NEW ZEALAND DATA SHEET

VIEKIRA PAK-RBV combination therapy pack

NAME OF THE MEDICINE

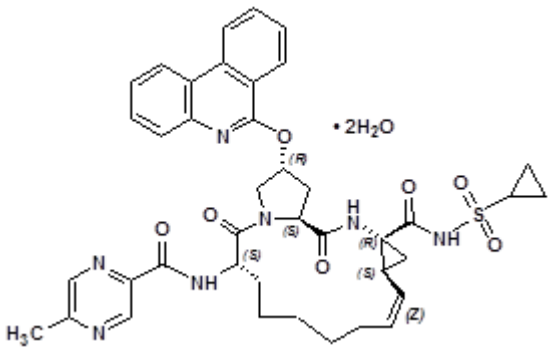
VIEKIRA PAK-RBV is a composite pack containing paritaprevir/ritonavir/ombitasvir 75/50/12.5 mg tablets copackaged with dasabuvir 250 mg tablets and 200 mg, 400 mg* or 600 mg* ribavirin tablets.

* Presentation not currently available in New Zealand.

Chemical Structure and Description of each Active Pharmaceutical Ingredient

Paritaprevir

Paritaprevir drug substance is manufactured as a dihydrate, but is dehydrated during the drug product manufacturing process and is amorphous and anhydrous in the final product. Paritaprevir dihydrate is chemically designated as (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:



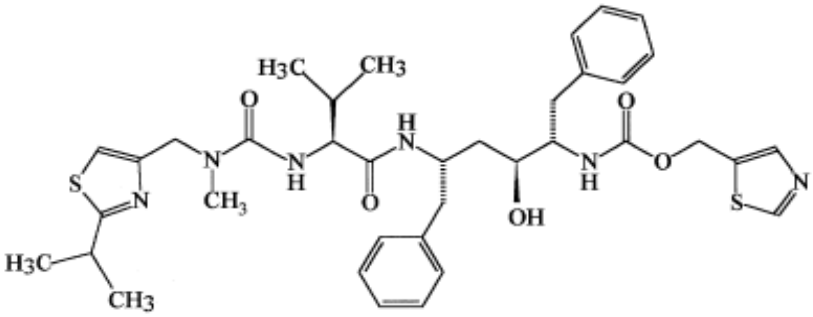
CAS Number: 1456607-71-8

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*-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-

tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is $C_{37}H_{48}N_6O_5S_2$ and the molecular weight is 720.95. Ritonavir has the following structural formula:

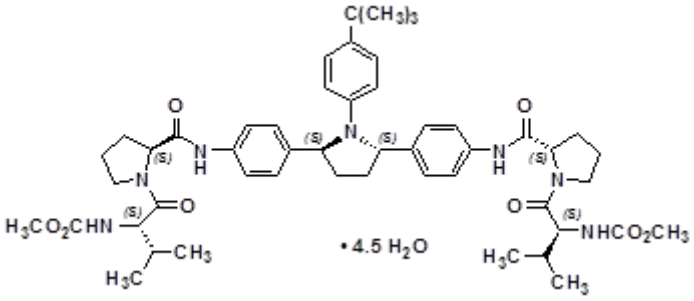


CAS Number: 155214-67-5

Ritonavir is white to off-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, but 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]bisbenzene-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:

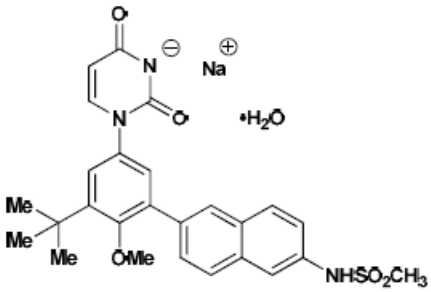


CAS Number: 1456607-70-7

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-*tert*-butyl-4-methoxy-5-6-[(methylsulfonyl)amino]naphthalene-2-ylphenyl)-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:

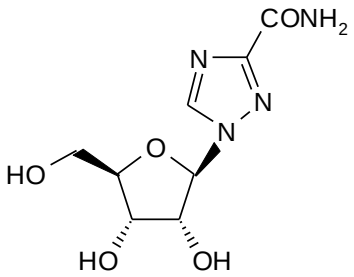


CAS Number: 1456607-55-8

Dasabuvir sodium monohydrate is a white to pale yellow 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).

Ribavirin

Ribavirin is chemically defined as 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide. The molecular formula of ribavirin is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2. Ribavirin has the following molecular structure:



CAS Number: 36791-05-5

Ribavirin is a white to off-white powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. Ribavirin has a pKa of 12.25.

DESCRIPTION

Paritaprevir, ritonavir, and ombitasvir are co-formulated as film-coated immediate release tablets. The tablet also contains 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.

Ribavirin is available as a blue-coloured (shade depending on strength), oblong, film-coated tablet for oral administration. Each tablet contains 200 mg, 400 mg, or 600 mg of ribavirin and the following inactive ingredients: microcrystalline cellulose, lactose, croscarmellose sodium, povidone, magnesium stearate, and purified water. The coating of the 200 mg tablet contains Opadry Blue 85F90614 (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and indigo carmine lake). The coating of the 400 mg tablet contains Opadry II blue (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and indigo carmine aluminium lake) and the coating of the 600 mg tablet contains Opadry II blue 85F90623 (polyvinyl alcohol, titanium dioxide, macrogol, purified talc, and brilliant blue aluminium lake).

PHARMACOLOGY

Pharmacodynamics

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

Mechanism of Action

VIEKIRA PAK-RBV combines ribavirin with three direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target the hepatitis C virus (HCV) at multiple steps in the viral lifecycle. Ribavirin is a synthetic nucleoside analogue that has shown *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin exerts its effects against HCV is unknown.

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

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.

Ribavirin

Ribavirin is a synthetic nucleoside analogue that shows *in vitro* activity against some RNA and DNA viruses. The mechanism by which ribavirin exerts its effects against HCV is unknown.

Oral formulations of ribavirin monotherapy have been investigated as therapy for chronic hepatitis C in several clinical trials. Results of these investigations showed that ribavirin monotherapy had no effect on eliminating hepatitis virus (HCV-RNA) or improving hepatic histology after 6 to 12 months of therapy and 6 months of follow-up. Monotherapy with ribavirin is not recommended.

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 for the human major metabolites of ombitasvir, M29 and M36 in the HCV replicon assay; M29 and M36 do not contribute to the 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 (RBV) 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. In the genotype 1a replicon, the activity of paritaprevir was reduced 20-, 37-, and 17-fold by the F43L, R155K and A156T substitutions, respectively. The activity of paritaprevir was reduced 96-fold by D168V, and 13- to 219-fold by each of the other D168 substitutions. The activity of paritaprevir in genotype 1a was not significantly affected (less than or equal to 3-fold) by single substitutions 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 3-fold relative to the single R155K or D168 substitution. In genotype 1b, substitutions R155Q, 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. Y56H alone could not be evaluated due to poor replication capacity; however, the combination of Y56H and D168A, D168V or D168Y reduced the activity of paritaprevir by 700-, 2472-, and 4118-fold, respectively.

In genotype 1a, substitutions M28T/V, Q30E/R, H58D, Y93C/H/L/N, and M28V + Q30R in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1a replicon, the activity of ombitasvir was reduced by 58- and 243-fold against the M28V and H58D substitutions, respectively, and 800- and 1675-fold by the Q30E/R and Y93C substitutions, respectively. Y93H, Y93N, or M28V + Q30R reduced the activity of ombitasvir by more than 40,000-fold. In genotype 1b, substitutions L31F/V, as well as Y93H alone or in combination with L28M, R30Q, L31F/M/V or P58S in HCV NS5A reduced susceptibility to ombitasvir. In the genotype 1b replicon, the activity of ombitasvir was reduced by less than 10-fold by variants at amino acid positions 30 and 31. The activity of ombitasvir was reduced by 77-, 284-, and 142-fold against the genotype 1b substitutions Y93H, R30Q in combination with Y93H, and

L31M in combination with Y93H, respectively. All other double substitutions of Y93H in combination with substitutions at positions 28, 31, or 58 reduced the activity of ombitasvir by more than 400-fold.

In genotype 1a, substitutions C316Y, M414T, N444K, E446K, Y448C/H, A553T, G554S, S556G/R, and Y561H in HCV NS5B reduced susceptibility to dasabuvir. In the genotype 1a replicon, the activity of dasabuvir was reduced 21- to 54-fold by the M414T, N444K, E446K, S556G, or Y561H substitutions; 152- to 261-fold by the A553T, G554S, or S556R substitutions; and 940- to 1472-fold by the C316Y and Y448C/H substitutions. 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/Y, S368T, N411S, M414I/T/V, Y448C/H, A553V, S556G, and D559G in HCV NS5B reduced susceptibility to dasabuvir. The activity of dasabuvir was reduced by 11- to 84-fold by N411S, M414I/T/V, Y448H, and S556G, 100- to 414-fold by C316H, S368T, Y448C, A553V, and D559G; and 1569-fold by the C316Y substitutions in the genotype 1b replicon. Dasabuvir retained full activity against replicons containing substitutions S282T in the nucleoside binding site, M423T in the lower thumb site, and P495A/S, P496S or V499A in the upper thumb site.

