NEW ZEALAND DATA SHEET – Trikafta®
(elexacaftor/tezacaftor/ivacaftor, ivacaftor)
film-coated tablets

1 Trikafta film-coated tablets

Trikafta (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 150 mg) film-coated tablets

Trikafta (elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and ivacaftor 75 mg) film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 150 mg
Morning dose
Each film-coated tablet contains 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor as a fixed dose combination tablet.

Evening dose
Each film-coated tablet contains 150 mg of ivacaftor.

Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and ivacaftor 75 mg
Morning dose
Each film-coated tablet contains 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor as a fixed dose combination tablet.

Evening dose
Each film-coated tablet contains 75 mg of ivacaftor.

Excipients with known effect:
lactose monohydrate

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Composite pack
Trikafta 100 mg/50 mg/75 mg and 150 mg film-coated tablets

Morning dose: *elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg*
Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (7.9 mm x 15.5 mm).

Evening dose: *Ivacaftor 150 mg film-coated tablet*
Light blue, capsule-shaped tablet printed with “V 150” in black ink on one side and plain on the other (16.5 mm x 8.4 mm).

Trikafta 50 mg/25 mg/37.5 mg and 75 mg film-coated tablets

Morning dose: *elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg*
Light orange, capsule-shaped tablet debossed with "T50" on one side and plain on the other (6.4 mm x 12.2 mm).

Evening dose: *Ivacaftor 75 mg film-coated tablet*
Light blue, capsule-shaped tablet printed with "V 75" in black ink on one side and plain on the other (12.7 mm x 6.8 mm).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene.

4.2 DOSE AND METHOD OF ADMINISTRATION

Trikafta should only be prescribed by physicians with experience in the treatment of CF. If the patient's genotype is unknown, confirm the presence of at least one *F508del* mutation using a genotyping assay.

Dosage
Adults and paediatric patients aged 6 years and older should be dosed according to Table 1

Table 1: Dosing Recommendation for Patients aged 6 Years and Older		
Age	**Morning Dose (2 tablets)**	**Evening Dose (1 tablet)**
6 to <12 years weighing <30 kg	elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	ivacaftor 75 mg
6 to <12 years weighing ≥30 kg	elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 150 mg
≥12 years	elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 150 mg

The morning and evening dose should be taken with fat-containing food, approximately 12 hours apart.

Missed dose
If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.
If more than 6 hours have passed since:

- the missed morning dose, the patient should take the missed dose as soon as possible and should not take the evening dose. The next scheduled morning dose should be taken at the usual time.
- the missed evening dose, the patient should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

Method of administration
For oral use. Patients should be instructed to swallow the tablets whole.

A fat-containing meal or snack should be consumed just before or just after dosing of Trikafta. Meals and snacks recommended in CF guidelines or meals recommended in standard nutritional guidelines contain adequate amounts of fat. A serving size of foods appropriate for age from a typical CF diet should be given. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, chocolate, whole milk, whole-milk dairy products, meats, avocado, hummus, oily fish, and soy-based products (tofu) (see section 5.2 PHARMACOKINETIC PROPERTIES).

Food or drink containing grapefruit should be avoided during treatment with Trikafta (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Dosage adjustment

Hepatic impairment

Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, Trikafta should be used with caution at a reduced dose (see Table 2).

Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with Trikafta.

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 4.8 UNDESIRABLE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

Table 2: Recommendation for Use in Patients with Hepatic Impairment

	Morning	**Evening**
Mild (Child-Pugh Class A)	No dose adjustment (Two elexacaftor/tezacaftor/ivacaftor tablets)	No dose adjustment (One ivacaftor tablet)
Moderate (Child-Pugh Class B)*	Use not recommended*	Use not recommended*
Severe (Child-Pugh Class C)	Should not be used	Should not be used

* Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, Trikafta should be used with caution at a reduced dose, as follows: two elexacaftor/tezacaftor/ivacaftor tablets alternating with one elexacaftor/tezacaftor/ivacaftor tablet taken in the morning, on alternate days. The evening dose of the ivacaftor tablet should not be taken.

Renal impairment

No dose adjustment is recommended for patients with mild and moderate renal impairment. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see section 5.2 PHARMACOKINETIC PROPERTIES).

Concomitant use of CYP3A inhibitors

When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin, verapamil) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole,

voriconazole, telithromycin, and clarithromycin), the dose should be reduced as in Table 3 (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 3: Dosing Schedule for Concomitant Use of Trikafta with Moderate and Strong CYP3A Inhibitors

Moderate CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose				
Two elexacaftor/tezacaftor/ivacaftor tablets	✓	-	✓	-
One ivacaftor tablet	-	✓	-	✓
Evening Dose^				
One ivacaftor tablet	No dose			
* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days. ^ The evening dose of ivacaftor should not be taken.				

Strong CYP3A Inhibitors			
	Day 1	**Day 2 and Day 3**	**Day 4#**
Morning Dose			
Two elexacaftor/ tezacaftor/ ivacaftor tablets	✓	-	✓
Evening Dose^			
One ivacaftor tablet	No dose		
# Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart. ^ The evening dose of ivacaftor tablet should not be taken.			

4.3 CONTRAINDICATIONS

In cases of hypersensitivity to the active substance or to any component of this medication, patients should not be treated with this medicine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment
Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with Trikafta. Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. For patients with moderate hepatic impairment, Trikafta should only be used if there is a clear medical need and the benefits are expected to outweigh the risks. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A) (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 5.2 PHARMACOKINETIC PROPERTIES).

Elevated transaminases and hepatic injury
Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving Trikafta. Trikafta should be used with caution in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) and only if the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.8 UNDESIRABLE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

Elevated transaminases are common in patients with CF and have been observed in some patients treated with Trikafta. In some instances, these elevations have been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, consider the benefits and risks of resuming treatment [see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.8 UNDESIRABLE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES].

