NEW ZEALAND DATA SHEET

1. VIEKIRA PAK COMBINATION THERAPY PACK

VIEKIRA PAK contains ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets copackaged with dasabuvir 250 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each co-formulated ombitasvir/paritaprevir/ritonavir film-coated tablet contains 12.5 mg of ombitasvir, 75 mg of paritaprevir and 50 mg of ritonavir.

For the full list of excipients, see section 6.1.

Each dasabuvir film-coated tablet contains 250 mg of dasabuvir (as sodium monohydrate).

Excipient with known effect: each film-coated tablet contains 44.94 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ombitasvir/paritaprevir/ritonavir 12.5/75/50 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VIEKIRA PAK 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 sections 4.2 Dose and method of administration, section 4.4 Special warnings and precautions for use, and section 5.1 Pharmacodynamic properties).

4.2 Dose and method of administration

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

Ombitasvir/paritaprevir/ritonavir tablets must be administered with dasabuvir tablets.

Recommended Dose in Adults

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

VIEKIRA PAK is used in combination with ribavirin in certain patient populations (see Table 1).

Refer to the Data Sheet for VIEKIRA PAK-RBV for the recommended dose of ribavirin. The 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 should be taken with food, without regard to fat or calorie content (see section 5.2 Pharmacokinetic properties*).*

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

Table 1: Treatment Regimen and Duration by Patient Population

Patient Population	Treatment	Duration	Ribavirin Dosage
HCV Genotype 1b, with or without cirrhosis	VIEKIRA PAK	12 weeks 8 weeks may be considered in previously untreated patients without advanced fibrosis or cirrhosis (see section 5.1 GARNET study)	No ribavirin required
HCV Genotype 1a, or unknown or mixed genotype 1, with or without cirrhosis	VIEKIRA PAK-RBV[a]	12 weeks[b]	Refer to the VIEKIRA PAK-RBV Data Sheet for ribavirin dose information. 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 HCV genotype 1a without cirrhosis (see section 5.1 Pharmacodynamic properties). 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 HCV genotype 1a-with cirrhosis who have had a previous null response to pegIFN and ribavirin (see section 5.1 Pharmacodynamic properties).

[#] The starting dose of ribavirin should be reduced in patients with renal impairment (creatinine clearance ≤50 mL/min). Haemoglobin should be monitored in these patients and RBV dose reduced if necessary. Refer to the VIEKIRA PAK-RBV Data Sheet for further information.

Note: VIEKIRA PAK–RBV is recommended in patients with an unknown HCV genotype 1 subtype or with mixed genotype 1. Refer to the VIEKIRA PAK-RBV Data Sheet for further information.

VIEKIRA PAK 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. Refer to the VIEKIRA PAK-RBV Data Sheet for further information.

Missed Dose

Inform patients that in case a dose of ombitasvir/paritaprevir/ritonavir 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 ombitasvir/paritaprevir/ritonavir is usually taken or more than 6 hours has passed since dasabuvir is usually taken, the missed dose should NOT be taken and the patient should take the next dose as per the usual dosing schedule.

If a dose of ribavirin is missed, refer to the VIEKIRA PAK-RBV Data Sheet for further information.

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

Use in Special Populations

Hepatic Impairment

No dose adjustment of VIEKIRA PAK is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) (see section 4.3 Contraindications, and section 4.4 Special warnings and precautions for use).

Liver Transplant Recipients

VIEKIRA PAK in combination with ribavirin is recommended for 24 weeks in liver transplant recipients. Refer to the VIEKIRA PAK-RBV Data Sheet for further information. A lower ribavirin dose at initiation may be appropriate. In the post-liver transplant study, ribavirin dosing was individualised and most patients received 600 to 800 mg per day (see section 5.1 Pharmacodynamic properties). For dosing recommendations with calcineurin inhibitors, refer to section 4.5 Interaction with other medicines and other forms of interaction.

HCV/HIV-1 Co-infection

For patients with HCV/HIV-1 co-infection, follow the standard dosage recommendations in Table 1. Refer to section 4.5 Interaction with other medicines and other forms of interaction for dosage recommendations for concomitant HIV-1 antiviral medicines.

Renal Impairment

No dose adjustment of VIEKIRA PAK is recommended in patients with mild, moderate or severe renal impairment. The efficacy and safety of VIEKIRA PAK has not been evaluated in patients with HCV with moderate or severe renal impairment. VIEKIRA PAK has not been studied in patients on dialysis. For patients that require ribavirin, refer to the VIEKIRA PAK-RBV Data Sheet for information regarding use in patients with renal impairment (see section 5.2 Pharmacokinetic properties).

Paediatric population

The pharmacokinetics, safety and efficacy of VIEKIRA PAK in children younger than 18 years of age have not been established.

4.3 Contraindications

Hypersensitivity to VIEKIRA PAK, or to any of its excipients.

Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C).

Medicines for which elevated plasma levels are associated with serious events and that are sensitive CYP3A substrates should not be co-administered with VIEKIRA PAK (see section 4.5 Interaction with other medicines and other forms of interaction).

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

Medicines 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. Medicines 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.

The following medicines are contraindicated with VIEKIRA PAK (see section 4.5 Interaction with other medicines and other forms of interaction):

- alfuzosin hydrochloride
- astemizole, terfenadine
- atorvastatin, lovastatin, simvastatin
- blonanserin
- carbamazepine, phenytoin, phenobarbital
- cisapride
- colchicine in patients with renal or hepatic impairment
- disopyramide

- dronedarone
- efavirenz
- ergotamine, dihydroergotamine, ergonovine, methylergonovine
- ethinyloestradiol-containing medications such as combined oral contraceptives
- fusidic acid
- gemfibrozil
- lurasidone
- oral midazolam, triazolam
- pimozide
- ranolazine
- rifampicin
- salmeterol
- St. John's wort (*Hypericum perforatum*)
- sildenafil (when used for the treatment of pulmonary arterial hypertension)

If VIEKIRA PAK is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen. Refer to the VIEKIRA PAK-RBV Data Sheet for additional contraindications, which include pregnancy, patients with a history of severe, unstable, or uncontrolled cardiac disease, and patients with haemoglobinopathies (e.g. thalassaemia or sickle-cell anaemia).