Effect of Baseline HCV Substitutions/Polymorphisms on Treatment Response

A pooled analysis of subjects 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 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 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 subjects with HCV genotype 1 chronic infection in the Phase 2b and 3 clinical trials who were treated with regimens containing paritaprevir, ombitasvir, and dasabuvir with or without ribavirin (for 8, 12, or 24 weeks), a total of 74 subjects (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 subjects, NS3 variants were observed in 50 subjects, NS5A variants were observed in 46 subjects, NS5B variants were observed in 37 subjects, and treatment-emergent variants were seen in all three drug targets in 30 subjects. In the seven genotype 1b-infected subjects, treatment-emergent variants were observed in NS3 in four subjects, in NS5A in two subjects, and in both NS3 and NS5A in one subject. No subjects with genotype 1b had treatment-emergent variants in all three drug targets.

Table 1: Treatment-Emergent Amino Acid Substitutions in the Pooled Analysis of VIEKIRA PAK and VIEKIRA PAK-RBV 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 two subjects 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 subjects.
e. Observed in combination in 6% (4/67) of the subjects.

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 subjects in Phase 2b trials. Paritaprevir treatment-emergent variants V36A/M, R155K or D168V were observed in NS3 in 47 subjects. Ombitasvir treatment-emergent variants M28T, M28V or Q30R in NS5A were observed in 32 subjects. Dasabuvir treatment-emergent variants M414T, G554S, S556G, G558R or D559G/N in NS5B were observed in 34 subjects.

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/VIEKIRA PAK-RBV-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.

Pharmacokinetics

The pharmacokinetic properties of the combination of paritaprevir, ombitasvir, ritonavir, and dasabuvir have been evaluated in healthy adult subjects and in subjects 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) (%CV)	**AUC_{0-24} (ng*hr/mL) (%CV)**
Paritaprevir	1470 (87)	6990 (96)
Ombitasvir	127 (31)	1420 (36)
Dasabuvir	1030 (31)	6840 (32)
Ritonavir	1600 (40)	9470 (41)

Absorption

Paritaprevir/ritonavir/ombitasvir and dasabuvir

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.

Ribavirin

Ribavirin is absorbed rapidly following oral administration of a single dose (median T_{max} = 1-2 hours). The mean terminal phase half-life of ribavirin following single doses of ribavirin ranges from 140 to 160 hours. Ribavirin data from the literature demonstrates absorption is extensive with approximately 10% of a radiolabelled dose excreted in the faeces. However, absolute bioavailability is approximately 45% to 65%, which appears to be due to first-pass metabolism. There is an approximately linear relationship between dose and AUC_{tf} following single doses of 200 to 1,200 mg ribavirin. Mean apparent oral clearance of ribavirin following single 600 mg doses ranges from 22 to 29 L/hr. Volume of distribution is approximately 4,500 L following administration of ribavirin. Ribavirin does not bind to plasma proteins.

Upon multiple dosing, ribavirin accumulates extensively in plasma with a six-fold ratio of multiple-dose to single-dose AUC_{12hr} based on literature data. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady state plasma concentrations of approximately 2,200 ng/mL.

The absolute bioavailabilities of ombitasvir and paritaprevir when administered with ritonavir are 48% and 53%, respectively. The absolute bioavailability of dasabuvir is estimated to be approximately 70%.

Effects of food on oral absorption

Paritaprevir/ritonavir/ombitasvir and dasabuvir

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-RBV should be taken with food without regard to fat or calorie content.

Ribavirin

The bioavailability of a single oral 600 mg dose of ribavirin was increased by co-administration with a high-fat meal. The ribavirin exposure parameters of $AUC_{(0-192h)}$ and C_{max} increased by 42% and 66%, respectively, when ribavirin tablet was taken with a high-fat breakfast compared to being taken in the fasted state. The clinical relevance of results from this single dose study is unknown. In order to achieve optimal ribavirin plasma concentrations, it is recommended to take ribavirin with food.

Distribution

Paritaprevir/ritonavir/ombitasvir and dasabuvir

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 0.01 to 30 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% 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.

Ribavirin

Ribavirin has been shown to produce high inter- and intra-subject pharmacokinetic variability following single oral doses (intra-subject variability of approximately 30% for both AUC and C_{max}), which may be due to extensive first-pass metabolism and transfer within and beyond the blood compartment.

Ribavirin transport in non-plasma compartments has been most extensively studied in red cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the high volume of distribution of ribavirin. The ratio of whole blood to plasma ribavirin concentrations is approximately 60:1; the excess of ribavirin in whole blood exists as ribavirin nucleotides sequestered in erythrocytes.

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 five 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 dose of ^{14}C-dasabuvir 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 (after correction for plasma protein binding) as the parent drug against genotype 1 *in vitro*.

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.

Ribavirin

Ribavirin has two pathways of metabolism: i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

<u>Elimination</u>

Paritaprevir

Following dosing of paritaprevir/ritonavir/ombitasvir with or without dasabuvir, the 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 87.8% 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, the 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. Unchanged ombitasvir accounted for 87.8% of the radioactivity in the faeces and 0.03% in the urine.

Dasabuvir

Following dosing of dasabuvir with paritaprevir/ritonavir/ombitasvir, the 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. Unchanged dasabuvir accounted for 26% of the radioactivity in the faeces and 0.03% in the urine.

Ritonavir

Following dosing of paritaprevir/ritonavir/ombitasvir, the 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.

Ribavirin

Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and faeces respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from non-plasma compartments. Multiple dose ribavirin apparent clearance was 22.4 (34%) L/hr.

Special Populations

Renal impairment

Paritaprevir/ritonavir/ombitasvir and dasabuvir

No dose adjustment of VIEKIRA PAK-RBV is recommended in subjects with mild, moderate or severe renal impairment. (Refer to DOSAGE AND ADMINISTRATION.) The efficacy and safety of VIEKIRA PAK-RBV have not been evaluated in HCV-infected subjects 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 subjects 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 subjects with mild renal impairment, 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 subjects with moderate renal impairment, 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 subjects with severe renal impairment, 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.

The apparent clearance of ribavirin is reduced in patients with creatinine clearance ≤50 mL/min, including patients with end-stage-renal disease (ESRD) on chronic haemodialysis, exhibiting approximately 30% of the value found in patients with normal renal function. Based on a small study in patients with moderate or severe renal impairment (creatinine clearance ≤50 mL/min) receiving reduced daily doses of 600 mg and 400 mg of ribavirin, respectively, ribavirin plasma exposure (AUC) was found to be higher compared to patients with normal renal function (creatinine clearance >80 mL/min) receiving the standard ribavirin dose. Patients with ESRD on chronic haemodialysis who received 200 mg daily doses of ribavirin, exhibited mean ribavirin exposure (AUC) approximately 80% of the value found in patients with normal renal function receiving the standard 1000/1200 mg ribavirin daily dose. Plasma ribavirin is removed by haemodialysis with an extraction ratio of approximately 50%; however, due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed from the body by haemodialysis. Increased rates of adverse drug reactions were observed in patients with moderate and severe renal impairment receiving the doses evaluated in this study. Though the dose of ribavirin would need to be reduced if used in patients with significant renal impairment, there are insufficient data on the safety and efficacy of ribavirin in such patients to support specific recommendations for dose adjustments (see DOSAGE AND ADMINISTRATION).

Hepatic impairment

Paritaprevir/ritonavir/ombitasvir and dasabuvir

No dosage adjustment of paritaprevir/ritonavir/ombitasvir and dasabuvir is required in patients with mild hepatic impairment (Child-Pugh A).

Paritaprevir/ritonavir/ombitasvir with dasabuvir is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. Paritaprevir/ritonavir/ombitasvir with dasabuvir is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see WARNINGS AND PRECAUTIONS, and CONTRAINDICATIONS).

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

In subjects with mild hepatic impairment, 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 subjects with moderate hepatic impairment, 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-RBV have not been established in HCV-infected patients with moderate hepatic impairment (Child-Pugh B); however, no dose adjustment is expected to be required based on pharmacokinetic studies.

In subjects with severe hepatic impairment, 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.

Single-dose pharmacokinetics of ribavirin in patients with mild, moderate or severe hepatic dysfunction (Child-Pugh Classification A, B or C) are similar to those of normal controls.

Elderly

No dose adjustment is necessary for paritaprevir/ritonavir/ombitasvir or dasabuvir in elderly patients. In Phase 3 clinical studies 187/2,292 (8.2%) of genotype 1 infected subjects were aged 65 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

In a published population pharmacokinetic study of RBV, age was not a key factor in the kinetics of ribavirin; renal function is the determining factor. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. The dose of ribavirin should be reduced in patients with creatinine clearance of 50 mL/min (see DOSAGE AND ADMINISTRATION).