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Trikafta efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

CYP3A inhibitors

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. Therefore the dose of Trikafta should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Table 3 in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation) a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating treatment with Trikafta. Cataracts were seen in juvenile rats treated with ivacaftor from postnatal Day 7 through 35 at oral dose levels of 10 mg/kg/day and higher (yielding systemic exposure in animals approximately 5 times lower than that in patients at the maximum recommended human dose [MRHD] based on summed AUCs of the ivacaftor component of Trikafta and its major metabolites). This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Patients after organ transplantation

Trikafta has not been studied in patients with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended (see Sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS for interactions with ciclosporin, everolimus, sirolimus or tacrolimus).

Use in the elderly

Clinical trials of Trikafta did not include any patients aged 65 years and older.

Paediatric use

The safety and efficacy of Trikafta in children aged less than 6 years have not been established (see sections 4.8 UNDESIRABLE EFFECTS and 5.1 PHARMACODYNAMIC PROPERTIES).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products affecting the pharmacokinetics of Trikafta

CYP3A inducers

Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced Trikafta efficacy. Co-administration of ivacaftor with rifampicin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration of Trikafta with strong CYP3A inducers is not recommended (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Examples of strong CYP3A inducers include:

- rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased elexacaftor AUC by 2.8- fold and tezacaftor AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of Trikafta should be reduced when co-administered with strong CYP3A inhibitors (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and Table 3in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9 to 2.3-fold. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dose of Trikafta should be reduced when co-administered with moderate CYP3A inhibitors (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Table 3 in section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin
- verapamil

Co-administration of Trikafta with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor. Food or drink containing grapefruit should be avoided during treatment with Trikafta (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 4 (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Table 4: Impact of Other Drugs on Elexacaftor, Tezacaftor and Ivacaftor

Dose and Schedule		Effect on ELX, TEZ and/or IVA PK	Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0	
			AUC	C_{max}
Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd	tezacaftor 25 mg qd + ivacaftor 50 mg qd	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
		↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Itraconazole 200 mg qd	elexacaftor 20 mg + tezacaftor 50 mg single dose	↑ Elexacaftor	2.83 (2.59, 3.10)	1.05 (0.977, 1.13)
		↑ Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
Ketoconazole 400 mg qd	ivacaftor 150 mg single dose	↑ Ivacaftor	8.45 (7.14, 10.0)	2.65 (2.21, 3.18)
Ciprofloxacin 750 mg q12h	tezacaftor 50 mg q12h + ivacaftor 150 mg q12h	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
		↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Rifampicin 600 mg qd	ivacaftor 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd	ivacaftor 150 mg q12h	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect is not clinically significant.

Medicinal products affected by Trikafta

CYP2C9 substrates
Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of Trikafta with warfarin is recommended. Other medicinal products for which exposure may be increased by Trikafta include glimepiride and glipizide; these medicinal products should be used with caution.

Potential for interaction with transporters
Co-administration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of Trikafta may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as ciclosporin, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Elexacaftor and M23-ELX (active metabolite) inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Tezacaftor/ivacaftor increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration of Trikafta may increase exposures of medicinal products that are substrates of

these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. In Study 445-102, mild increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX.

Hormonal contraceptives
Trikafta has been studied with ethinyl oestradiol/levonorgestrel and was found to have no clinically relevant effect on the exposures of the oral contraceptive. Trikafta is not expected to have an impact on the efficacy of oral contraceptives.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 5.

Table 5: Impact of Elexacaftor, Tezacaftor and Ivacaftor on Other Drugs

Dose and Schedule		**Effect on Other Drug PK**	**Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0**	
			AUC	**C_{max}**
Midazolam 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol* ↑ Levonorgestrel*	1.33 (1.20, 1.49) 1.23 (1.10, 1.37)	1.26 (1.14, 1.39) 1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939; 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics
* Effect not clinically significant (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
Category B3
Category B3 drugs have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Elexacaftor, tezacaftor, ivacaftor and/or their metabolites were shown to cross the placenta in laboratory animal species (rats and/or rabbits).

Elexacaftor

Elexacaftor was not teratogenic in rats at oral doses up to 40 mg/kg/day or up to 125 mg/kg/day in rabbits (yielding systemic exposure in animals approximately 9 and 4 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the elexacaftor component of Trikafta and M23-ELX [for rat], or AUC of the elexacaftor component of Trikafta [for rabbit]). Effects on embryofetal development were limited to lower mean fetal body weight (at ≥ 25 mg/kg/kg/day). Pup birth and postnatal body weights were reduced in rats with maternal treatment at 10 mg/kg/day during gestation and lactation.

Tezacaftor

No evidence of harm to the fetus was observed with tezacaftor in developmental toxicity study in rats at oral doses up to 100 mg/kg/day (yielding systemic exposure in animals approximately 3 times greater than that in patients at the MRHD based on summed AUCs of the tezacaftor component of Trikafta and its pharmacologically active M1 metabolite, M1-TEZ). In the rabbit, lower fetal body weights were noted at an oral dose of 50 mg/kg/day (the highest dose tested; yielding exposure around the same as at the MRHD), which occurred in conjunction with significant maternal toxicity. However, no effects on embryo fetal survival and no malformations were observed with tezacaftor in the species. Fetal body weight was unaffected in rabbits at 25 mg/kg/day (yielding exposure 4 times lower than that at the MRHD based on summed AUCs of tezacaftor and its M1 metabolite).

Ivacaftor

Developmental toxicity studies with ivacaftor revealed no teratogenicity in rats at oral doses up to 200 mg/kg/day or rabbits at oral doses up to 100 mg/kg/day (yielding systemic exposure in the respective animal species approximately 5 and ≥3 times greater, than that in patients at the MRHD based on summed AUCs of the ivacaftor component of Trikafta and its major metabolites. Fetal weight was decreased and the incidence of minor fetal skeletal abnormalities was increased in rats treated at 200 mg/kg/day; these effects were observed in conjunction with maternal toxicity.

No adequate and well-controlled studies of Trikafta in pregnant women have been conducted. Because animal reproduction studies are not always predictive of human response, Trikafta should be used during pregnancy only if the potential benefits outweigh the potential risks.

Breastfeeding

Elexacaftor, tezacaftor and ivacaftor are excreted into the milk of lactating female rats. Exposure of ^{14}C-elexacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.4, 2, and 1.5 times, respectively, the value observed in plasma (based on $AUC_{0\text{-}24h}$). Because it is not known if elexacaftor, tezacaftor, ivacaftor, or their metabolites are excreted in human milk, Trikafta should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant.