4.4 Special warnings and precautions for use

Patients previously treated with direct-acting antiviral agents

The efficacy of VIEKIRA PAK has not been studied in patients who have previously failed therapy with a treatment regimen that includes VIEKIRA PAK or other direct-acting antiviral agents, with or without ribavirin.

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 ombitasvir/paritaprevir/ritonavir 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 medicine exposure.

For patients with cirrhosis:

- Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, or 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 patients. These ALT elevations were significantly more frequent in female patients who were using ethinyloestradiol-containing medications such as combined oral contraceptives, contraceptive patches, or contraceptive vaginal rings (see section 4.3 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 (see section 4.3 Contraindications). Alternative contraceptive agents or methods of contraception (e.g. progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyloestradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.

Patients 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 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, Sirolimus and Everolimus

Co-administration of VIEKIRA PAK with systemic tacrolimus, sirolimus or everolimus increases the concentrations of the immunosuppressant via CYP3A inhibition (see section 5.1 Pharmacodynamic properties). Serious and/or life threatening events have been observed with co-administration of VIEKIRA PAK with systemic tacrolimus and a similar risk can be expected with sirolimus and everolimus.

Avoid concomitant use of tacrolimus or sirolimus with VIEKIRA PAK unless the benefits outweigh the risks. If tacrolimus or sirolimus and VIEKIRA PAK are used concomitantly, caution is advised. Refer to section 4.5 Interaction with other medicines and other forms of interaction for recommended doses and monitoring strategies. Everolimus cannot be used due to lack of suitable dose strengths for dose adjustments.

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

Use with Fluticasone (Glucocorticoids Metabolised by CYP3A)

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

Use with Quetiapine

The use of VIEKIRA PAK with quetiapine is not recommended due to increases in quetiapine exposure. If co-administration is necessary, reduce the quetiapine dose to 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 is required in patients with mild hepatic impairment (Child-Pugh A). VIEKIRA PAK is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) (see section 4.3 Contraindications, and section 5.2 Pharmacokinetic properties).

Co-administration with Other Direct-Acting Antivirals against HCV

Co-administration of VIEKIRA PAK 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 has not been established in patients with HCV genotypes other than genotype 1.

Use in the Elderly (≥65 years of age)

No dose adjustment of VIEKIRA PAK is warranted in elderly patients. In Phase 3 clinical trials, 187/2,292 (8.2%) of patients with HCV genotype 1 were aged 65 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. The safety and effectiveness of VIEKIRA PAK has not been established in patients aged 70 years or older.

Effect on Laboratory Tests

Changes in selected laboratory parameters are described in Table 2. A side-by-side tabulation is provided to simplify presentation; direct comparisons should not be made across trials that differ in study design.

Table 2: Selected Treatment-Emergent Laboratory Abnormalities

Laboratory Parameters	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)
	VIEKIRA PAK-RBV 12 Weeks N = 770 n (%)	Placebo 12 Weeks N = 255 n (%)	VIEKIRA PAK-RBV 12 Weeks N = 401 n (%)	VIEKIRA PAK 12 Weeks N = 509 n (%)	VIEKIRA PAK-RBV 12 or 24 Weeks N = 380 n (%)
ALT					
>5-20 × ULN* (Grade 3)	6/765 (0.8%)	10/254 (3.9%)	3/401 (0.7%)	1/509 (0.2%)	4/380 (1.1%)
>20 × ULN (Grade 4)	3/765 (0.4%)	0	0	0	2/380 (0.5%)
Haemoglobin					
<10-8 g/dL (Grade 2)	41/765 (5.4%)	0	23/401 (5.7%)	0	30/380 (7.9%)
<8-6.5 g/dL (Grade 3)	1/765 (0.1%)	0	2/401 (0.5%)	0	3/380 (0.8%)
<6.5 g/dL (Grade 4)	0	0	0	0	1/380 (0.3%)
Total Bilirubin					
>3-10 × ULN (Grade 3)	19/765 (2.5%)	0	23/401 (5.7%)	2/509 (0.4%)	37/380 (9.7%)
>10 × ULN (Grade 4)	1/765 (0.1%)	0	0	0	0

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

Serum ALT Elevations

During clinical trials with VIEKIRA PAK, less than 1% of patients 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 section 4.4 Special warnings and precautions for use).

Serum Bilirubin Elevations

Transient elevations in bilirubin (predominantly indirect) were observed in patients receiving VIEKIRA PAK, related to the inhibition of the bilirubin transporters OATP1B1/1B3 by

paritaprevir and ribavirin-induced haemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with aminotransferase elevations. The frequency of indirect bilirubin elevations was lower among patients 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.

4.5 Interaction with other medicines and other forms of interaction

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

Effect of VIEKIRA PAK on Concomitant Medications

Table 3 lists:

- Medicines which do not require dose adjustment when co-administered with VIEKIRA PAK. Clinically relevant changes warranting dose adjustment were not observed in the exposures of these medicines when co-administered with VIEKIRA PAK.
- Medicines which require dose adjustment when co-administered with VIEKIRA PAK. Clinically relevant changes were observed in the exposures of these medicines and hence dose adjustment is recommended for these medicines.
- Medicines which are not recommended to be co-administered with VIEKIRA PAK. Please also consult the list of contraindicated medications.