Paediatric population (<18 years of age)

The pharmacokinetics, safety and efficacy of VIEKIRA PAK-RBV 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.

Sex or bodyweight

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

Dose adjustment is required for ribavirin based on weight (see DOSAGE and ADMINISTRATION).

CLINICAL TRIALS

The efficacy and safety of VIEKIRA PAK and VIEKIRA PAK-RBV was evaluated in seven randomised Phase 3 clinical trials, including two trials exclusively in subjects with cirrhosis (Child-Pugh A), in over 2,600 subjects with HCV genotype 1 infection, as summarised in Table 3.

Table 3: Phase 3 Randomised, Global Multicentre Trials Conducted with VIEKIRA PAK and VIEKIRA PAK-RBV

Trial[1]	Number of subjects (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)	179	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 subjects 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 subjects were defined as either: prior relapsers (subjects with HCV RNA undetectable at or after the end of at least 36 weeks of pegylated interferon (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 log10 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 log10 IU/mL reduction in HCV RNA at week 12 or received at least 4 weeks of pegIFN/RBV treatment and achieved a <1 log10 IU/mL reduction in HCV RNA at week 4). TURQUOISE III also enrolled less well characterised failures of pegIFN/RBV treatment.

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

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

Pooled Analyses of Clinical Trials

Durability of Response

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

Pooled Efficacy Analyses

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

Among subjects 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)
Other pegIFN/RBV failures	0	0	0	100% (18/18)[+]
Prior pegIFN/RBV null responder	95% (83/87)	93% (39/42) (24 weeks)	100% (32/32)	100% (7/7)
TOTAL	**96% (569/593)**	**93% (125/134)***	**100% (301/301)**	**100% (60/60)**

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

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 HCV genotype 1 chronic infection without cirrhosis. VIEKIRA PAK-RBV was given for 12 weeks of treatment. Subjects randomised to the placebo arm received placebo for 12 weeks, after which they received open-label VIEKIRA PAK-RBV for 12 weeks.

Treated subjects (N=631) had a median age of 52 years (range: 18 to 70); 64.8% were born between 1945 and 1965; 54.5% were male; 5.4% were Black and 5.1% were Hispanic or Latino; 16.2% had a body mass index (BMI) 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; and 32.3% had HCV genotype 1b infection.

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

Table 5: SVR12 for Genotype 1-Infected Treatment-Naïve Subjects 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 subjects 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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV for subjects with HCV genotype 1 infection who were treatment-naïve, without cirrhosis.

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

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >70%) across subgroups defined by:

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

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

Significantly more subjects (352/363 = 97.0%) who received VIEKIRA PAK-RBV had normalised alanine aminotransferase (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 HCV genotype 1b chronic infection without cirrhosis. Subjects were randomised in a 1:1 ratio to receive VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks of treatment.

Treated subjects (N=419) had a median age of 50 years (range: 19 to 70); 54.9% were born between 1945 and 1965, 45.8% were male; 4.8% were Black; 1.7% were Hispanic or Latino; 16.5% had a BMI 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 subjects 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-RBV (99.5%).

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

Treatment Outcome	**VIEKIRA PAK for 12 Weeks**					
	VIEKIRA PAK-RBV			**VIEKIRA PAK**		
	n/N	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Overall SVR12	**209/210**	**99.5**	**98.6, 100.0**	**209/209**	**100**	**98.2, 100.0**
Outcome for subjects 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		0/209	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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for subjects with HCV genotype 1b infection who were treatment-naïve without cirrhosis.

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >73%) across subgroups defined by:

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

In addition, subjects 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 HCV genotype 1a chronic infection without cirrhosis. Subjects were randomised in a 1:2 ratio to receive VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks of treatment.

Treated subjects (N=305) had a median age of 54 years (range: 19 to 70); 72.5% were born between 1945 and 1965, 65.2% were male; 11.8% were Black; 9.2% were Hispanic or Latino; 19.7% had a BMI 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 subjects who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL IV. VIEKIRA PAK was not non-inferior to VIEKIRA PAK-RBV.

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

Treatment Outcome	12 Weeks					
	VIEKIRA PAK-RBV			VIEKIRA PAK		
	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 subjects 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 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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for subjects with HCV genotype 1a infection who were treatment-naïve without cirrhosis.

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >65%) across subgroups defined by:

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

In addition, subjects 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 subjects with HCV genotype 1 chronic infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. VIEKIRA PAK-RBV was given for 12 weeks of treatment. Subjects who were randomised to the placebo arm received placebo for 12 weeks, after which they received VIEKIRA PAK-RBV for 12 weeks.

Treated subjects (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 and 1965; 57.6% were male; 8.1% were Black and 6.3% were Hispanic or Latino; 19.8% had a BMI 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; and 41.4% had HCV genotype 1b infection.

Table 8 shows the SVR12 rates for treatment-experienced subjects with genotype1-infection receiving VIEKIRA PAK-RBV for 12 weeks in SAPPHIRE-II.

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

	VIEKIRA PAK-RBV for 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 subjects 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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

No subjects with HCV genotype 1b infection experienced on-treatment virologic failure and 2 subjects with HCV genotype1b infection experienced relapse.

In the primary efficacy analysis, VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for subjects with HCV genotype 1 infection who were treatment-experienced without cirrhosis.

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

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >60%) across subgroups defined by:

- *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 BMI, history of depression or bipolar disorder, fibrosis stage

In addition, subjects 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 HCV genotype 1b chronic infection without cirrhosis who did not achieve SVR with prior treatment with pegIFN/RBV. Subjects were randomised, in a 1:1 ratio, to receive VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks of treatment.

Treated subjects (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 and 1965; 54.2% were male; 3.9% were Black; 1.7% were Hispanic or Latino; 21.8% had a BMI 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 subjects who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL II. In this study, VIEKIRA PAK without ribavirin had a similar SVR12 rate (100%) compared to VIEKIRA PAK-RBV (97.7%).

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

Treatment Outcome	12 Weeks					
	VIEKIRA PAK-RBV			VIEKIRA PAK		
	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 subjects 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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for subjects with HCV genotype 1b infection who were treatment-experienced without cirrhosis.

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >64%) across subgroups defined by:

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

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

Clinical Trial in Subjects with Cirrhosis

TURQUOISE-II (M13-099) – Genotype 1, Treatment-Naïve or Treatment-Experienced Subjects with Compensated Cirrhosis

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

Treated subjects (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 and 1965; 70.3% were male; 3.2% were Black; 11.8% were Hispanic or Latino; 28.4% had a BMI 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, and 31.3% had HCV genotype 1b infection.

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

Table 10: SVR12 for Genotype 1-Infected Subjects 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 subjects 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 subjects).
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 subjects with HCV RNA <25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for subjects assigned to 12 or 24 weeks of treatment, respectively.
d. Other includes subjects 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 (based upon telaprevir plus pegIFN/RBV) for subjects with HCV genotype 1 infection with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

These baseline factors were not associated with lower SVR12 rates (lower 95% confidence bound >43%) across subgroups defined by:

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

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

TURQUOISE-III: Clinical Trial of GT1b-Infected Subjects with Compensated Cirrhosis

TURQUOISE-III was a Phase 3b, open-label, single-arm, multicentre study evaluating the efficacy and safety of VIEKIRA PAK administered for 12 weeks in HCV GT1b-infected, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. Treated subjects (N = 60) had a median age of 60.5 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment experienced (included 12 null and partial responders and six other subjects with less well-characterised non-response); 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 subjects with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

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

Treatment Outcome	VIEKIRA PAK 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 subjects without SVR12	
On-treatment VF[a]	0
Relapse[b]	0
Other[c]	0

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 subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

See also ADVERSE REACTIONS section for discussion of safety information for TURQUOISE-III.

CORAL-I: Clinical Trial in Liver Transplant Recipients

The safety and efficacy of VIEKIRA PAK-RBV was studied in 34 HCV genotype 1-infected liver transplant recipients who were at least 12 months post-transplantation at enrolment. The primary objectives of this study were to assess the safety and the percentage of subjects achieving SVR12 following 24 weeks of treatment with VIEKIRA PAK-RBV. 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-RBV and at the end of treatment.

34 subjects (29 with HCV genotype 1a infection and five 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. 33 out of the 34 subjects (97.1%) achieved SVR12 (96.6% in subjects with genotype 1a infection and 100% in subjects with genotype 1b infection). One subject with HCV genotype 1a infection relapsed post-treatment.

See also ADVERSE REACTIONS section for discussion of safety information for CORAL-I.

TURQUOISE-I: Clinical Trial in Subjects with HCV Genotype 1 Infection and 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-RBV was evaluated in 63 subjects 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. Subjects 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 subjects (N = 63) had a median age of 51 years (range: 31 to 69); 24% of subjects were Black; 81% of subjects had IL28B non-CC genotype; 19% of subjects had compensated cirrhosis; 67% of subjects were HCV treatment-naïve; 33% of subjects had failed prior treatment with pegIFN/RBV; 89% of subjects had HCV genotype 1a infection. Table 12 shows the SVR12 rates for subjects with HCV genotype 1 infection and HIV-1 co-infection in TURQUOISE-I.