Fertility

There are no data available on the effect of elexacaftor, tezacaftor, and ivacaftor on fertility in humans.

Elexacaftor impaired male and female fertility in rats at oral doses of 75 mg/kg/day and 35 mg/kg/day in the respective sexes (yielding systemic exposure in animals approximately 6 and 7 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the elexacaftor component of Trikafta and its major active metabolite, M23-ELX).

Tezacaftor did not affect fertility or reproductive performance indices in male and female rats at oral doses up to 100 mg/kg/day (yielding systemic exposure in animals approximately 3 times greater than that in patients at the MRHD based on summed AUCs of the tezacaftor component of Trikafta and its pharmacologically active metabolite, M1-TEZ).

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding systemic exposure in animals approximately 10 and 5 times greater, respectively, than that in patients at the MRHD based on summed AUCs of the ivacaftor component of Trikafta and its major metabolites) when dams were dosed prior to and during early pregnancy. The pregnancy rate was decreased, oestrus cycling was disrupted, and pre-implantation loss was increased. These effects occurred in the presence of significant maternal toxicity. No effects on male or female fertility and reproductive performance indices were observed at ≤100 mg/kg/day (yielding systemic exposure in animals approximately 5 and 3 times greater, respectively, than that in patients at the MRHD based on the summed AUCs of the ivacaftor component of Trikafta and its major metabolites).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Trikafta is not expected to have an impact on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile
The safety profile of Trikafta is based on data from 510 patients in two double-blind, controlled, phase 3 studies of 24 weeks and 4 weeks treatment duration (Studies 445-102 and 445-103). In the two controlled phase 3 studies, a total of 257 patients aged 12 years and older received at least one dose of Trikafta.

In Study 445-102, the proportion of patients who discontinued study drug prematurely due to adverse events was 1% for Trikafta-treated patients and 0% for placebo-treated patients.

Serious adverse drug reactions that occurred more frequently in Trikafta-treated patients compared to placebo were rash events in 3 (1.5%) Trikafta-treated patients vs.1 (0.5%) placebo. The most common (≥10%) adverse drug reactions in patients treated with Trikafta were headache, diarrhoea and upper respiratory tract infection.

The safety profile of Trikafta was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Table 6 shows adverse events with an incidence of at least 10% in any treatment group from the double-blind, placebo-controlled, Phase 3 clinical Study 445-102 (24 weeks duration).

Table 6: Adverse Events with an Incidence of at Least 10% in Any Treatment Group of Patients Aged 12 Years and Older who were Heterozygous for the *F508del* Mutation in the CFTR Gene

Preferred Term	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)
Infective pulmonary exacerbation of cystic fibrosis	44 (21.8)	95 (47.3)
Sputum increased	40 (19.8)	39 (19.4)
Headache	35 (17.3)	30 (14.9)
Cough	34 (16.8)	77 (38.3)
Diarrhoea	26 (12.9)	14 (7.0)
Upper respiratory tract infection	24 (11.9)	22 (10.9)
Nasopharyngitis	22 (10.9)	26 (12.9)
Oropharyngeal pain	20 (9.9)	25 (12.4)
Haemoptysis	11 (5.4)	28 (13.9)
Fatigue	9 (4.5)	20 (10.0)

Tabulated list of adverse reactions

Table 7 shows adverse drug events occurring in ≥8% of Trikafta-treated patients and at a frequency higher than placebo by ≥1% in Study 445-102. Adverse drug events for Trikafta are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7: Adverse Drug Reactions by Preferred Term, Incidence and Frequency				
System Organ Class (SOC)	**Adverse Drug Reactions (Preferred Term)**	**Trikafta N=202 n (%)**	**Placebo N=201 n (%)**	**Frequency for Trikafta**
Infections and Infestations	Upper respiratory tract infection	24 (11.9)	22 (10.9)	very common
Nervous System Disorder	Headache	35 (17.3)	30 (14.9)	very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	19 (9.4)	15 (7.5)	common
	Rhinorrhoea	17 (8.4)	6 (3.0)	common
Gastrointestinal disorders	Diarrhoea	26 (12.9)	14 (7.0)	very common
	Abdominal pain	20 (9.9)	12 (6.0)	common
Skin and subcutaneous tissue disorders	Rash	18 (8.9)	9 (4.5)	common
Investigations	Alanine aminotransferase increased	20 (9.9)	7 (3.5)	common
	Aspartate aminotransferase increased	19 (9.4)	4 (2.0)	common
	Blood creatine phosphokinase increased	19 (9.4)	9 (4.5)	common

Safety data from the following studies were consistent with the safety data observed in Study 445-102.

- A 4-week, randomized, double-blind, active-controlled study in 107 patients (Study 445-103).
- A 96-week, open-label safety and efficacy study (Study 445-105) for patients rolled over from Studies 445-102 and 445-103, with interim analysis performed on 509 patients including 58 patients with ≥48 weeks of cumulative treatment with Trikafta.
- An 8-week, randomized, double-blind, active-controlled study in 258 patients (study 445-104).
- A 24-week, open-label study (Study 445-106) in 66 patients aged 6 to less than 12 years.

Detailed description of selected adverse events

Laboratory Abnormalities

Transaminase elevations

In Study 445-102, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the ULN was 1.5%, 2.5%, and 7.9% in Trikafta-treated patients and 1.0%, 1.5%, and 5.5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations was 10.9% in Trikafta-treated patients and 4.0% in placebo-treated patients. No Trikafta-treated patients discontinued treatment for elevated transaminases (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

During Study 445-106 in patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 x ULN were 0%, 1.5%, and 10.6%, respectively. No Trikafta-treated patients had transaminase elevation >3 x ULN associated with elevated total

bilirubin >2 x ULN or discontinued treatment due to transaminase elevations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Rash Events
In Study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in Trikafta-treated patients and 6.5% in placebo-treated patients. The rash events were generally mild to moderate in severity. The incidence of rash events by patient sex was 5.8% in males and 16.3% in females in Trikafta-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients.

