reactions (greater than 20% of patients) were fatigue and nausea. The proportion of patients who permanently discontinued treatment due to adverse events was 1.2% (25/2,044). 1.3% (27/2,044) of patients interrupted treatment due to adverse events. 7.7% (158/2,044) of patients had ribavirin dose reductions due to adverse events.

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

<u>VIEKIRA PAK without Ribavirin in Patients with Genotype 1 Hepatitis C Infection</u>

In patients receiving VIEKIRA PAK without ribavirin, pruritus was the only identified adverse reaction (of reactions that occurred in ≥ 5% of patients)when a comparison of patients who received VIEKIRA PAK without RBV was made to studies which included both VIEKIRA PAK with ribavirin and placebo.

The proportion of patients who permanently discontinued treatment due to adverse events was 0.3% (2/588). 0.5% (3/588) patients had treatment interruptions due to adverse events.

Table 16 lists adverse drug reactions from two randomised placebo-controlled trials (SAPPHIRE I and SAPPHIRE II) that occurred with at least 5% higher frequency among patients receiving VIEKIRA PAK in combination with ribavirin compared to patients receiving placebo, regardless of relationship to

VIEKIRA PAK. In addition, Table 16 includes rates of these adverse events from three trials in which patients received VIEKIRA PAK with or without ribavirin (PEARL II, PEARL III, and PEARL IV), and rates of these adverse events from the trial in patients with cirrhosis who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 or 24 weeks (TURQUOISE II). A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in design.

Table 16: Side-by-Side Tabulation of Adverse Event Rates in Phase 3 Trials Based on Adverse Reactions* (All Grades)

	SAPPHIRE I and II		**PEARL II, III and IV**		**TURQUOISE II (patients with cirrhosis)**
Adverse Reaction	**VIEKIRA PAK + RBV 12 Weeks N = 770 n (%)**	**Placebo 12 Weeks N = 255 n (%)**	**VIEKIRA PAK + RBV 12 Weeks N = 401 n (%)**	**VIEKIRA PAK 12 Weeks N = 509 n (%)**	**VIEKIRA PAK + RBV 12 or 24 Weeks N = 380 n (%)**
Fatigue	263 (34.2)	67 (26.3)	120 (29.9)	135 (26.5)	148 (38.9)
Nausea	172 (22.3)	38 (14.9)	63 (15.7)	43 (8.4)	72 (18.9)
Pruritus	121 (15.7)	11 (4.3)	48 (12.0)	31 (6.1)**	71 (18.7)
Insomnia	108 (14.0)	19 (7.5)	49 (12.2)	26 (5.1)	63 (16.6)
Asthenia	104 (13.5)	17 (6.7)	36 (9.0)	20 (3.9)	51 (13.4)
Anaemia	41 (5.3)	0	30 (7.5)	1 (0.2)	34 (8.9)

*Adverse drug reactions for VIEKIRA PAK with ribavirin listed are those with a 5% higher frequency among patients receiving VIEKIRA PAK in combination with ribavirin compared to patients receiving placebo in SAPPHIRE I and II.

** Adverse drug reaction for VIEKIRA PAK defined as the subset of ADRs for the VIEKIRA PAK- RBV for which the risk difference (VIEKIRA PAK-RBV minus VIEKIRA PAK) in PEARL II, III, and IV was at least 5.0 % lower than the risk difference (VIEKIRA PAK minus placebo) in SAPPHIRE I and II.

The majority of adverse events in the Phase 3 clinical trials were of grade 1 severity. The safety profile of VIEKIRA PAK with ribavirin was consistent with the known safety profile of ribavirin.

In addition to the adverse reaction listed in Table 16, treatment-emergent adverse events that occurred with at least 2% frequency and less than 5% higher frequency among patients receiving VIEKIRA PAK-RBV compared to patients receiving placebo (SAPPHIRE I and II), are listed below by system organ class.