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

	VIEKIRA PAK-RBV 12 Weeks N = 31	**VIEKIRA PAK-RBV 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 subjects not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.
c. These virologic failures appear to have resulted from reinfection based on phylogenetic analyses of baseline and virologic failure samples.
d. Other includes subjects not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In TURQUOISE-I, the SVR12 rates in HCV/HIV-1 co-infected subjects were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected subjects. All seven subjects with genotype 1b infection and 51 of 56 subjects with genotype 1a infection achieved SVR12. Five of six subjects with compensated cirrhosis in each arm achieved SVR12.

See also ADVERSE REACTIONS section for discussion of safety information for TURQUOISE-I.

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 subjects 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 subjects 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% had not been previously treated for HCV.

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

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to VIEKIRA PAK, ribavirin, or to any of their excipients.

Contraindicated in patients with severe hepatic impairment (Child-Pugh C).

Drugs for which elevated plasma levels are associated with serious events and that are sensitive CYP3A substrates should not be co-administered with VIEKIRA PAK-RBV (see INTERACTIONS WITH OTHER MEDICINES).

Drugs that are strong CYP2C8 inhibitors may increase dasabuvir plasma concentrations and should not be co-administered with VIEKIRA PAK-RBV.

Drugs that are moderate or strong inducers of CYP3A may result in substantial lowering of plasma concentrations of paritaprevir, ombitasvir and dasabuvir and should not be co-administered with VIEKIRA PAK-RBV. Drugs that are strong inducers of CYP2C8 may result in substantial lowering of plasma concentrations of dasabuvir and should not be co-administered with VIEKIRA PAK-RBV.

The following drugs are contraindicated with VIEKIRA PAK-RBV (see INTERACTIONS WITH OTHER MEDICINES):

- alfuzosin hydrochloride
- astemizole, terfenadine
- blonanserin
- carbamazepine, phenytoin, phenobarbital
- cisapride
- colchicine in patients with renal or hepatic impairment
- dronedarone
- efavirenz
- ergotamine, dihydroergotamine, ergonovine, methylergonovine
- ethinyl oestradiol-containing medications such as combined oral contraceptives
- fusidic acid
- gemfibrozil
- lovastatin, simvastatin
- lurasidone
- oral midazolam, triazolam
- pimozide
- ranolazine
- rifampicin
- salmeterol
- St. John's Wort (*Hypericum perforatum*)
- sildenafil (when used for the treatment of pulmonary arterial hypertension)

The following contraindications to ribavirin also apply:

- Pregnant women (see PRECAUTIONS). Ribavirin must not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- Men whose female partners are pregnant (see PRECAUTIONS).
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.
- Severe hepatic dysfunction or decompensated liver disease.
- Haemoglobinopathies (e.g. thalassaemia, sickle-cell anaemia).

PRECAUTIONS

VIEKIRA PAK-RBV efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes VIEKIRA PAK-RBV 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 1-4 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.

For patients with cirrhosis:

• Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal haemorrhage).
• Perform hepatic laboratory testing including direct bilirubin levels 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 aminotransferase (ALT) to greater than five times the upper limit of normal (ULN) occurred in approximately 1% of all subjects (see ADVERSE REACTIONS). These ALT elevations were significantly more frequent in female subjects who were using ethinyloestradiol-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 2 weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.

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

Subjects using oestrogens other than ethinyloestradiol, such as oestradiol and conjugated oestrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any oestrogens (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 repeated and monitored closely:

- Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discoloured faeces.

- VIEKIRA PAK-RBV should be discontinued if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

Use with Tacrolimus

Co-administration of VIEKIRA PAK-RBV 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-RBV with systemic tacrolimus.

Avoid concomitant use of tacrolimus with VIEKIRA PAK-RBV unless the benefits outweigh the risks. If tacrolimus and VIEKIRA PAK-RBV are used concomitantly, tacrolimus should not be administered on the day VIEKIRA PAK-RBV is initiated. Beginning the day after VIEKIRA PAK-RBV 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 (see **INTERACTIONS WITH OTHER MEDICINES**).

Tacrolimus whole-blood concentrations should be monitored upon initiation and throughout co-administration with VIEKIRA PAK-RBV, 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 prescribing information for additional dosing and monitoring instructions.

Use with Fluticasone (Glucocorticoids Metabolised by CYP3A)

Use caution when administering VIEKIRA PAK-RBV 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-RBV 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-RBV with quetiapine is not recommended due to increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to a sixth of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for the recommendations on monitoring adverse reactions.

Hepatic Impairment

No dose adjustment of VIEKIRA PAK-RBV is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK-RBV is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. VIEKIRA PAK-RBV is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS and PHARMACOLOGY).

Co-administration with Other Direct-Acting Antivirals against HCV

Co-administration of VIEKIRA PAK or VIEKIRA PAK-RBV with other direct-acting antivirals has not been studied and therefore cannot be recommended.

Use in Patients with Other HCV Genotypes

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

Pregnancy and Concomitant Use with Ribavirin

Ribavirin may cause birth defects and/or death of the exposed foetus. (See CONTRAINDICATIONS). Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients as significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners as well as male patients and their female partners must use at least two effective forms of contraception during treatment and for at least 6 months after treatment has concluded. See additional information on specific hormonal contraceptives below and in PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES. Routine monthly pregnancy tests must be performed during this time

Haemolysis and Cardiovascular System

Although ribavirin has no direct cardiovascular effects, anaemia associated with ribavirin may result in deterioration of cardiac function, or exacerbation of the symptoms of coronary disease, or both. Thus, ribavirin must be administered with caution to patients with pre-existing cardiac disease. Cardiac status must be assessed before start of therapy and monitored clinically during therapy; if any deterioration occurs, therapy should be discontinued (see DOSAGE AND ADMINISTRATION). Patients with a history of congestive heart failure, myocardial infarction, and/or previous or current arrhythmic disorders must be closely monitored. It is recommended that those patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of therapy. There are no data in children or adolescents with a history of cardiac disease.

Gout

Uric acid may increase with ribavirin due to haemolysis and therefore patients predisposed to gout should be carefully monitored.

Acute Hypersensitivity

If an acute hypersensitivity reaction to ribavirin (e.g. urticaria, angioedema, bronchoconstriction, or anaphylaxis) develops, ribavirin must be discontinued immediately and appropriate medical therapy instituted. Transient rashes do not necessitate interruption of treatment.

Renal Impairment

The pharmacokinetics of ribavirin are altered in patients with renal dysfunction due to reduction of apparent clearance in these patients. Therefore, it is recommended that renal function be evaluated in all patients prior to initiation of ribavirin, preferably by estimating the patient's creatinine clearance. Substantial increases in ribavirin plasma concentrations are seen at the recommended dosing regimen in patients with serum creatinine >2 mg/dl or with creatinine clearance <50 mL/minute. The dose of ribavirin should be reduced in patients with creatinine clearance less than or equal to 50 mL/min. (see DOSAGE AND ADMINISTRATION). Haemoglobin concentrations should be monitored intensively during treatment in patients with renal dysfunction and corrective actions taken as necessary (see DOSAGE AND ADMINISTRATION).

Effects on Fertility

Ribavirin

No reproductive studies have been conducted with ribavirin combination therapy. In animal studies, ribavirin produced changes in sperm at doses below the clinical dose. Ribavirin has induced testicular toxicity in mice and rats. In a 3 to 6-month gavage study in mice, ribavirin significantly increased the percentage of morphologically abnormal sperm at 15 mg/kg/day (approximately 0.1 times the clinical exposure (AUC) at the maximum recommended dose) and above (see PRECAUTIONS), and reduced spermatid and sperm concentrations at 35 mg/kg/day and above. After cessation of dosing, mice almost completely recovered from testicular toxicity within one to two spermatogenesis cycles i.e. approximately 1.5 to 3 months. In rats, gavage doses of 160 mg/kg/day (approximately 0.4 times the clinical exposure (AUC) at the maximum recommended dose) for 9 weeks reduced spermatid counts and lowered epididymal weights, and testicular tubular atrophy occurred after administration of 160 mg/kg/day in the diet for 30 days. Testicular toxicity was not observed in other rat studies at gavage doses of up to 200 mg/kg/day for 90 days, or at 90 mg/kg/day in the diet for 12 months.

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 X.

Extreme care must be taken to avoid pregnancy in female patients and female partners of male patients taking VIEKIRA PAK-RBV.

VIEKIRA PAK-RBV must not be used during pregnancy. Women of childbearing potential and their male partners should not receive VIEKIRA PAK-RBV unless they are using effective contraception during the therapy period (see CONTRAINDICATIONS and PRECAUTIONS). In addition, effective contraception should be used for 6 months (24 weeks) post-therapy, based on a multiple dose ribavirin half-life of 12 days.