A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, consider interrupting Trikafta and hormonal contraceptives. Following the resolution of rash, consider resuming Trikafta without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

Increased Creatine Phosphokinase
In Study 445-102, the incidence of maximum creatine phosphokinase >5 x the ULN was 10.4% in Trikafta-treated patients and 5.0% in placebo-treated patients. No Trikafta-treated patients discontinued treatment for increased creatine phosphokinase.

Increased Blood Pressure
In Study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for Trikafta-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).

The proportion of patients who had systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on at least two occasions was 5.0% and 3.0% in Trikafta-treated patients respectively, compared with 3.5% and 3.5% in placebo-treated patients, respectively.

Post-marketing experience
The following adverse reactions have been identified during post approval use of Trikafta. 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.

Liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension. Liver injury characterized by concomitant transaminase (ALT and AST) and total bilirubin elevations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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

4.9 OVERDOSE

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

No specific antidote is available for overdose with Trikafta. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Respiratory system, Other respiratory system products; ATC code: R07AX32

Mechanism of action
Elexacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of *F508del*-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of *F508del*-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. Clinical outcomes were consistent with *in vitro* results and indicate that a single *F508del* mutation is sufficient to result in a significant clinical response (see *Clinical Efficacy*).

Clinical trials

Pharmacodynamic effects
Effects on sweat chloride
In Study 445-102 (patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor [minimal function mutation]), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period. The treatment difference between Trikafta and placebo for mean absolute change in sweat chloride from baseline through Week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3; $P<0.0001$).

In Study 445-103 (patients homozygous for the *F508del* mutation), the treatment difference between Trikafta and tezacaftor/ivacaftor for mean absolute change in sweat chloride from baseline at Week 4 was -45.1 mmol/L (95% CI: -50.1, -40.1, $P<0.0001$).

In Study 445-104 (patients heterozygous for the *F508del* mutation and a gating or residual function mutation on the second allele), following a 4-week ivacaftor or tezacaftor/ivacaftor run-in period, the mean absolute change in sweat chloride from baseline through Week 8 for the Trikafta group was -22.3 mmol/L (95% CI: -24.5, -20.2; $P<0.0001$). The treatment difference of Trikafta compared to the control group (ivacaftor or tezacaftor/ivacaftor) was -23.1 mmol/L (95% CI: -26.1, -20.1; $P<0.0001$).

In Study 445-106 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2).

Cardiovascular Effects
Effect on QT interval
At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Heart Rate
In Study 445-102, mean decreases in heart rate of 3.7 to 5.8 beats per minute (bpm) from baseline (76 bpm) were observed in Trikafta-treated patients.

Clinical efficacy and safety
The efficacy of Trikafta in patients with CF was demonstrated in three Phase 3, double-blind, controlled studies (Studies 445-102, 445-103, and 445-104), a phase 3 open-label extension study (Study 445-105), and a phase 3 open-label study (445-106). These studies enrolled CF patients with at least one *F508del* mutation. Significant clinical benefit was demonstrated in all studies.

Patients in studies 445-102, 445-103, 445-104, and 445-106 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies. Patients had a confirmed diagnosis of CF and at least one *F508del* mutation.

Patients who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 x ULN, or total bilirubin ≥2 x ULN), were excluded. Patients in studies 445-102 and 445-103 were eligible to roll over into a 96-week open-label extension study (445-105). Patients in studies 445-104 and 445-106 were eligible to roll over into a 96-week open-label extension study.

***Study 445-102*: *S*tudy in patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR / non-responsive CFTR protein**
Study 445-102 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor (minimal function mutation).* A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomized and dosed to receive Trikafta or placebo. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).
*Contact sponsor (see section 8 SPONSOR) for list of mutations enrolled in study 102.

In Study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24. Treatment with Trikafta compared to placebo resulted in statistically significant improvement in $ppFEV_1$ of 14.3 percentage points (95% CI: 12.7, 15.8; P<0.0001) (Table 8). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained through the 24-week treatment period (Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region. A total of 18 patients receiving Trikafta had $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population. See Table 8 for a summary of primary and key secondary outcomes.

Table 8: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)			
Analysis	**Statistic**	**Placebo N=203**	**Trikafta N=200**
Primary			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key Secondary			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through Week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 1.13 (0.07)
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 18.1 (1.1)
$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index. ‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. †† Estimated event rate per year was calculated based on 48 weeks per year.			

At Week 24 the proportion of patients who remained free from pulmonary exacerbations was significantly higher for patients treated with Trikafta compared with placebo. The rate ratio of exacerbations through Week 24 in patients treated with Trikafta was 0.37 (95% CI: 0.25, 0.55; *P*<0.0001), representing a reduction relative to placebo of 63% (see Figure 2).