Table 3: Effect of VIEKIRA PAK on Concomitant Medications

Medicines which do not require dose adjustment when co-administered with VIEKIRA PAK	**Medicines for which dose adjustments and/or clinical monitoring are recommended when co-administered with VIEKIRA PAK**	**Medicines which are not recommended to be administered with VIEKIRA PAK**
• abacavir • buprenorphine • dolutegravir • duloxetine • emtricitabine • escitalopram • lamivudine • metformin • methadone • norethisterone (norethindrone) • paracetamol • raltegravir • sofosbuvir • sulfamethoxazole • tenofovir • trimethoprim • zolpidem	• alprazolam • amiodarone • amlodipine • atazanavir[a] • bepridil • candesartan • carisoprodol • colchicine • cyclobenzaprine • cyclosporine • darunavir • darunavir/ritonavir[b] • diazepam • digoxin • diltiazem • fluindione (INR monitoring recommended) • furosemide • hydrocodone • ketoconazole • lidocaine (systemic) • losartan • nifedipine • omeprazole • pravastatin • propafenone • quinidine • rosuvastatin • valsartan • verapamil • vitamin K antagonists (INR monitoring recommended) • voriconazole • warfarin (INR monitoring recommended) (see Table 4 for pharmacokinetic interactions)	• atazanavir/ritonavir[c] • everolimus • fluticasone (see section 4.4 Special warnings and precautions for use) • lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily)[d] • quetiapine (see section 4.4 Special warnings and precautions for use) • rilpivirine (morning or evening administration – see Table 4)[e] • sirolimus • tacrolimus

a. Atazanavir should be co-administered with VIEKIRA PAK without additional ritonavir.
b. Ritonavir should NOT be administered with darunavir (once daily or twice daily) when dosed with VIEKIRA PAK. When darunavir is not administered with VIEKIRA PAK, 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.
d. Lopinavir/ritonavir (800/200 mg once daily or 400/100 mg twice daily) is not recommended to be administered with VIEKIRA PAK 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 with rilpivirine once daily is not recommended due to potential for QT interval prolongation with higher exposures of rilpivirine.

Table 4 summarises the effect of VIEKIRA PAK on the pharmacokinetics of co-administered medicines which showed clinically relevant changes.

For information regarding clinical recommendations, refer to Medicine Interactions, Table 5.

Table 4: Medicine Interactions – Pharmacokinetic Parameters for Co-administered Medicine in the Presence of a Combination of ombitasvir/paritaprevir/ritonavir, and dasabuvir

Co-administered Medicine	Dose of Co-administered Medicine (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Medicine 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

Co-administered Medicine	Dose of Co-administered Medicine (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
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 nordiazepam				1.10 (1.03, 1.19)	0.56 (0.45, 0.70)	NA
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

Co-administered Medicine	Dose of Co-administered Medicine (mg)	Duration of Co-administration	n	Ratio (with or without VIEKIRA PAK) of Co-administered Medicine Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
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)
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 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 with medicines 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 medicines.

VIEKIRA PAK 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 does not affect these active renal elimination pathways.

If VIEKIRA PAK is co-administered with a vitamin K antagonist, close monitoring of INR is recommended. This is due to liver function changes during treatment with VIEKIRA PAK.

Potential for Other Medicines to Affect VIEKIRA PAK

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

Co-administration of VIEKIRA PAK with medicines that induce CYP2C8 is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect. Additionally, medicines 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.

Overall, VIEKIRA PAK may be co-administered with medicines that are CYP3A inhibitors, while medicines that are strong CYP2C8 inhibitors or CYP3A/2C8 inducers are not recommended with VIEKIRA PAK. CYP3A4 inducers can potentially increase the risk of experiencing adverse effects (see section 4.3 Contraindications).

Co-administration of carbamazepine with VIEKIRA PAK 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 with carbamazepine may lead to loss of virologic response and is therefore contraindicated (see section 4.3 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 (see section 4.3 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.

Established and Other Potential Drug Interactions

The drug interaction profile of VIEKIRA PAK has been characterised for a number of commonly co-prescribed medications to provide guidance for healthcare providers (see Table 5).

If a patient is already taking medication(s) or initiating a medication while receiving VIEKIRA PAK 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, doses should be re-adjusted after administration of VIEKIRA PAK is completed.

Table 5 provides the effect of co-administration of VIEKIRA PAK on concentrations of concomitant medicines. See section 4.3 Contraindications for medicines that are contraindicated with VIEKIRA PAK. Dose adjustment is not required for VIEKIRA PAK when administered with the concomitant medications listed in Table 5.

Table 5: Established Drug Interactions Based on Drug Interaction Trials. Dose Adjustment is Not Required for VIEKIRA PAK