The use of two reliable forms of contraception is recommended.

There are no studies in pregnant women. Animal teratology studies have not been conducted with paritaprevir/ritonavir/ombitasvir and dasabuvir in combination with ribavirin; however, studies with ribavirin alone have shown that this is teratogenic in animals (see below). It should be assumed that the teratogenic effects of ribavirin will also be caused by the drug combination.

Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted. In rats and rabbits, a gavage dose of 1 mg/kg/day, and in hamsters a dose of 2.5 mg/kg/day, administered during the period of organogenesis, was associated with embryotoxic or teratogenic effects. Malformations of the skull, palate, eye, jaw, limbs, skeleton and gastrointestinal tract were noted.

Based on postmarketing surveillance, there are reports of congenital abnormalities, childhood disorders and miscarriages in female patients directly exposed to ribavirin during pregnancy and those female patients whose male partners were exposed to ribavirin therapy. The relationship of these outcomes to ribavirin exposure is unknown.

Use in Lactation

It is not known whether paritaprevir, ritonavir, ombitasvir, dasabuvir and their metabolites or ribavirin are excreted in human breastmilk. 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, breastfeeding must be discontinued prior to initiation of treatment.

Paediatric Use

The safety and effectiveness of VIEKIRA PAK-RBV in children younger 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, 187/2,292 (8.2%) of genotype 1-infected subjects were aged 65 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects. The safety and effectiveness of VIEKIRA PAK-RBV has not been established in patients aged 70 years or older.

Specific pharmacokinetic evaluations of ribavirin for elderly subjects have not been performed. The risk of toxic reactions to this drug may be greater in patients with impaired renal function. The dose of ribavirin should be reduced in patients with creatinine clearance less than or equal to 50 mL/min. (see DOSAGE AND ADMINISTRATION).

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*).

Ribavirin

Ribavirin was positive *in vitro* in the Balb/3T3 cell transformation assay. It was equivocal in the mouse lymphoma (L5178Y) assay and was positive *in vivo* in a mouse micronucleus assay. Ribavirin was negative in a range of other assays for gene mutations (*Salmonella typhimurium*, host-mediated assay) and chromosomal damage (dominant lethal assay in rats)

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

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

Ribavirin is mutagenic in some *in vivo* and *in vitro* genotoxicity assays. Conventional carcinogenicity rodent studies with low exposures compared to human exposure under therapeutic conditions did not reveal tumorigenicity of ribavirin. In addition, in a 26-week carcinogenicity study using the heterozygous p53 (+/-) mouse model, ribavirin did not produce tumours at the maximally tolerated dose of 300 mg/kg/day.

Effect on Laboratory Tests

Changes in selected laboratory parameters are described in Table 13. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in study design.

Table 13: Selected Treatment Emergent Laboratory Abnormalities

Laboratory Parameters	SAPPHIRE I and II (subjects without cirrhosis)		PEARL II, III and IV (subjects without cirrhosis)		TURQUOISE II (subjects 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

ALT = alanine aminotransferase. *ULN: Upper Limit of Normal according to testing laboratory.

Serum ALT Elevations

During clinical trials with VIEKIRA PAK-RBV, less than 1% of subjects who were not on systemic oestrogen-containing medications experienced transient serum ALT levels greater than five 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 subjects receiving VIEKIRA PAK-RBV, 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. Bilirubin elevations were not associated with aminotransferase elevations. The frequency of indirect bilirubin elevations was lower among subjects who did not receive ribavirin.

Risk of Hepatitis B Virus Reactivation

Cases of hepatitis B virus (HBV) reactivation, some resulting in liver failure or death, have been reported during treatment with HCV direct-acting antiviral agents in HBV/HCV co-infected patients. HBV reactivation is characterised by an abrupt increase in HBV replication, manifesting as an increase in serum HBV DNA level. In patients with resolved HBV infection (HBsAg negative and anti-HBc positive), reappearance of HBsAg can occur. HBV reactivation is often followed by abnormal liver function tests, i.e. increases in aminotransferase and/or bilirubin levels.

HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients, including those with past HBV infection, are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines.

Effects on Ability to Drive and Use Machinery

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-RBV.

INTERACTIONS WITH OTHER MEDICINES

Drug interaction studies were performed with VIEKIRA PAK-RBV and other drugs likely to be co-administered and drugs commonly used as probes for pharmacokinetic interactions. Drug interaction studies were performed with VIEKIRA PAK and antiretroviral drugs or immunosuppressants to facilitate dosing recommendations in special populations including HCV-HIV co-infected subjects or liver or kidney post-transplant subjects.

Effect of VIEKIRA PAK-RBV on Concomitant Medications

Table 14 lists:

- Drugs which do not require dose adjustment when co-administered with VIEKIRA PAK-RBV. Clinically relevant changes warranting dose adjustment were not observed in the exposures of these drugs when co-administered with VIEKIRA PAK-RBV.
- Drugs which require dose adjustment when co-administered with VIEKIRA PAK-RBV. Clinically relevant changes were observed in the exposures of these drugs and hence dose adjustment is recommended for these drugs.
- Drugs which are not recommended to be co-administered with VIEKIRA PAK-RBV.

Table 14: Effect of VIEKIRA PAK-RBV on Concomitant Medications

Drugs which do not require dose adjustment when co-administered with VIEKIRA PAK-RBV	Drugs for which dose adjustments and/or clinical monitoring are recommended when co-administered with VIEKIRA PAK-RBV	Drugs which are not recommended to be administered with VIEKIRA PAK-RBV
• abacavir • buprenorphine • digoxin (therapeutic drug monitoring recommended) • dolutegravir • duloxetine • emtricitabine • escitalopram • lamivudine • metformin • methadone • norethisterone (norethindrone) • paracetamol • raltegravir • sofosbuvir • sulfamethoxazole • tenofovir • trimethoprim • warfarin (INR monitoring recommended) • zolpidem	• alprazolam • amlodipine • atazanavir • carisoprodol • cyclobenzaprine • cyclosporine • darunavir • darunavir/ritonavir[b] • diazepam • digoxin • furosemide • hydrocodone • ketoconazole • omeprazole • pravastatin, rosuvastatin • sirolimus (see Table 13 for pharmacokinetic interactions)	• atazanavir/ritonavir[c] • lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily)[d] • rilpivirine (morning or evening administration)[e] • everolimus[f] • tacrolimus

a. Atazanavir should be co-administered with VIEKIRA PAK-RBV without additional ritonavir.
b. Ritonavir should NOT be administered with darunavir (once daily or twice daily) when dosed with VIEKIRA PAK-RBV. When darunavir is not administered with VIEKIRA PAK-RBV, 100 mg ritonavir should be administered with darunavir.
c. Atazanavir with ritonavir increased paritaprevir exposures up to 3.2-fold and hence atazanavir/ritonavir is not recommended to be administered with VIEKIRA PAK-RBV.
d. Lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily) is not recommended to be administered with VIEKIRA PAK-RBV because of an increase in paritaprevir exposures (Cmax and AUC increases up to 6.1-fold) and due to higher total doses of ritonavir (300 mg/day).
e. Co-administration of VIEKIRA PAK-RBV with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher exposures of rilpivirine.
f. Co-administration of VIEKIRA PAK-RBV with everolimus is not recommended because of a significant increase in everolimus exposures, which cannot be properly dose-adjusted with available dose strengths.

Table 15 summarises the effect of VIEKIRA PAK-RBV on the pharmacokinetics of co-administered drugs which showed clinically relevant changes.

For information regarding clinical recommendations, refer to Drug Interactions, Table 16.

Table 15: Drug Interactions – Pharmacokinetic Parameters for Co-administered Drug in the Presence of a Combination of paritaprevir/ritonavir/ombitasvir, and dasabuvir

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
				C_{max}	AUC	C_{trough}
alprazolam	0.5	1 day	12	1.09 (1.03, 1.15)	1.34 (1.15, 1.55)	NA
amlodipine	5	1 day	14	1.26 (1.11, 1.44)	2.57 (2.31, 2.86)	NA
carisoprodol	250	1 day	14	0.54 (0.47, 0.63)	0.62 (0.55, 0.70)	NA
carisoprodol's metabolite meprobamate				1.17 (1.10, 1.25)	1.09 (1.03, 1.16)	NA
cyclobenzaprine	5	1 day	14	0.68 (0.61, 0.75)	0.60 (0.53, 0.68)	NA
cyclobenzaprine's metabolite nor-cyclobenzaprine				1.03 (0.87, 1.23)	0.74 (0.64, 0.85)	NA
cyclosporine	30	1 day	10	1.01 (0.85, 1.20)	5.69 (4.67, 6.93)	15.8[a, b] (13.8, 18.1)
diazepam	2	1 day	13	1.18 (1.07, 1.30)	0.78 (0.73, 0.82)	NA
diazepam's metabolite				1.10 (1.03,	0.56	NA