Figure 1: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Study 445-102

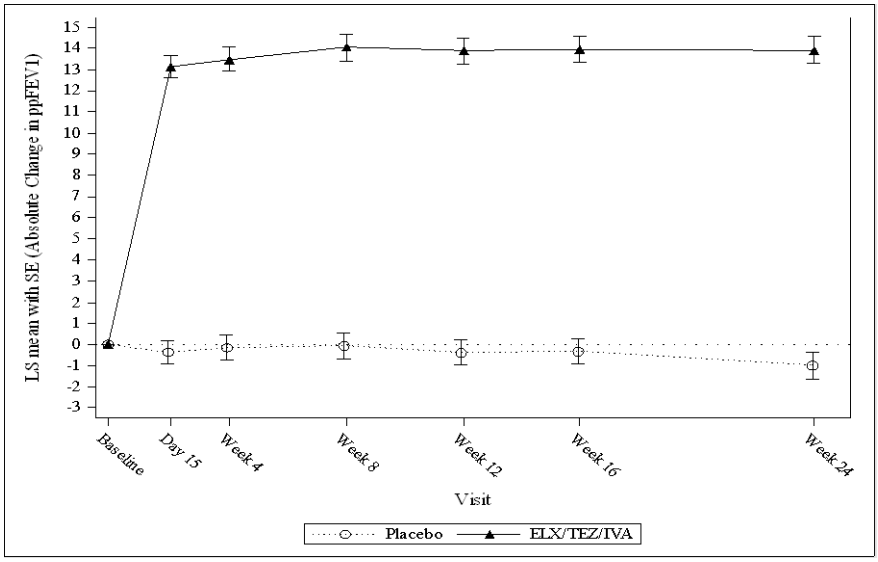
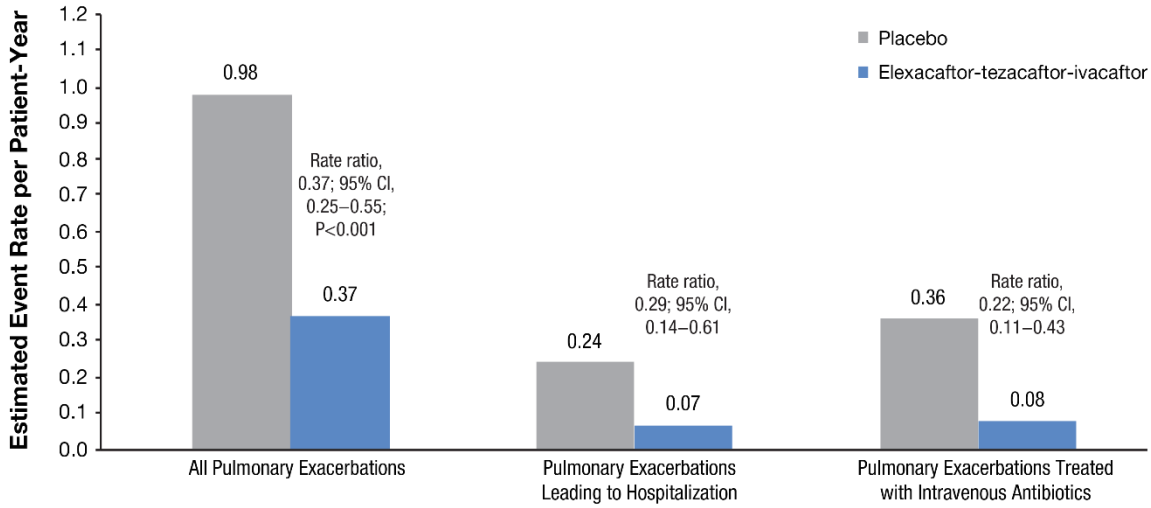


Figure 2: Pulmonary Exacerbations at week 24 in Study 445-102 - Overall estimated annualized rate of pulmonary exacerbations (key secondary endpoint), the estimated annualized rate of pulmonary exacerbations leading to hospitalization, and the estimated annualized rate of pulmonary exacerbations treated with intravenous antibiotics. CI denotes confidence interval.



***Study 445-103:* Study in patients who are homozygous for the *F508del* mutation and randomized to Trikafta or SYMDEKO tablets**

Study 445-103 was a 4-week, randomized, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received SYMDEKO (tezacaftor/ivacaftor and ivacaftor regimen) during a 4-week open-label run-in period and were then randomized and dosed to receive Trikafta or SYMDEKO during a 4-week double-blind treatment period. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline, following the SYMDEKO run-in period was 60.9% (range: 35.0%, 89.0%).

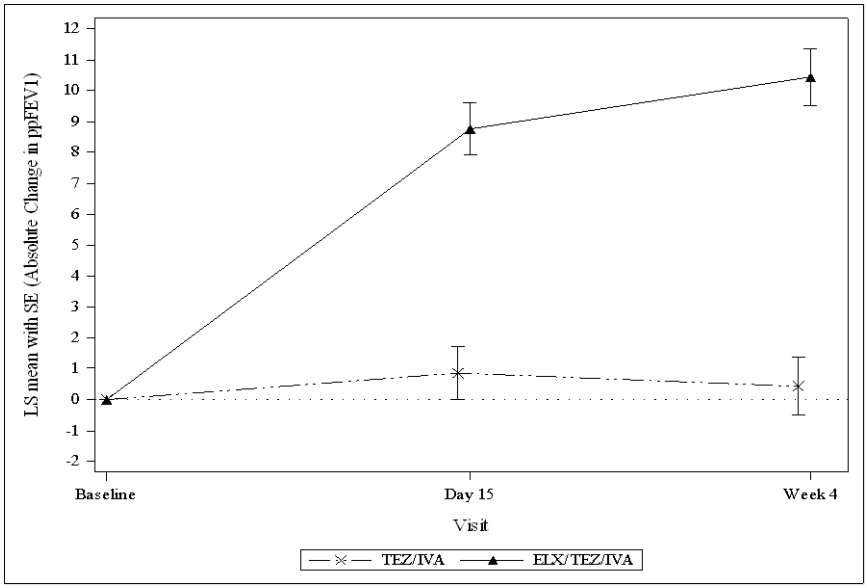
In Study 445-103 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with Trikafta compared to the SYMDEKO resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; *P*<0.0001) (Table 9). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region. See Table 9 for a summary of primary and key secondary outcomes.

Table 9: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103)

Analysis*	Statistic	SYMDEKO N=52	Trikafta N=55
Primary			
Average absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key secondary			
Average absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 16.0 (2.0)

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
* Baseline for primary and key secondary endpoints is defined as the end of the 4-week SYMDEKO run-in period.

Figure 3: Absolute Change from Baseline in Percent Predicted FEV1 at Each Visit in Study 445-103



***Study 445-104*: Study in patients aged 12 years and older who are heterozygous for the *F508del* mutation and a gating or residual function mutation**

Study 445-104 was an 8-week, randomized, double-blind, active-controlled study in patients who were heterozygous for the *F508del* mutation and a gating or residual function (RF) mutation on the second allele. Patients aged 12 years and older and with a ppFEV1 between 40-90% at screening received either KALYDECO (for F/G patients) or SYMDEKO (for F/RF patients) during a 4-week open label run in period. Patients with the *F/R117H* genotype received ivacaftor during the run-in period. Patients were then randomized to the Trikafta group or remained on the CFTR modulator therapy received during the run-in period. The mean age at baseline, following the run-in period, was 37.7 years, and the mean ppFEV1 at baseline was 67.6% (range: 29.7%, 113.5%).