Concomitant Medicine Class: Medicine Name	Effect on Concentration	Clinical Comments
ANGIOTENSIN 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*, propafenone*	↑ antiarrhythmic agents	Decrease in dose and therapeutic concentration monitoring (if available) is recommended for the antiarrhythmic agents when co-administered with VIEKIRA PAK.
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 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 is required. See also the colchicine prescribing information. Use of colchicine is contraindicated with VIEKIRA PAK 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 without additional ritonavir. The ritonavir in VIEKIRA PAK will provide atazanavir boosting.
atazanavir/ritonavir	↑ paritaprevir	Atazanavir with ritonavir should not be co-administered with VIEKIRA PAK.
darunavir	↓ darunavir (C_{trough})	Darunavir (without ritonavir) should be co-administered at the same time as VIEKIRA PAK without additional ritonavir. The ritonavir in VIEKIRA PAK will provide darunavir boosting.
darunavir/ritonavir	↓ darunavir (C_{trough})	Darunavir dose should be taken without additional ritonavir when co-administered with VIEKIRA PAK. The ritonavir in VIEKIRA PAK 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.
rilpivirine	↑ rilpivirine	The co-administration of VIEKIRA PAK 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, give one fifth of the total daily dose of cyclosporine once daily with ombitasvir/paritaprevir/ritonavir. Monitor cyclosporine levels and adjust dose and/or dosing frequency as needed. Upon completion of VIEKIRA PAK, the appropriate dose of cyclosporine should be guided by assessment of cyclosporine blood concentrations.
everolimus	↑ everolimus	Co-administration of VIEKIRA PAK with everolimus is not recommended due to a significant increase in everolimus exposures, which cannot be properly dose adjusted with available dose strengths.
sirolimus	↑ sirolimus	Avoid concomitant use of sirolimus with VIEKIRA PAK unless the benefits outweigh the risks. If sirolimus and VIEKIRA PAK are used concomitantly, administer sirolimus 0.2 mg twice a week (every 3 or 4 days on the same two days each week). Upon initiation of VIEKIRA PAK, sirolimus whole blood concentrations should be monitored every 4 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus. Sirolimus dose and/or dosing frequency should be adjusted as needed throughout co-administration with VIEKIRA PAK (see section 4.4 Special warnings and precautions for use). Five days after completion of VIEKIRA PAK treatment, the sirolimus dose and dosing frequency prior to receiving VIEKIRA PAK should be resumed, along with routine monitoring of sirolimus whole blood concentrations.
tacrolimus	↑ tacrolimus	Avoid concomitant use of tacrolimus with VIEKIRA PAK unless the benefits outweigh the risks. If tacrolimus and VIEKIRA PAK are used concomitantly, tacrolimus should not be administered on the day VIEKIRA PAK is initiated. Beginning the day after VIEKIRA PAK is initiated, reinitiate tacrolimus at a reduced dose based on tacrolimus whole blood

		concentrations. The recommended tacrolimus dosing is 0.5 mg every 7 days (see section 4.4 Special warnings and precautions for use). Tacrolimus whole-blood concentrations should be monitored upon initiation and throughout co-administration with VIEKIRA PAK, and the dose and/or dosing frequency should be adjusted as needed. Upon completion of VIEKIRA PAK treatment, the appropriate dose and dosing frequency of tacrolimus should be guided by assessment of tacrolimus whole 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.
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 3 and 4. 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		

Medicines with No Observed Interactions with VIEKIRA PAK

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 medicines with VIEKIRA PAK:

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

4.6 Fertility, pregnancy and lactation

Fertility

Paritaprevir/ritonavir

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

Ombitasvir

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

Dasabuvir

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

Pregnancy

Pregnancy Category B3

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

Note that VIEKIRA PAK-RBV is contraindicated during pregnancy (Category X).

Animal Data

No effects on embryofoetal development have been noted in studies in animals with paritaprevir/ritonavir (in combination), ombitasvir and its major inactive human metabolites (M29, M36) or dasabuvir. For paritaprevir/ritonavir, the highest doses tested produced exposures equal to 98-fold (mouse) or 8-fold (rat) (for paritaprevir and 8-fold (mouse) or 3-fold (rat) for ritonavir) the exposures in humans at the recommended clinical doses. For ombitasvir, the highest dose tested produced exposures equal to 28-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26 times higher in mice than in humans at the recommended clinical dose.

Developmental toxicity has been observed in embryofoetal development studies with ritonavir alone. In rats, early resorptions, decreased foetal body weight and ossification delays and developmental variations occurred at a maternally toxic dosage of 75 mg/kg/day. A slight increase in the incidence of cryptorchidism was also noted in rats given 35 mg/kg/day. Developmental toxicity observed in rabbits (resorptions, decreased litter size and decreased foetal weights) also occurred at a maternally toxic dosage of 110 mg/kg/day. For dasabuvir, the highest dose tested produced exposures equal to 24-fold (rat) or 6-fold (rabbit) the exposures in humans at the recommended clinical dose.

Breastfeeding

It is not known whether paritaprevir, ritonavir, ombitasvir, dasabuvir and their metabolites 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Trials Experience

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

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

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

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

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

VIEKIRA PAK in Patients with HCV Genotype 1

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

Table 6 lists adverse drug reactions from two randomised placebo-controlled trials (SAPPHIRE I and SAPPHIRE II) that occurred with at least 5% higher frequency among patients receiving VIEKIRA PAK-RBV compared to patients receiving placebo, regardless of relationship to VIEKIRA PAK. In addition, Table 6 includes rates of these adverse events from three trials in which patients received VIEKIRA PAK with or without ribavirin (PEARL II, PEARL III, and PEARL IV), and rates of these adverse events from the trial in patients with cirrhosis who received VIEKIRA PAK-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 6: Side-by-Side Tabulation of Adverse Event Rates in Phase 3 Trials Based on Adverse Reactions* (All Grades)

	SAPPHIRE I and II (patients without cirrhosis)		PEARL II, III and IV (patients without cirrhosis)		TURQUOISE II (patients with cirrhosis)
Adverse Reaction	**VIEKIRA PAK-RBV 12 Weeks N = 770 n (%)**	**Placebo 12 Weeks N = 255 n (%)**	**VIEKIRA PAK-RBV 12 Weeks N = 401 n (%)**	**VIEKIRA PAK** 12 Weeks N = 509 n (%)**	**VIEKIRA PAK-RBV 12 or 24 Weeks N = 380 n (%)**
Fatigue	263 (34.2)	67 (26.3)	120 (29.9)	135 (26.5)	148 (38.9)
Nausea	172 (22.3)	38 (14.9)	63 (15.7)	43 (8.4)	72 (18.9)
Pruritus	121 (15.7)	11 (4.3)	48 (12.0)	31 (6.1)	71 (18.7)
Insomnia	108 (14.0)	19 (7.5)	49 (12.2)	26 (5.1)	63 (16.6)
Asthenia	104 (13.5)	17 (6.7)	36 (9.0)	20 (3.9)	51 (13.4)
Anaemia	41 (5.3)	0	30 (7.5)	1 (0.2)	34 (8.9)

*Adverse drug reactions for VIEKIRA PAK listed are those with a 5% higher frequency among patients receiving VIEKIRA PAK-RBV compared to patients 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 6, treatment-emergent adverse events that occurred with at least 2% frequency and less than 5% higher frequency among patients receiving VIEKIRA PAK-RBV compared to patients receiving placebo (SAPPHIRE I and II), are listed below by system organ class.