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
nordiazepam				1.19)	(0.45, 0.70)	
everolimus	0.75	1 day	12	4.74 (4.29, 5.25)	27.12 (24.5, 30.1)	16.10 (14.5, 17.9)[a, c]
furosemide	20	1 day	12	1.42 (1.17, 1.72)	1.08 (1.00, 1.17)	NA
hydrocodone	5	1 day	15	1.27 (1.14, 1.40)	1.9 (1.72, 2.10)	NA
ketoconazole	400	1 day	12	1.15 (1.09, 1.21)	2.17 (2.05, 2.29)	NA
omeprazole	40	1 day	11	0.62 (0.48, 0.80)	0.62 (0.51, 0.75)	NA
pravastatin	10	14 days	12	1.37 (1.11, 1.69)	1.82 (1.60, 2.08)	NA
rilpivirine	25 (morning)	14 days	20	2.55 (2.08, 3.12)	3.25 (2.80, 3.77)	3.62 (3.12, 4.21)
	25 (evening)	14 days	20	2.16 (1.79, 2.61)	2.50 (2.05, 3.06)	2.87 (2.28, 3.62)
	25 (night: 4 hrs after dinner)	14 days	20	3.00 (2.50, 3.59)	3.43 (3.03, 3.89)	3.73 (3.16, 4.40)
rosuvastatin	5	14 days	11	7.13 (5.11, 9.96)	2.59 (2.09, 3.21)	0.59 (0.51, 0.69)

Co-administered Drug	Dose of Co-administered Drug (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
sirolimus	0.5	1 day	11	6.40 (5.34, 7.68)	37.99 31.5, 45.8)	19.55 (16.7, 22.9)[a, b]
tacrolimus	2	1 day	12	3.99 (3.21, 4.97)	57.13 (45.5, 71.7)	16.56 (12.97, 21.16)[a, b]

NA: Not available
a. Dose normalised cyclosporine and tacrolimus ratios
b. C_{24}: concentration at 24 hours following single dose of cyclosporine, digoxin or tacrolimus.
c. C_{12}: concentration at 12 hours following single dose of everolimus.

While ritonavir alone is shown to induce multiple CYPs *in vitro*, VIEKIRA PAK does not significantly affect CYP2C9 at clinically relevant concentrations. Co-administration of VIEKIRA PAK-RBV can decrease exposures of medicinal products that are metabolised by CYP2C19 which may require dose adjustment/clinical monitoring. Paritaprevir, ritonavir and dasabuvir are *in vitro* inhibitors of P-gp, however, no significant change was observed in the exposures of the sensitive P-gp substrate, digoxin, when administered with VIEKIRA PAK.

Paritaprevir inhibits UGT1A1, OATP1B1 and OATP1B3, and paritaprevir and ritonavir also inhibit OATP2B1. Paritaprevir and dasabuvir inhibit MRP2 *in vitro.* Paritaprevir, ritonavir and dasabuvir are inhibitors of BCRP. Paritaprevir, ombitasvir, and dasabuvir are inhibitors of UGT1A1, and ritonavir is an inhibitor of CYP3A4. Co-administration of VIEKIRA PAK-RBV with drugs that are primarily metabolised by CYP3A, or are substrates of UGT1A1 (e.g. raltegravir), BCRP (e.g. rosuvastatin), OATP1B1 or OATP1B3 (e.g. pravastatin) may result in increased plasma concentrations of such drugs.

VIEKIRA PAK-RBV does not inhibit organic anion transporter (OAT1) *in vivo* and is not expected to inhibit organic cation transporters (OCT1 and OCT2), organic anion transporters (OAT3), or multidrug and toxin extrusion proteins (MATE1 and MATE2K) at clinically relevant concentrations; therefore VIEKIRA PAK-RBV does not affect these active renal elimination pathways.

Potential for Other Drugs to Affect VIEKIRA PAK-RBV

Co-administration of VIEKIRA PAK-RBV with strong inhibitors of CYP3A may increase paritaprevir concentrations up to 2-fold. Co-administration of VIEKIRA PAK-RBV with drugs that induce CYP3A is expected to decrease dasabuvir, paritaprevir, ombitasvir and ritonavir plasma concentrations and reduce their therapeutic effect.

Co-administration of VIEKIRA PAK-RBV with drugs that induce CYP2C8 is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect. Additionally, drugs that are strong CYP2C8 inhibitors may increase dasabuvir concentrations and can prolong the effect of dasabuvir potentially increasing the risk of dasabuvir-related adverse effects.
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-RBV.

Overall, VIEKIRA PAK-RBV may be co-administered with drugs that are CYP3A inhibitors, while drugs that are strong CYP2C8 inhibitors or CYP3A/2C8 inducers are not recommended with VIEKIRA PAK-RBV. CYP3A4 inducers can potentially increase the risk of experiencing adverse effects (see CONTRAINDICATIONS).

Co-administration of carbamazepine with VIEKIRA PAK (without ribavirin) led to approximately 66 - 71%, 83 - 88%, 30 - 32% and 55 - 70% decrease in paritaprevir, ritonavir, ombitasvir and dasabuvir exposures (C_{max} and AUC), respectively. There was no clinically relevant change in carbamazepine exposures; however, exposures of carbamazepine's metabolite, carbamazepine-10, 11-epoxide, decreased by 16 - 43%. Concomitant use of VIEKIRA PAK-RBV with carbamazepine may lead to loss of virologic response and is therefore contraindicated (see CONTRAINDICATIONS).

The effect of gemfibrozil was evaluated with paritaprevir/ritonavir in combination with dasabuvir. In the presence of gemfibrozil, paritaprevir exposures (C_{max} and AUC) increased by 21 - 38% while dasabuvir C_{max} and AUC showed an increase of 2-fold and 11-fold respectively. Concomitant use of gemfibrozil is therefore contraindicated with VIEKIRA PAK-RBV (see CONTRAINDICATIONS).

Paritaprevir, dasabuvir and ritonavir are substrates of P-gp. Paritaprevir and dasabuvir are substrates of BCRP. Paritaprevir is a substrate of OATP1B1 and OATP1B3. Inhibition of P-gp, BCRP, OATP1B1 or OATP1B3 is not expected to show clinically relevant increases in exposures of VIEKIRA PAK-RBV.

Established and Other Potential Drug Interactions

The drug interaction profile of VIEKIRA PAK (without ribavirin) has been characterised for a number of commonly co-prescribed medications to provide guidance for health care providers (see Table 16).

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

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

Table 16 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant drugs. See CONTRAINDICATIONS for drugs that are contraindicated with VIEKIRA PAK-RBV. Dose adjustment is not required for VIEKIRA PAK-RBV when administered with the concomitant medications listed in Table 16.

Table 16: Established Drug Interactions Based on Drug Interaction Trials. Dose Adjustment is Not Required for VIEKIRA PAK-RBV

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comments
ANGIOTENSION RECEPTOR BLOCKERS e.g.		
valsartan* losartan* candesartan*	↑ angiotensin receptor blockers	Decrease the dose of the angiotensin receptor blockers and monitor patients.
ANTIARRHYTHMICS		
digoxin	↔ digoxin	While no dose adjustment is necessary for digoxin, appropriate monitoring of serum digoxin levels is recommended.
amiodarone*, bepridil*, lidocaine (systemic) quinidine*, disopyramide*, propafenone*	↑ antiarrhythmic agents	Decrease in dose and therapeutic concentration monitoring (if available) is recommended for the antiarrhythmic agents when co-administered with VIEKIRA PAK-RBV.
ANTICOAGULANTS		
warfarin	↔ warfarin	While no dose adjustment is necessary for warfarin, appropriate monitoring of international normalised ratio (INR) is recommended.
fluindione*	↓ fluindione	Appropriate monitoring of international normalized ratio (INR) is recommended.
ANTIFUNGALS		
ketoconazole	↑ ketoconazole	Doses of ketoconazole greater than 200 mg/day are not recommended.
voriconazole*	↓ voriconazole	Co-administration of VIEKIRA PAK-RBV with voriconazole is not recommended unless an assessment of the benefit-to-risk ratio justifies the use of voriconazole.
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-RBV is required. See also the colchicine prescribing information. Use of colchicine is contraindicated with VIEKIRA PAK-RBV in patients with renal or hepatic impairment.