Following a 4-week KALYDECO or SYMDEKO run-in period, the primary endpoint of within-group mean absolute change in $ppFEV_1$ from baseline through Week 8 for the Trikafta group resulted in statistically significant improvement in $ppFEV_1$ of 3.7 percentage points (95% CI: 2.8, 4.6; $P<0.0001$) (See Table 10). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15. Overall improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ geographic region, and genotype groups (F/G or F/RF).

See Table 10 for a summary of primary and secondary outcomes in the overall trial population.

In a subgroup analysis of patients with an F/G genotype, the treatment difference of Trikafta (N=50) compared with KALYDECO(N=45) for mean absolute change in $ppFEV_1$ was 5.8 percentage points (95% CI: 3.5, 8.0). In a subgroup analysis of patients with an F/RF genotype, the treatment difference of Trikafta (N=82) compared with SYMDEKO(N=81) for mean absolute change in $ppFEV_1$ was 2.0 percentage points (95% CI: 0.5, 3.4). The results of the F/G and the F/RF genotype subgroups for improvement in sweat chloride and CFQ-R respiratory domain score were consistent with the overall results.

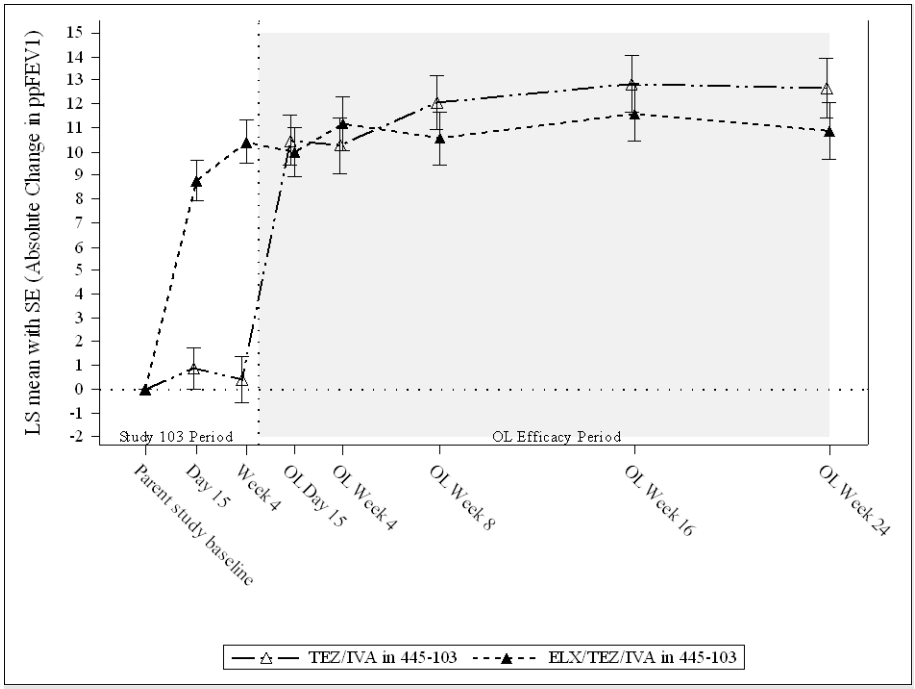
Table 10: Primary and Secondary Efficacy Analyses, Full Analysis Set (Study 445-104)			
Analysis*	**Statistic**	**Control group# N=126**	**Trikafta N=132**
Primary			
Absolute change in ppFEV$_1$ from baseline through Week 8 (percentage points)	Within-group change (95% CI) *P* value	0.2 (-0.7, 1.1) NA	3.7 (2.8, 4.6) *P*<0.0001
Key and other secondary			
Absolute change in sweat chloride from baseline through Week 8 (mmol/L)	Within-group change (95% CI) *P* value	0.7 (-1.4, 2.8) NA	-22.3 (-24.5, -20.2) *P*<0.0001
Absolute change in ppFEV$_1$ from baseline through Week 8 compared to the control group (percentage points)	Treatment difference (95% CI) *P* value	NA NA	3.5 (2.2, 4.7) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 8 compared to the control group (mmol/L)	Treatment difference (95% CI) *P* value	NA NA	-23.1 (-26.1, -20.1) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through Week 8 (points)	Within-group change (95% CI)	1.6 (-0.8, 4.1)	10.3 (8.0, 12.7)
Absolute change in CFQ-R respiratory domain score from baseline through Week 8 compared to the control group (points)	Treatment difference (95% CI)	NA	8.7 (5.3, 12.1)
ppFEV$_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and secondary endpoints is defined as the end of the 4-week run-in period of KALYDECO or SYMDEKO. # KALYDECO group or SYMDEKO group.			

Study 445-105

An ongoing, 96-week open-label extension study to evaluate the safety and efficacy of long-term treatment with Trikafta is being conducted in patients who rolled over from Studies 445-102 and 445-103. For patients homozygous for the *F508del* mutation who rolled over from Study 445-103 (N=107), an interim efficacy analysis was conducted when they completed Week 24 visit of Study 445-105.

Patients who received Trikafta in Study 445-103, and continued on treatment in Study 445-105, showed sustained improvements in ppFEV$_1$ through 28 weeks of cumulative treatment (i.e., through Week 24 in Study 445-105) (see Figure 4). These patients had an annualized pulmonary exacerbation event rate of 0.30 through Week 24 and a mean absolute change in BMI of 1.27 kg/m^2 at Week 24 of Study 445-105. Improvements seen in sweat chloride and CFQ-R respiratory domain score at Week 4 in Study 445-103 were sustained through 24 weeks of treatment in Study 445-105. Substantial improvements in BMI-z score and weight were observed following 24 weeks of Trikafta treatment in Study 445-105.