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

Liver Transplant Recipients

The type of adverse events experienced by HCV genotype 1 liver transplant recipients who were treated with VIEKIRA PAK-RBV (in addition to their immunosuppressant medications) was similar to those experienced by patients 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 patients 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 patients (29.4%) had at least one post-baseline haemoglobin value of less than 10 g/dL. Ten of 34 patients (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 patients required erythropoietin, all of whom initiated ribavirin at the starting dose of 1000 to 1200 mg daily. No patient received a blood transfusion.

HCV/HIV-1 Co-infected Patients

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

VIEKIRA PAK in HCV GT1b Patients with Compensated Cirrhosis

VIEKIRA PAK was assessed in 60 patients with HCV genotype 1b and compensated cirrhosis who were treated for 12 weeks (TURQUOISE-III) (see section 5.1 Pharmacodynamic properties). The most commonly reported adverse events (greater than or equal to 20% of patients) were fatigue and diarrhoea. One patient (2%) experienced a grade 2 post-baseline haemoglobin decrease. Post-baseline Grade 2 increases in total bilirubin occurred in 12 (20%) patients. No patients experienced a grade 3 or higher post-baseline decrease in haemoglobin or total bilirubin increase. One patient (2%) experienced a Grade 3 ALT elevation.

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

VIEKIRA PAK without Ribavirin for 8 Weeks in Patients with Treatment-Naïve HCV GT1b without Cirrhosis

The overall safety profile in patients with treatment-naïve non-cirrhotic HCV genotype 1b, treated for 8 weeks, was similar to that observed in those treated for 12 weeks.

Post-Marketing Adverse Reactions

The following adverse reactions have been identified during post-approval use of ombitasvir/paritaprevir/ritonavir 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: Anaphylactic reactions and other hypersensitivity reactions (including tongue and lip swelling) have been observed.

Hepatobiliary Disorders: Hepatic decompensation and hepatic failure (see section 4.4 Special precautions and warnings for use).

Skin and Subcutaneous Tissue Disorders: Erythema multiforme has been observed.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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.

For advice on the management of overdose contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

VIEKIRA PAK combines 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.

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.

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

In greater than 500 baseline samples of genotype 1a viruses 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 baseline samples of genotype 1b viruses 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 patients with HCV genotype 1a and 1b, 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 patients with chronic HCV genotype 1 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 patients (3%) experienced virologic failure (primarily post-treatment relapse). Treatment-emergent variants and their prevalence in these virologic failure populations are shown in Table 7. In the 67 patients with HCV genotype 1a-, NS3 variants were observed in 50 patients, NS5A variants were observed in 46 patients, NS5B variants were observed in 37 patients, and treatment-emergent variants were seen in all three drug targets in 30 patients. In the seven patients with HCV genotype 1b, treatment-emergent variants were observed in NS3 in four patients, in NS5A in two patients, and in both NS3 and NS5A in one patient. No patients with genotype 1b had treatment-emergent variants in all three drug targets.

Table 7: 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 patients of the same subtype.
b. N = 66 for the NS5B target.
c. Substitutions were observed in combination with other emergent substitutions at NS3 position R155 or D168.
d. Observed in combination in patients with HCV genotype 1b.
e. Observed in combination in 6% (4/67) of the patients.

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

Persistence of Resistance-Associated Substitutions

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

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

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

Cross-Resistance

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

Clinical efficacy and safety

The efficacy and safety of VIEKIRA PAK was evaluated in eight randomised Phase 3 clinical trials, including two trials exclusively in patients with cirrhosis (Child-Pugh A), in over 2,600 patients with chronic HCV genotype 1, as summarised in Table 8.

Table 8: Phase 3 Randomised, Global Multicentre Trials with VIEKIRA PAK and VIEKIRA PAK-RBV

Trial[1]	Number of patients (treated[2])	HCV Genotype (GT)	Summary of Study Design[3]
Treatment-naïve[4], without cirrhosis			
SAPPHIRE I	631	GT1	Arm A: VIEKIRA PAK-RBV Arm B: Placebo
PEARL III	419	GT1b	Arm A: VIEKIRA PAK-RBV Arm B: VIEKIRA PAK
PEARL IV	305	GT1a	Arm A: VIEKIRA PAK-RBV Arm B: VIEKIRA PAK
GARNET (open-label)	166	GT1b	VIEKIRA PAK (8 weeks)
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 patients who were randomised and received at least one dose of VIEKIRA PAK.
3 Treatment duration was 12 weeks for all arms, except for TURQUOISE II which included a 24 week arm, and GARNET, which had an 8-week duration.
4 Treatment-naïve was defined as not having received any prior therapy for HCV.
5 Treatment-experienced patients were defined as either: prior relapsers (patients with HCV RNA undetectable at or after the end of at least 36 weeks of 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 eight trials, the ombitasvir/paritaprevir/ritonavir dose was 150/100/25 mg once daily and the dasabuvir dose was 250 mg twice daily. For patients who received ribavirin, the ribavirin dose was 1000 mg per day for patients weighing less than 75 kg or 1200 mg per day for patients weighing greater than or equal to 75 kg.

Sustained virologic response (SVR; virologic cure) was defined as unquantifiable or undetectable HCV RNA 12 weeks after the end of treatment (SVR12) in the Phase 3 trials. Treatment duration was fixed in each trial and was not guided by patients' HCV RNA levels (no-response guided algorithm). Plasma HCV RNA values were measured during the clinical trials using the COBAS TaqMan HCV test (version 2.0), for use with the High Pure System (except GARNET, which used COBAS Ampliprep/COBAS TaqMan HCV Test 2.0). The High Pure system assay had a lower limit of quantification (LLOQ) of 25 IU per mL and the Ampliprep assay had a LLOQ of 15 IU per mL.