Gastrointestinal Disorders:	Diarrhoea and vomiting
Investigations:	Haemoglobin decreased
Metabolism and Nutrition Disorders:	Decreased appetite
Nervous System Disorders:	Dizziness and headache
Psychiatric Disorders:	Sleep disorder
Respiratory, Thoracic and Mediastinal Disorders:	Cough and dyspnoea
Skin and Subcutaneous Tissue Disorders:	Dry skin, and rash

Liver Transplant Recipients

The type of adverse events experienced by genotype 1 HCV-infected liver transplant recipients who were treated with VIEKIRA PAK with ribavirin (in addition to their immunosuppressant medications) was similar to those experienced by patients treated with VIEKIRA PAK with ribavirin in phase 3 clinical trials; however some events were increased in frequency. Adverse events occurring in >20%

of post-liver transplant patients included fatigue 50.0%, headache 44.1%, cough 32.4%, diarrhea 26.5%, insomnia 26.5%, asthenia 23.5%, nausea 23.5%, anaemia 20.6%, muscle spasms 20.6% and rash 20.6%. Ten patients (29.4%) had at least one postbaseline haemoglobin value of less than 10 g/dL. Ten of 34 patients (29.4%) underwent dose modification due to decrease in haemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates (Refer to the Dosage and Administration section). Five patients required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No patient received a blood transfusion.

HCV/HIV-1 co-infected Patients

The overall safety profile in HCV genotype 1/HIV-1 co-infected patients was similar to that observed in HCV genotype 1 mono-infected patients. Transient elevations in total bilirubin >3 x ULN (mostly indirect) occurred in 17 (27.0%) patients; 15 of these 17 patients were receiving atazanavir at the time of bilirubin elevation, and 9 of the 17 patients also had adverse events of ocular icterus, jaundice or hyperbilirubinemia. Elevations in total bilirubin greater than 2 x ULN (mostly indirect) occurred in 34 (54%) patients. Twenty four of these 34 patients were receiving atazanavir at the time of bilirubin elevation.

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 patients had CD4+ T-cell counts decrease to less than 200 cells/mm^3 during treatment without a decrease in CD4%. Two patients experienced an AIDS-related opportunistic infection, however there were not deemed treatment related.

VIEKIRA PAK without Ribavirin in GT1b-infected Patients with Compensated Cirrhosis

VIEKIRA PAK without ribavirin was assessed in 60 patients with genotype 1b infection and compensated cirrhosis who were treated for 12 weeks (TURQUOISE-III) (see CLINICAL TRIALS). The most commonly reported adverse events (greater than or equal to 20% of patients) were fatigue and diarrhea. One patient (2%) experienced a grade 2 post-baseline haemoglobin decrease. Post-baseline Grade 2 increases in total bilirubin occurred in 12 (20%) patients. No patients experienced a grade 3 or higher post-baseline decrease in haemoglobin or total bilirubin increase. One patient (2%) experienced a Grade 3 ALT elevation.

One patient (2%) had a serious adverse event. One patient (2%) interrupted treatment due to an adverse event and no patient permanently discontinued treatment due to adverse events.

Post-Marketing Adverse Reactions

The following adverse reactions have been identified during post approval use of paritaprevir/ritonavir/ombitasvir with and without dasabuvir. 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 tongue and lip swelling) have been observed (see CONTRAINDICATIONS).
Rare cases of Stevens-Johnson syndrome have been reported for ritonavir.

Hepatobiliary Disorders: Hepatic decompensation, hepatic failure and Hepatitis B Reactivation have been observed (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Prior to initiation of VIEKIRA PAK, assess for laboratory and clinical evidence of hepatic decompensation

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

Ombitasvir/paritaprevir/ritonavir tablets are not recommended for administration as monotherapy and must be administered with dasabuvir tablets.

Recommended Dose in Adults

The recommended oral dose of VIEKIRA PAK is two paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening).

VIEKIRA PAK is used in genotype 1b-infected patients, and can be considered as a therapeutic option for non-cirrhotic, treatment-naïve patients with genotype 1a infection (see CLINICAL TRIALS and Table 17).

Patients should be instructed to swallow the tablets whole (i.e. patients should not chew, break or dissolve the tablets).

To maximise absorption, VIEKIRA PAK should be taken with food without regard to fat or calorie content (see PHARMACOLOGY*).*
Table 17 shows the recommended treatment regimen and duration based on patient population.