Figure 4: Absolute Change in Percent Predicted FEV_1 From Baseline at Each Visit in Study 445-103 and in Study 445-105 for Patients that Rolled Over From Study 445-103



Study 445-106: **Study in patients 6 through 11 years old who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation**

Study 445-106 was a 24-week open-label study in 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation. Patients weighing <30 kg at baseline were administered elexacaftor 100 mg once daily (qd)/tezacaftor 50 mg qd/ivacaftor 75 mg every 12 hours (q12h), and patients weighing ≥30 kg at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients had a screening $ppFEV_1$ ≥40% [mean $ppFEV_1$ at baseline of 88.8% (range: 39.0%, 127.1%)] and weighed ≥15 kg.

The pharmacokinetic profile, safety, and efficacy of Trikafta in patients with CF aged 6 to less than 12 years are supported by evidence from studies of Trikafta in patients aged 12 years and older (studies 445-102, 445-103 and 445-104), with additional data from a 24-week, open-label, phase 3 study in 66 patients aged 6 to less than 12 years (Study 445-106).

In Study 445-106 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were evaluation of pharmacokinetics, and efficacy including absolute change in $ppFEV_1$, sweat chloride (see pharmacodynamics section), CFQ-R respiratory domain score, and $LCI_{2.5}$ from baseline through Week 24; measure of growth parameters (weight, height, BMI; and associated z-scores) from baseline at Week 24; and number of pulmonary exacerbations from baseline through Week 24. See Table 11 for a summary of secondary efficacy outcomes.

Table 11: Secondary Efficacy Analyses, Full Analysis Set (Study 445-106)	
Analysis	**Within-group change (95% CI) for Trikafta N=66**
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	10.2 (7.9, 12.6)
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	-60.9 (-63.7, -58.2)
Absolute change in CFQ-R Respiratory Domain score from baseline through Week 24 (points)	7.0 (4.7, 9.2)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	1.02 (0.76, 1.28)
Absolute change in BMI-for-age z-score from baseline at Week 24	0.37 (0.26, 0.48)
Absolute change in weight from baseline at Week 24 (kg)	3.0 (2.5, 3.5)
Absolute change in weight-for-age z-score from baseline at Week 24	0.25 (0.16, 0.33)
Absolute change in height from baseline at Week 24 (cm)	2.3 (1.9, 2.7)
Absolute change in height-for-age z-score from baseline at Week 24	-0.05 (-0.12, 0.01)
Number of pulmonary exacerbations through Week 24‡	4 (0.12) ††
Absolute change in $LCI_{2.5}$ from baseline through Week 24	-1.71 (-2.11, -1.30)
CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index; LCI: Lung Clearance Index. ‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms. †† Number of events and estimated event rate per year based on 48 weeks per year.	

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. Following initiation of once-daily dosing of elexacaftor and tezacaftor and twice-daily dosing of ivacaftor, plasma concentrations of elexacaftor, tezacaftor and ivacaftor reach steady state within approximately 7 days for elexacaftor, within 8 days for tezacaftor, and within 3-5 days for ivacaftor. Upon dosing elexacaftor/tezacaftor/ivacaftor to steady state, the accumulation ratio is approximately 3.6 for elexacaftor, 2.8 for tezacaftor and 4.7 for ivacaftor. Key pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor at steady state in patients with CF aged 12 years and older are shown in Table 12.

Table 12: Mean (SD) Pharmacokinetic Parameters of Elexacaftor, Tezacaftor and Ivacaftor at Steady State in Patients with CF Aged 12 Years and Older			
	Drug	**C_{max} (mcg/mL)**	**$AUC_{0\text{-}24h}$ or $AUC_{0\text{-}12h}$ (mcg·h/mL)***
Elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	Elexacaftor	9.15 (2.09)	162 (47.5)
	Tezacaftor	7.67 (1.68)	89.3 (23.2)
	Ivacaftor	1.24 (0.34)	11.7 (4.01)
*$AUC_{0\text{-}24h}$ for elexacaftor and tezacaftor and $AUC_{0\text{-}12h}$ for ivacaftor			

Absorption
The absolute bioavailability of elexacaftor when administered orally in the fed state is approximately 80%. Elexacaftor is absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 6 hours (4 to 12 hours) while the median (range) t_{max} of tezacaftor and ivacaftor is approximately 3 hours (2 to 4 hours) and 4 (3 to 6 hours), respectively.

Elexacaftor exposure (AUC) increases approximately 1.9- to 2.5-fold when administered with a moderate-fat meal relative to fasted conditions. Ivacaftor exposure increases approximately 2.5- to 4-fold when administered with fat-containing meals relative to fasted conditions, while food has no effect on the exposure of Tezacaftor (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Distribution
Elexacaftor is >99% bound to plasma proteins and tezacaftor is approximately 99% bound to plasma proteins, in both cases primarily to albumin. Ivacaftor is approximately 99% bound to plasma proteins, primarily to albumin, and also to alpha 1-acid glycoprotein and human gamma-globulin. After oral administration of Trikafta, the mean (±SD) apparent volume of distribution of elexacaftor, tezacaftor and ivacaftor was 53.7 L (17.7), 82.0 L (22.3) and 293 L (89.8), respectively. Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.

Metabolism
Elexacaftor is metabolized extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 200 mg ^{14}C-elexacaftor to healthy male subjects, M23-ELX was the only major circulating metabolite. M23-ELX is considered pharmacologically active.

Tezacaftor is metabolized extensively in humans, mainly by CYP3A4/5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of tezacaftor in humans. M1 has similar apparent potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. Another minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor.

Ivacaftor is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolized primarily by CYP3A4/5. M1-IVA and M6-IVA are the two major metabolites of ivacaftor in humans. M1-IVA has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6-IVA is not considered pharmacologically active.

Elimination
Following multiple dosing in the fed state, the mean (±SD) apparent clearance values of elexacaftor, tezacaftor and ivacaftor at steady state were 1.18 (0.29) L/h, 0.79 (0.10) L/h and 10.2 (3.13) L/h, respectively. The mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor following administration of the elexacaftor/tezacaftor/ivacaftor fixed-dose combination tablets are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.

Following oral administration of ^{14}C-elexacaftor alone, the majority of elexacaftor (87.3%) was eliminated in the faeces, primarily as metabolites.

Following oral administration of ^{14}C-tezacaftor alone, the majority of the dose (72%) was excreted in the faeces (unchanged or as the M2-TEZ) and about 14% was recovered in urine (mostly as M2-TEZ), resulting in a mean overall recovery of 86% up to 26 days after the dose.