Pooled Analyses of Clinical Trials

Durability of Response

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

Pooled Efficacy Analyses

In phase 3 clinical trials, 1088 patients (including 194 with cirrhosis) received the recommended regimen for their HCV subtype, cirrhosis status and previous treatment. Table 9 shows SVR rates for these patients.

Among patients who received the recommended regimen, 97% achieved SVR (95% with cirrhosis and 97% without cirrhosis). Virologic breakthrough was seen in 0.6% of patients, and 1.5% experienced post-treatment relapse.

Table 9: 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 patients received 12 weeks of therapy except for those with cirrhosis and HCV GT1a who had previously had a null response to pegIFN/RBV who received 24 weeks of therapy.
[+] Other types of pegIFN/RBV failure include less well documented non-response, relapse/breakthrough or other pegIFN failure.

Impact of Ribavirin Dose Adjustment on Probability of SVR

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

Clinical Trials in Treatment-Naïve Adults

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

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

Treated patients (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; and 32.3% had HCV genotype 1b.

Table 10 shows the SVR12 rates for HCV genotype 1, treatment-naïve patients receiving VIEKIRA PAK-RBV for 12 weeks in SAPPHIRE-I.

Table 10: SVR12 for HCV Genotype 1 Treatment-Naïve Patients in SAPPHIRE-I

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

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA <25 IU/mL during treatment, confirmed 1 log10 IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

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

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

Baseline factors that were not associated with lower SVR12 rates (lower 95% confidence interval of >70%) were:

- *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, patients for whom ribavirin dose was reduced did not have lower SVR12 rates.

Significantly more patients (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 chronic HCV genotype 1b without cirrhosis. Patients were randomised in a 1:1 ratio to receive VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks of treatment.

Treated patients (N=419) had a median age of 50 years (range: 19 to 70); 54.9% were born between 1945 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 11 shows the SVR12 rates for HCV genotype 1b, treatment-naïve patients who received VIEKIRA PAK with or without 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 11: SVR12 for HCV Genotype 1b Treatment-Naïve Patients 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 patients without SVR12	1/210	0.5		2/209	1.0	
On-treatment VF[a]	1/210	0.5		0/209	0	
Relapse[b]	0/210	0		0/209	0	
Other[c]	0/210	0		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 patients with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for patients with HCV genotype 1b 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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

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

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

Treated patients (N=305) had a median age of 54 years (range: 19 to 70); 72.5% were born between 1945 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 12 shows the SVR12 rates for genotype HCV 1a, treatment-naïve patients who received VIEKIRA PAK or VIEKIRA PAK-RBV for 12 weeks in PEARL IV. VIEKIRA PAK was not non-inferior to VIEKIRA PAK-RBV.

Table 12: SVR12 for HCV Genotype 1a Treatment-Naïve Patients 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 patients without SVR12						
On-treatment VF[a]	1/100	1.0		6/205	2.9	
Relapse[b]	1/98	1.0		10/194	5.2	
Other[c]	1/100	1.0		1/205	0.5	

CI = confidence interval, VF = virologic failure

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA <25 IU/mL during treatment, confirmed 1 log10 IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA <25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for patients with HCV genotype 1a 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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

GARNET – Genotype 1b, Treatment-Naïve

GARNET was an open-label, single-arm, multicentre study evaluating the efficacy and safety of VIEKIRA PAK for 8 weeks in treatment-naïve adults with HCV genotype 1b without cirrhosis.

Treated patients (N=166) had a median age of 53 years (range: 22 to 82); 56.6% were female; 3.0 % were Asian; 0.6% were Black; 14.5% had a body mass index of at least 30 kg per m^2; 68.5% had IL28B non-CC genotype; 7.2% had baseline HCV RNA levels of at least 6,000,000 IU per mL; 9% had advanced fibrosis (F3) and 98.2% had HCV genotype 1b infection (one patients each had genotype 1a, 1d, and 6 infection).

Table 13 shows the SVR12 rates for treatment-naïve patients with HCV genotype 1b without cirrhosis, who received ombitasvir/paritaprevir/ritonavir and dasabuvir for 8 weeks in GARNET.

Table 13: Treatment outcome for treatment-naïve patients with HCV Genotype 1b without Cirrhosis

Treatment Outcome	VIEKIRA PAK for 8 Weeks % (n/N)
SVR12 F0-F3	98.2% (160/163)[a]
SVR12 F0-F2	99.3% (147/148)[b]
Outcome for subjects without SVR12	
On-treatment VF[c]	0% (0/163)
Relapse[d]	1.2% (2/161)
Other[e]	0.6% (1/163)

VF = virologic failure

a. Excludes three subjects without genotype 1b infection.
b. Excludes F3 patients for whom the SVR rate was 86.6% (13/15) due to two relapses.
c. On-treatment VF was defined as confirmed HCV ≥ 15 IU/mL after HCV RNA <15 IU/mL during treatment, confirmed 1 log10 IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 15 IU/mL with at least 6 weeks of treatment.
d. Relapse was defined as confirmed HCV RNA ≥ 15 IU/mL post-treatment before or during SVR12 window among subjects with HCV RNA <15 IU/mL at last observation during at least 51 days of treatment.
e. Other includes subjects who did not achieve SVR12 but did not experience on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

Clinical Trials in Treatment-Experienced Adults

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

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

Treated patients (N = 394) had a median age of 54 years (range 19 to 71); 49.0% were prior pegIFN/RBV null responders; 21.8% were prior pegIFN/RBV partial responders, and 29.2% were prior pegIFN/RBV relapsers; 73.9% were born between 1945 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; and 41.4% had HCV genotype 1b.