CALCIUM CHANNEL BLOCKERS		
amlodipine nifedipine* diltiazem* verapamil*	↑ calcium channel blockers	Decrease the dose of the calcium channel blocker. The dose of amlodipine should be decreased by at least 50%. Clinical monitoring of patients is recommended.
DIURETICS		
furosemide	↑ furosemide (C_{max})	Clinical monitoring of patients is recommended. A decrease in dose up to 50% can be considered based on clinical response.
HIV-ANTIVIRAL AGENTS		
atazanavir	↑ paritaprevir	Atazanavir (without ritonavir) should be co-administered at the same time as VIEKIRA PAK-RBV without additional ritonavir. The ritonavir in VIEKIRA PAK-RBV will provide atazanavir boosting.
atazanavir/ritonavir	↑ paritaprevir	Atazanavir with ritonavir should not be co-administered with VIEKIRA PAK-RBV.
darunavir	↓ darunavir (C_{trough})	Dunavir (without ritonavir) should be co-administered at the same time as VIEKIRA PAK-RBV without additional ritonavir. The ritonavir in VIEKIRA PAK-RBV will provide darunavir boosting.
darunavir/ritonavir	↓ darunavir (C_{trough})	Darunavir dose should be taken without additional ritonavir when co-administered with VIEKIRA PAK-RBV. The ritonavir in VIEKIRA PAK-RBV will provide darunavir boosting.
lopinavir/ritonavir	↑ paritaprevir	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-RBV.
rilpivirine	↑ rilpivirine	The co-administration of VIEKIRA PAK-RBV with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher exposures of rilpivirine.
HMG CoA REDUCTASE INHIBITORS		
rosuvastatin	↑ rosuvastatin	Rosuvastatin dose should not exceed 10 mg per day.
pravastatin	↑ pravastatin	Reduce pravastatin dose by half. Pravastatin dose should not exceed 40 mg per day.
IMMUNOSUPPRESSANTS		
cyclosporine	↑ cyclosporine	During co-administration with VIEKIRA PAK-RBV, give one fifth of the total daily dose of cyclosporine once daily with paritaprevir/ritonavir/ombitasvir. Monitor cyclosporine levels and adjust dose and/or dosing frequency as needed. Upon completion of VIEKIRA PAK-RBV, the

		appropriate dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations.
everolimus	↑ everolimus	Co-administration of VIEKIRA PAK-RBV with everolimus is not recommended due to a significant increase in everolimus exposures.
sirolimus	↑ sirolimus	When co-administering with VIEKIRA PAK-RBV, administer 0.2 mg sirolimus twice a week (every 3 or 4 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-RBV treatment, the appropriate dose and dosing frequency of sirolimus should be guided by assessment of sirolimus blood concentrations.
tacrolimus	↑ tacrolimus	Co-administration of VIEKIRA PAK-RBV with systemic tacrolimus increases the concentrations of tacrolimus via CYP3A inhibition (see Table 15). It is recommended to avoid concomitant use of tacrolimus with VIEKIRA PAK-RBV unless the benefits outweigh the risks. If tacrolimus and VIEKIRA PAK-RBV are used concomitantly, tacrolimus should not be administered on the day VIEKIRA PAK-RBV is initiated. Beginning the day after VIEKIRA PAK-RBV 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-RBV, and the dose and/or dosing frequency should be adjusted as needed. Upon completion of VIEKIRA PAK-RBV treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus blood concentrations.
MUSCLE RELAXANTS		
carisoprodol	↓ carisoprodol ↔ meprobamate (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.

NARCOTIC ANALGESICS		
hydrocodone	↑ hydrocodone	A reduction of dose by 50% and/or clinical monitoring should be considered when co-administered with VIEKIRA PAK-RBV.
PROTON PUMP INHIBITORS		
omeprazole	↓ omeprazole	Use higher doses of omeprazole if clinically indicated.
SEDATIVES/HYPNOTICS		
alprazolam	↑ alprazolam	Clinical monitoring of patients is recommended. A decrease in alprazolam dose can be considered based on clinical response.
diazepam	↓ diazepam ↓ nordiazepam (metabolite of diazepam)	No dose adjustment required; increase dose if clinically indicated.
See Tables 12 and 13. The direction of the arrow indicates the direction of the change in AUC (↑ = *increase of more than 20%* for concomitant medication and 100% increase for DAAs*,* ↓ = *decrease of more than 20%* for concomitant medication and 50% decrease for DAAs*,* ↔ = *no change or change less than limits described above)*. * not studied		

Drugs with No Observed Interactions with VIEKIRA PAK-RBV

Drug interaction studies in subjects reveal no clinically significant interaction between VIEKIRA PAK and the following commonly co-prescribed medications. No dose adjustments are required when co-administering these drugs with VIEKIRA PAK-RBV:

- buprenorphine
- methadone, naloxone
- duloxetine, escitalopram
- metformin
- norethisterone (norethindrone)
- abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, tenofovir
- paracetamol
- sofosbuvir
- sulfamethoxazole, trimethoprim
- zolpidem

Ribavirin

Any potential for interactions may persist for up to 2 months (five half-lives for ribavirin) after cessation of ribavirin therapy due to its long half-life.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated no cytochrome P450 enzyme mediated metabolism of ribavirin. Ribavirin does not inhibit cytochrome P450 enzymes. There is no evidence from toxicity studies that ribavirin induces liver enzymes. Therefore, there is a minimal potential for P450 enzyme-based interactions.

Nucleoside Analogues

Ribavirin was shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine. The clinical significance of these findings is unknown. However, these *in vitro* findings raise the possibility that concurrent use of ribavirin with either zidovudine or stavudine might lead to increased HIV plasma viraemia. Therefore, it is recommended that plasma HIV RNA levels be closely monitored in patients treated with ribavirin concurrently with either of these two agents. If HIV RNA levels increase, the use of ribavirin concomitantly with reverse transcriptase inhibitors must be reviewed.

Didanosine (ddI) and Stavudine

Co-administration of ribavirin and didanosine is not recommended. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased *in vitro* when didanosine is co-administered with ribavirin. Reports of fatal hepatic failure as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactataemia/lactic acidosis have been reported with use of ribavirin. Co-administration of ribavirin and didanosine is also not recommended due to the risk of mitochondrial toxicity. Moreover, co-administration of ribavirin and stavudine should be avoided to limit the risk of overlapping mitochondrial toxicity.

Azathioprine

Ribavirin, by having an inhibitory effect on inosine monophosphate dehydrogenase, may interfere with azathioprine metabolism possibly leading to an accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity in patients treated with azathioprine. The use of ribavirin and peginterferon alfa-2a concomitantly with azathioprine should be avoided. In individual cases where the benefit of administering ribavirin concomitantly with azathioprine warrants the potential risk, it is recommended that close haematologic monitoring be done during concomitant azathioprine use to identify signs of myelotoxicity, at which time treatment with these drugs should be stopped.

HIV-HCV Co-Infected Patients

No apparent evidence of drug interaction was observed in 47 HIV-HCV co-infected patients who completed a 12-week pharmacokinetic substudy to examine the effect of ribavirin on the intracellular phosphorylation of some nucleoside reverse transcriptase inhibitors (NRTIs) (lamivudine and zidovudine or stavudine). However, due to high variability, the confidence intervals were quite wide. Plasma exposure of ribavirin did not appear to be affected by concomitant administration of (NRTIs).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see PRECAUTIONS). Consideration should be given to replacing zidovudine in a combination ART regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

ADVERSE EFFECTS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, rates of adverse reactions observed in clinical trials of VIEKIRA PAK-RBV 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 subjects who received VIEKIRA PAK with or without ribavirin.

VIEKIRA PAK-RBV in Subjects with HCV Genotype 1 Infection (Including Subjects with Cirrhosis)

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

The safety profile of VIEKIRA PAK-RBV in subjects with cirrhosis was similar to that of subjects without cirrhosis.

VIEKIRA PAK in Subjects with HCV Genotype 1 Infection

In subjects receiving VIEKIRA PAK (i.e. without ribavirin), pruritus was the only identified adverse reaction. The proportion of subjects who permanently discontinued treatment due to adverse events was 0.3% (2/588). 0.5% (3/588) subjects had treatment interruptions due to adverse events.

Table 17 lists adverse drug reactions from two randomised placebo-controlled trials (SAPPHIRE I and SAPPHIRE II) that occurred with at least 5% higher frequency among subjects receiving VIEKIRA PAK-RBV compared to subjects receiving placebo, regardless of relationship to VIEKIRA PAK-RBV. In addition, Table 17 includes rates of these adverse events from three trials in which subjects received VIEKIRA PAK with or without ribavirin (PEARL II, PEARL III, and PEARL IV), and rates of these adverse events from the trial in subjects with cirrhosis who received 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 17: Side-by-Side Tabulation of Adverse Event Rates in Phase 3 Trials Based on Adverse Reactions* (All Grades)

	SAPPHIRE I and II (subjects without cirrhosis)		PEARL II, III and IV (subjects without cirrhosis)		TURQUOISE II (subjects 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-RBV listed are those with a 5% higher frequency among subjects receiving VIEKIRA PAK-RBV compared to subjects receiving placebo in SAPPHIRE I and II.
** Adverse drug reactions for VIEKIRA PAK defined as the subset of ADRs for 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-RBV minus placebo) in SAPPHIRE I and II. Pruritus was the only adverse reaction for VIEKIRA PAK (without ribavirin) according to this definition.