Following oral administration of ^{14}C-ivacaftor alone, the majority of ivacaftor (87.8%) was eliminated in the faeces after metabolic conversion.

For elexacaftor, tezacaftor and ivacaftor there was negligible urinary excretion of unchanged drug.

Hepatic impairment
Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 25% higher AUC and a 12% higher C_{max} for elexacaftor, 20% higher AUC but similar C_{max} for tezacaftor, and a 1.5-fold higher AUC and a 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 4.8 UNDESIRABLE EFFECTS).

Tezacaftor and ivacaftor
Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and a 10% higher C_{max} for tezacaftor, and 1.5-fold higher AUC but similar C_{max} for ivacaftor compared with healthy subjects matched for demographics.

Ivacaftor
In a study with ivacaftor alone, subjects with moderately impaired hepatic function had similar ivacaftor C_{max}, but an approximately 2.0-fold higher ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics.

Renal impairment
Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or in patients with end stage renal disease.

In human pharmacokinetic studies of elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor in urine (only 0.23%, 13.7% [0.79% as unchanged drug], and 6.6% of total radioactivity, respectively).

Based on population pharmacokinetic (PK) analysis, exposure of elexacaftor was similar in patients with mild renal impairment (N=75, eGFR 60 to less than 90 mL/min/1.73 m^2) relative to those with normal renal function (N=341, eGFR 90 mL/min/1.73 m^2 or greater).

In population PK analysis conducted in 817 patients administered tezacaftor alone or in combination with ivacaftor in Phase 2 or Phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Special Population

Paediatric patients 6 to less than 18 years of age

Elexacaftor, tezacaftor and ivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group and dose administered in Table 13. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 6 to less than 18 years of age are within the range observed in patients aged 18 years and older.

Table 13: Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures Observed at Steady State by Age Group and Dose Administered

Age group	Dose	ELX $AUC_{0\text{-}24h,ss}$ (mcg·h/mL)	TEZ $AUC_{0\text{-}24h,ss}$ (mcg·h/mL)	IVA $AUC_{0\text{-}12h,ss}$ (mcg·h/mL)
Patients aged 6 to <12 years weighing <30 kg (N=36)	elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ ivacaftor 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to <12 years weighing ≥30 kg (N=30)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)
Adolescent patients (12 to <18 years) (N=72)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	147 (36.8)	88.8 (21.8)	10.6 (3.35)
Adult patients (≥18 years) (N=179)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	168 (49.9)	89.5 (23.7)	12.1 (4.17)

SD: Standard Deviation; AUC_{ss}: area under the concentration versus time curve.

Gender

Based on population PK analysis, the exposures of elexacaftor, tezacaftor and ivacaftor are similar in males and females.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Elexacaftor, tezacaftor and ivacaftor were all negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, in vitro chromosomal aberration assay (in TK6 [human lymphoblastoid] cells for elexacaftor, and in Chinese hamster ovary cells for tezacaftor and ivacaftor), and *in vivo* bone marrow micronucleus test (performed in rats with elexacaftor, and in mice for tezacaftor and ivacaftor).

Carcinogenicity

Elexacaftor was not carcinogenic in a 6-month study in transgenic (Tg.rasH2) mice, involving oral administration at doses up to 50 mg/kg/day (yielding systemic exposure 8-fold higher than in patients at the MRHD based on summed AUCs for elexacaftor and M23-ELX).

No evidence of tumourigenicity by tezacaftor was observed in a 6-month study in transgenic (Tg.rasH2) mice and in a conventional 2-year study in rats, conducted by the oral route. The highest doses tested (500 mg/kg/day in mice, 50 mg/kg/day in male rats and 75 mg/kg/day in female rats) yielded exposure to tezacaftor and its M1 and M2 metabolites that was 1.5-fold higher in mice, 1.2-fold higher in male rats, and 2.1-fold higher in female rats than in patients at the MRHD (based on summed AUCs).

Two-year oral studies in mice and rats demonstrated that ivacaftor was not carcinogenic in either species. Plasma exposures to ivacaftor in mice at the non-carcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 5- to 9-fold higher than the plasma levels measured in humans following Trikafta therapy, and at least 1.1- to 2.3-fold higher with respect to the summed AUC for ivacaftor and its major metabolites. Plasma exposures to ivacaftor in rats at the non-carcinogenic dosage (50 mg/kg/day, the highest dosage tested) were approximately 20- to 36-fold higher than the plasma levels measured in humans following Trikafta therapy, and 6- to 9-fold higher with respect to the summed AUC for ivacaftor and its major metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Trikafta Tablets (elexacaftor/tezacaftor/ivacaftor 100mg/50mg/75mg or 50mg/25mg/37.5mg)
Hypromellose
Hypromellose acetate succinate
Sodium lauryl sulfate
Croscarmellose sodium
Microcrystalline cellulose
Magnesium stearate

Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg
OPADRY Complete Film Coating System 20A130036 ORANGE

Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg
OPADRY Complete Film Coating System 20A130039 ORANGE

Ivacaftor Tablets
Silicon dioxide
Croscarmellose sodium
Hypromellose acetate succinate
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate
Carnauba wax

Ivacaftor 150 mg
OPADRYII complete film coating system 85F90614 Blue
OPACODE monogramming ink S-1-17823 BLACK

Ivacaftor 75 mg
OPADRY II complete film coating system 85F105098 Blue

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Trikafta (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 150 mg) film-coated tablets
36 months

Trikafta (elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg and ivacaftor 75 mg) film-coated tablets
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Store in original container.

6.5 NATURE AND CONTENTS OF THE CONTAINER

Blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminum foil lidding.

Pack sizes
Trikafta [co-pack]: Pack size of 84 tablets (56 elexacaftor/tezacaftor/ivacaftor tablets and 28 ivacaftor tablets)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
P O Box 62027
Sylvia Park
AUCKLAND 1644
New Zealand

Telephone: (09) 918 5100
e-mail: VertexMedicalInfo@vrtx.com

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
09 December 2021

10 DATE OF REVISION