Table 14 shows the SVR12 rates for treatment-experienced patients with HCV genotype 1 receiving VIEKIRA PAK-RBV for 12 weeks in SAPPHIRE-II.

Table 14: SVR12 for HCV Genotype 1 Treatment-Experienced Patients 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 patients without SVR12			
On-treatment VF[a]	0/297	0	
Relapse[b]	7/293	2.4	
Other[c]	4/297	1.3	

CI = confidence interval, VF = virologic failure

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

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

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

Significantly more patients (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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

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

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

Treated patients (N=179) had a median age of 57 years (range: 26 to 70); 35.2% were prior pegIFN/RBV null responders; 28.5% were prior pegIFN/RBV partial responders, and 36.3% were prior pegIFN/RBV relapsers; 70.9% were born between 1945 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 15 shows the SVR12 rates for HCV genotype 1b, treatment-experienced patients 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 15: SVR12 for HCV Genotype 1b Treatment-Experienced Patients 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 patients without SVR12						
On-treatment VF[a]	0/88	0		0/91	0	
Relapse[b]	0/88	0		0/91	0	
Other[c]	2/88	2.3		0/91	0	

CI = confidence interval, VF = virologic failure

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

In the primary efficacy analysis, VIEKIRA PAK and VIEKIRA PAK-RBV demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for patients with HCV genotype 1b 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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

Clinical Trial in Patients with Cirrhosis

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

TURQUOISE-II was a randomised, global multicentre, open-label trial conducted exclusively in 380 patients with HCV genotype 1 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 patients (N=380) had a median age of 58 years (range: 21 to 71); 42.1% were treatment-naïve, 36.1% were prior pegIFN/RBV null responders; 8.2% were prior pegIFN/RBV partial responders, 13.7% were prior pegIFN/RBV relapsers; 85.5% were born between 1945 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, and 31.3% had HCV genotype 1b.

Table 16 shows the SVR12 rates for patients with HCV genotype 1 with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 16: SVR12 for Patients with HCV Genotype 1with Cirrhosis who were Treatment-Naïve or Previously Treated with pegIFN/RBV

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

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

a. 97.5% confidence intervals are used for the primary efficacy endpoints (overall SVR12 rate); 95% confidence intervals are used for additional efficacy endpoints (SVR12 rates in patients with HCV genotype 1a and 1b patients).
b. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA <25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
c. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA <25 IU/mL at last observation during at least 11 or 22 weeks of treatment, for patients assigned to 12 or 24 weeks of treatment, respectively.
d. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

In the primary efficacy analysis, VIEKIRA PAK-RBV administered for 12 or 24 weeks demonstrated superiority to the historical control (based upon telaprevir plus pegIFN/RBV) for patients with HCV genotype 1 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, patients who underwent ribavirin dose modifications did not have lower SVR12 rates.

TURQUOISE-III: Clinical Trial of Patients with HCV GT1b 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 patients with HCV GT1b, treatment-naïve and previous pegIFN/RBV treatment-experienced adults with compensated cirrhosis. Treated patients (N = 60) had a median age of 60.5 years (range: 26 to 78); including 45% treatment-naïve and 55% pegIFN/RBV treatment experienced (included 12 null and partial responders and six other patients 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 17 shows the SVR12 rates for patients with HCV genotype 1b with cirrhosis who were treatment-naïve or previously treated with pegIFN/RBV.

Table 17: SVR12 for Patients with HCV Genotype 1b 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 patients 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 patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.
c. Other includes patients not achieving SVR12 but not experiencing on-treatment VF or relapse (e.g. missing HCV RNA values in the SVR12 window).

See also section 4.8 Undesirable effects 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 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 patients 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 patients (29 with HCV genotype 1a and five with HCV genotype 1b) were enrolled who had not received treatment for HCV after transplantation and had a METAVIR fibrosis score of F2 or less. 33 out of the 34 patients (97.1%) achieved SVR12 (96.6% in patients with HCV genotype 1a and 100% in patients with HCV genotype 1b). One patient with HCV genotype 1a relapsed post-treatment.

See also section 4.8 Undesirable effects section for discussion of safety information for CORAL-I.

TURQUOISE-I: Clinical Trial in Patients with HCV Genotype 1 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 patients with chronic HCV genotype 1 co-infected with HIV-1. See section 4.2 Dose and method of administration for dosing recommendations in HCV/HIV-1 co-infected patients. Patients were on a stable HIV-1 antiretroviral therapy (ART) regimen that included ritonavir-boosted atazanavir or raltegravir, co-administered with a backbone of tenofovir plus emtricitabine or lamivudine.

Treated patients (N = 63) had a median age of 51 years (range: 31 to 69); 24% of patients were Black; 81% of patients had IL28B non-CC genotype; 19% of patients had compensated cirrhosis; 67% of patients were HCV treatment-naïve; 33% of patients had failed prior treatment with pegIFN/RBV; 89% of patients had HCV genotype 1a. Table 18 shows the SVR12 rates for patients with HCV genotype 1 and HIV-1 co-infection in TURQUOISE-I.

Table 18: SVR12 for HIV-1 Co-infected Patients 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 patients not achieving SVR12		
On-treatment virologic failure[a]	0	1
Post-treatment relapse[b]	1	2[c]
Other[d]	1	0

a. On-treatment VF was defined as confirmed HCV ≥ 25 IU/mL after HCV RNA < 25 IU/mL during treatment, confirmed 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir, or HCV RNA persistently ≥ 25 IU/mL with at least 6 weeks of treatment.
b. Relapse was defined as confirmed HCV RNA ≥ 25 IU/mL post-treatment before or during SVR12 window among patients with HCV RNA < 25 IU/mL at last observation during at least 11 weeks of treatment.
c. These virologic failures appear to have resulted from reinfection based on phylogenetic analyses of baseline and virologic failure samples.
d. Other includes patients not achieving SVR12 but not experiencing on-treatment 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 patients were consistent with SVR12 rates in the phase 3 trials of HCV mono-infected patients. All seven patients with HCV genotype 1b and 51 of 56 patients with HCV genotype 1a achieved SVR12. Five of six patients with compensated cirrhosis in each arm achieved SVR12.