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

In addition to the adverse reaction listed in Table 17, treatment-emergent adverse events that occurred with at least 2% frequency and less than 5% higher frequency among subjects receiving VIEKIRA PAK-RBV compared to subjects 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-RBV (in addition to their immunosuppressant

medications) was similar to those experienced by subjects treated with VIEKIRA PAK-RBV in phase 3 clinical trials; however some events were increased in frequency. Adverse events occurring in >20% of post-liver transplant subjects included fatigue 50.0%, headache 44.1%, cough 32.4%, diarrhoea 26.5%, insomnia 26.5%, asthenia 23.5%, nausea 23.5%, anaemia 20.6%, muscle spasms 20.6%, and rash 20.6%. Ten subjects (29.4%) had at least one post-baseline haemoglobin value of less than 10 g/dL. Ten of 34 subjects (29.4%) dose modified due to decrease in haemoglobin and 2.9% (1/34) had an interruption of ribavirin. Ribavirin dose modification did not impact SVR rates. Five subjects required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No subject received a blood transfusion.

HCV/HIV-1 Co-infected Subjects

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

VIEKIRA PAK in GT1b-infected Subjects with Compensated Cirrhosis

VIEKIRA PAK was assessed in 60 subjects with genotype 1b infection and compensated cirrhosis who were treated for 12 weeks (TURQUOISE-III) (see CLINICAL STUDIES). The most commonly reported adverse events (greater than or equal to 20% of subjects) were fatigue and diarrhoea. One subject (2%) experienced a grade 2 post-baseline haemoglobin decrease. Post-baseline Grade 2 increases in total bilirubin occurred in 12 (20%) subjects. No subjects experienced a grade 3 or higher post-baseline decrease in haemoglobin or total bilirubin increase. One subject (2%) experienced a Grade 3 ALT elevation.

One subject (2%) had a serious adverse event. One subject (2%) interrupted treatment due to an adverse event and no subject 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).

Hepatobiliary Disorders: Hepatic decompensation and hepatic failure (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

VIEKIRA PAK is fixed-dose combination tablets of paritaprevir/ritonavir/ombitasvir, copackaged with dasabuvir tablets. VIEKIRA PAK-RBV is fixed-dose combination tablets of paritaprevir/ritonavir/ombitasvir, copackaged with dasabuvir tablets and ribavirin tablets.

Paritaprevir/ritonavir/ombitasvir tablets 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 combination with ribavirin in certain patient populations (see Table 18).

The recommended dose of ribavirin depends on patient's bodyweight (<75 kg = 1000 mg and ≥75 kg = 1200 mg), and should be taken with food in two divided doses (morning and evening). Patients should be instructed to swallow the tablets whole (i.e. patients should not chew, break or dissolve the tablet).

To maximise absorption, VIEKIRA PAK-RBV should be taken with food, without regard to fat or calorie content (see PHARMACOLOGY*).*

Table 18 shows the recommended treatment regimen and duration based on patient population.

Table 18: Treatment Regimen and Duration by Patient Population

Patient Population	Treatment	Duration	Ribavirin Dosage
Genotype 1b, with or without cirrhosis	VIEKIRA PAK	12 weeks	No ribavirin required
Genotype 1a, or unknown or mixed genotype 1 infection, with or without cirrhosis	VIEKIRA PAK-RBV[a]	12 weeks[b]	Ribavirin to be taken in two divided doses (morning and evening) with food. Patients <75 kg = 1000 mg, taken as 2 x 200 mg tablets in the morning and 3 x 200 mg tablets in the evening. Patients ≥75 kg = 1200 mg, taken as 3 x 200 mg tablets in the morning and 3 x 200 mg tablets in the evening.

[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 decisions 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 are 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-RBV should be taken as directed for the prescribed duration, without interruption. If VIEKIRA PAK is used in combination with ribavirin, ribavirin should be administered for the same duration as VIEKIRA PAK.

Missed Dose

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

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

If more than 12 hours has passed since paritaprevir/ritonavir/ombitasvir 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.

If a dose of ribavirin is missed, 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-RBV to make up for a missed dose.

Dosage Modification of Ribavirin for Adverse Reactions

If suspected severe adverse reactions or laboratory abnormalities related to RBV develop during the combination therapy, modify the dosages of RBV until the adverse reactions abate.

Guidelines were developed in clinical trials for RBV dose modification (see RBV Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia, Table 19).

If intolerance persists after dose adjustment, discontinuation of ribavirin therapy may be needed.

Table 19: RBV Dosage Modification Guidelines for Management of Treatment-Emergent Anaemia

Laboratory Values	Reduce Only Ribavirin Dose to 600 mg/Day* if:	Discontinue Ribavirin if:**
Haemoglobin in Patients with No Cardiac Disease	<100 g/l	<85 g/l
Haemoglobin: Patients with History of Stable Cardiac Disease	>20 g/l decrease in haemoglobin during any 4-week period during treatment (permanent dose reduction)	<120 g/l despite 4 weeks at reduced dose

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

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

Use in Special Populations

Liver Transplant Recipients

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

HCV/HIV-1 Co-infection

For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in Table 18. Refer to DRUG INTERACTIONS for dosage recommendations for concomitant HIV-1 antiviral drugs.

Hepatic Impairment

No dosage adjustment of VIEKIRA PAK-RBV is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK-RBV is not recommended in patients with moderate hepatic impairment (Child-Pugh B). A decision to initiate treatment in patients with Child-Pugh B should be guided by assessment of the potential benefits and risks for the individual. VIEKIRA PAK-RBV is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS and PRECAUTIONS).

Hepatic function does not affect the pharmacokinetics of ribavirin (see Pharmacokinetics). Therefore, no dose adjustment of ribavirin is required in patients with hepatic impairment.

Renal Impairment

No dose adjustment of paritaprevir/ritonavir/ombitasvir or dasabuvir is recommended in subjects with mild, moderate or severe renal impairment. The efficacy and safety of VIEKIRA PAK-RBV have not been evaluated in HCV-infected subjects with moderate or severe renal impairment. VIEKIRA PAK-RBV has not been studied in patients on dialysis. For patients that require ribavirin, refer to the ribavirin prescribing information for information regarding use in patients with renal impairment (see PHARMACOLOGY).

The recommended dose regimens of ribavirin give rise to substantial increases in plasma concentrations of ribavirin in patients with renal impairment. There are insufficient data on the safety and efficacy of ribavirin in patients with serum creatinine >2 mg/dL or creatinine clearance <50 mL/min, whether or not on haemodialysis, to support recommendations for dose adjustments. Therefore, ribavirin should be used in such patients only when this is considered to be essential. Therapy should be initiated (or continued if renal impairment develops while on therapy) with extreme caution and intensive monitoring of haemoglobin concentrations, with corrective action as may be necessary, should be employed throughout the treatment period (see PRECAUTIONS and Pharmacokinetics).

Elderly Patients over the Age of 65 Years

There does not appear to be a significant age-related effect on the pharmacokinetics of ribavirin. However, as in younger patients, renal function must be determined prior to administration of ribavirin.

Patients under the Age of 18 Years

Treatment with ribavirin tablet is not recommended for use in children and adolescents (<18 years) due to insufficient data on safety and efficacy in combination with VIEKIRA PAK-RBV.

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 and appropriate symptomatic treatment instituted immediately.

No cases of overdose of ribavirin have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these instances ribavirin was administered intravenously. Due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed by haemodialysis.

For information on the management of overdose contact the National Poisons Centre on 0800 764 766.

PRESENTATION AND STORAGE CONDITIONS

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.

Ribavirin 200 mg tablets are light-blue, film-coated, oblong-shaped and debossed with “200” on one side and “3RP” on the other side.

Ribavirin 400 mg tablets are blue, film-coated, oblong-shaped and debossed with “400” on one side and “3RP” on the other side†.

Ribavirin 600 mg tablets are deep-blue, film-coated, oblong-shaped and debossed with “600” on one side and “3RP” on the other 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.

Store below 25°C in a dry place.

VIEKIRA PAK-RBV with 200 mg ribavirin contains a monthly carton of VIEKIRA PAK and a HDPE bottle of 168 tablets of ribavirin 200 mg.

VIEKIRA PAK-RBV with 400 mg ribavirin contains a monthly carton of VIEKIRA PAK and a HDPE bottle of 56 tablets of ribavirin 400 mg†.

VIEKIRA PAK-RBV with 1000 mg ribavirin contains a monthly carton of VIEKIRA PAK and four PVC/PCTFE(Aclar)/Al blister cartons of seven tablets of ribavirin 600 mg† and seven tablets of 400 mg ribavirin†. The ribavirin carton indicates which tablets need to be taken in the morning and evening.

VIEKIRA PAK-RBV with 1200 mg ribavirin contains a monthly carton of VIEKIRA PAK and four PVC/PCTFE(Aclar)/Al blister cartons of 14 tablets of ribavirin 600 mg† **or** a HDPE bottle of 56 tablets of ribavirin 600 mg†. The ribavirin carton and bottle indicates how many tablets need to be taken in the morning and evening.

† Note: presentations of VIEKIRA PAK-RBV with ribavirin 400 mg and/or 600 mg tablets are not currently available in New Zealand.

Store below 25°C in a dry place.

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