Table 17: Treatment Regimen and Duration by Patient Population

Patient Population	Treatment	Duration	Ribavirin Dosage
Genotype 1a, with or without cirrhosis	VIEKIRA PAK- RBV[a]*	12 weeks[b]	< 75 kg = 1000 mg ≥ 75 kg = 1200 mg Ribavirin is to be taken in two doses, morning and evening
Genotype 1b, with or without cirrhosis	VIEKIRA PAK	12 weeks	Not Applicable

a VIEKIRA PAK without ribavirin can be considered as a therapeutic option for treatment-naïve patients with genotype 1a infection without cirrhosis (see CLINICAL TRIALS). Treatment decision should be guided by an assessment of the potential benefits and risks and available alternative therapies for the individual patient.

b 24 weeks of VIEKIRA PAK–RBV is recommended for patients with genotype 1a-infection with cirrhosis who have had a previous null response to pegIFN and ribavirin (see CLINICAL TRIALS).

Note: VIEKIRA PAK-RBV is recommended in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.

VIEKIRA PAK should be taken as directed for the prescribed duration, without interruption.

Missed Dose

Inform patients that in case a dose of paritaprevir, ritonavir, ombitasvir 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.

Use in Special Populations

Hepatic Impairment

No dose 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 hepatic impairment (Child-Pugh B and C) (see CONTRAINDICATIONS and PRECAUTIONS).

Liver Transplant Recipients

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

Renal Impairment

Based on the pharmacokinetic data in HCV uninfected subjects (n=24), no dose adjustment of VIEKIRA PAK is recommended in patients with mild, moderate or severe renal impairment. The efficacy and safety of VIEKIRA PAK have not been evaluated in HCV-infected patients with moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients on dialysis.

HCV/HIV-1 coinfection

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 17. Refer to INTERACTIONS WITH OTHER MEDICINES for dosage recommendations for concomitant HIV-1 antiviral drugs

Drug interactions need to be carefully taken into account in the setting of HIV co-infection. For extensive details on Drug Interactions with antiretroviral therapy, refer to INTERACTIONS WITH OTHER MEDICINES.

Atazanavir can be used in combination with Viekira Pak, if administered at the same time. To be noted, atazanavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of Viekira Pak-RBV. The combination carries an increased risk for hyperbilirubinemia (including ocular icterus), in particular when ribavirin is part of the hepatitis C regimen.

Darunavir, dosed 800 mg once daily, if administered at the same time as Viekira Pak-RBV and dasabuvir, can be used in the absence of extensive PI resistance (darunavir exposure lowered). To be noted, darunavir should be taken without ritonavir, since ritonavir 100 mg once daily is provided as part of Viekira Pak-RBV.

HIV protease inhibitors other than atazanavir and darunavir (e.g., indinavir, saquinavir, tipranavir, lopinavir/ritonavir) are contraindicated (see CONTRAINDICATIONS).

Raltegravir exposure is substantially increased (2-fold). The combination was not linked to any particular safety issues in a limited set of patients treated for 12-24 weeks.

Rilpivirine exposure is substantially increased (3-fold) when rilpivirine is given in combination with Viekira Pak-RBV and dasabuvir, with a consequent potential for QT-prolongation. If an HIV protease inhibitor is added (atazanavir, darunavir), rilpivirine exposure may increase even further and is therefore not recommended. Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring.

NNRTIs other than rilpivirine (efavirenz, etravirine and nevirapine) are contraindicated (see CONTRAINDICATIONS).

OVERDOSAGE

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

For information on the management of overdose in Australia contact the Poison Information Centre on 131126 and in New Zealand call 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets are pink-coloured, film-coated, oblong biconvex shaped, debossed with “AV1” on one side.

Dasabuvir 250 mg tablets are beige-coloured, film-coated, oval-shaped, debossed with “AV2” on one side

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 daily dose pack contains four tablets: two 75 mg/50 mg/12.5 mg paritaprevir/ritonavir/ombitasvir tablets and two 250 mg dasabuvir tablets in PVC/PE/PCTFE(Aclar)/Al blisters, and indicates which tablets need to be taken in the morning and evening.

Storage Conditions

Store below 25°C in a dry place.

NAME AND ADDRESS OF THE SPONSOR

AbbVie Pty Ltd
Level 7, 241 O'Riordan Street
Mascot NSW 2020
Australia

AbbVie Limited
6th Floor, 156-158 Victoria St
Wellington, 6011
New Zealand

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

10 July 2015

DATE OF MOST RECENT AMENDMENT

21 March 2017