See also section 4.8 Undesirable effects 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 patients with HCV genotype 1 who were on stable doses of methadone (N=19) or buprenorphine +/- naloxone (N=19) received 12 weeks of VIEKIRA PAK-RBV. Treated patients had a median age of 51 years (range: 26 to 64); 65.8% were male and 5.3% were Black. A majority (86.8%) had baseline HCV RNA levels of at least 800,000 IU/mL and a majority (84.2%) had HCV genotype 1a; 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 patients achieved SVR12. No patients experienced on-treatment virologic failure or relapse.

Paediatric population

The pharmacokinetics, safety and efficacy of VIEKIRA PAK in children younger than 18 years of age have not been established.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of the combination of paritaprevir, ombitasvir, ritonavir, and dasabuvir have been evaluated in healthy adult subjects and in patients with chronic hepatitis C. Table 19 shows geometric mean C_{max} and AUC_{0-24} of ombitasvir/paritaprevir/ritonavir 25/150/100 mg once daily with dasabuvir 250 mg twice daily following multiple doses with food in healthy volunteers.

Table 19: Geometric Mean C_{max} and AUC_{0-24} of Multiple Doses of ombitasvir/paritaprevir/ritonavir 25/150/100 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

Ombitasvir/paritaprevir/ritonavir and dasabuvir

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

The absolute 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

Ombitasvir/paritaprevir/ritonavir and dasabuvir

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

Distribution

Ombitasvir/paritaprevir/ritonavir and dasabuvir

Ombitasvir, paritaprevir, ritonavir and dasabuvir are highly bound to plasma proteins. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The blood-to-plasma concentration ratios in humans 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.

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.

Elimination

Paritaprevir

Following dosing of ombitasvir/paritaprevir/ritonavir 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 ombitasvir/paritaprevir/ritonavir 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 ombitasvir/paritaprevir/ritonavir, 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 ombitasvir/paritaprevir/ritonavir, 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.

Special Populations

Renal impairment

Ombitasvir/paritaprevir/ritonavir and dasabuvir

No dose adjustment of VIEKIRA PAK is recommended in patients with mild, moderate or severe renal impairment (see section 4.2 Dose and method of administration). The efficacy and safety of VIEKIRA PAK have not been evaluated in patients with HCV with moderate or severe renal impairment. Pharmacokinetics of the combination of paritaprevir 150 mg, ombitasvir 25 mg, and ritonavir 100 mg, with or without dasabuvir 400 mg were evaluated in patients with mild (CrCl: 60 to 89 mL/min), moderate (CrCl: 30 to 59 mL/min) and severe (CrCl: 15 to 29 mL/min) renal impairment.

In patients with mild renal impairment, 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 those subjects with normal renal function.

In patients 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 those subjects with normal renal function.

In patients 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 those subjects with normal renal function.

Hepatic impairment

Ombitasvir/paritaprevir/ritonavir and dasabuvir

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

Ombitasvir/paritaprevir/ritonavir with dasabuvir is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C) (see section 4.4 Special warnings and precautions for use, and section 4.3 Contraindications).

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

In patients 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 those subjects with normal hepatic function.

In patients 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 those subjects with normal hepatic function.

In patients 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 those subjects with normal hepatic function.

Elderly (≥65 years of age)

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

Paediatric population (<18 years of age)

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

Race or ethnicity

No dose adjustment is necessary for ombitasvir/paritaprevir/ritonavir or dasabuvir based on race or ethnicity.

Sex or bodyweight

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

5.3 Preclinical safety data

Genotoxicity

Paritaprevir

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

Ombitasvir

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

Dasabuvir

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

Ritonavir

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

Carcinogenicity

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

Two-year carcinogenicity studies have been conducted in rodents with ritonavir alone at dietary levels of 50, 100 and 200 mg/kg/day in mice, and 7, 15 and 30 mg/kg/day in rats. In male mice there was a dose-dependent increase in the incidence of hepatocellular adenomas, and adenomas and carcinomas combined, both reaching statistical significance

only at the high-dose. In female mice there were small, statistically significant increases in these tumour incidences only at the high-dose. In rats, there were no tumorigenic effects.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets

Tablet core
Copovidone
Vitamin E polyethylene glycol succinate
Propylene glycol monolaurate
Sorbitan monolaurate
Colloidal anhydrous silica (E551)
Sodium stearyl fumarate

Film-coating
Polyvinyl alcohol (E1203)
Polyethylene glycol 3350
Talc (E553b)
Titanium dioxide (E171)
Iron oxide red (E172)

Dasabuvir 250 mg tablets

Tablet core

Microcrystalline cellulose (E460(i))
Lactose monohydrate
Copovidone
Croscarmellose sodium
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)
Polyethylene glycol 3350
Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

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 12.5 mg/75 mg/50 mg ombitasvir/paritaprevir/ritonavir 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.

6.6 Special precautions for disposal and other handling

Any used medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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

Telephone number: (0800) 900 030

9. DATE OF FIRST APPROVAL

20 August 2015

10. DATE OF REVISION OF THE TEXT

16 August 2018

Version 14

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Section 4.2 Dose and administration; section 4.3 Contraindications; and section 4.4 Special warnings and precautions for use	Patients with moderate hepatic impairment i.e. Child-Pugh B are contraindicated with VIEKIRA PAK use.
Section 5.2 Pharmacokinetic properties	Patients with moderate hepatic impairment i.e. Child-Pugh B are contraindicated with VIEKIRA PAK use. Removal of statement with regards to safety and efficacy not established in patients with moderate hepatic impairment and no dose adjustment required.