▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ALYFTREK (VANZACAFTOR/TEZACAFTOR/DEUTIVACAFTOR) FILM–COATED TABLETS

1 NAME OF THE MEDICINE

Alyftrek: vanzacaftor, tezacaftor and deutivacaftor in combination.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alyftrek 10/50/125 vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets
Each film-coated tablet contains 10 mg of vanzacaftor (as calcium), 50 mg of tezacaftor and 125 mg of deutivacaftor as a fixed-dose combination.

Alyftrek 4/20/50 vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets
Each film-coated tablet contains 4 mg of vanzacaftor (as calcium), 20 mg of tezacaftor and 50 mg of deutivacaftor as a fixed-dose combination.

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

3 PHARMACEUTICAL FORM

Film-coated tablets

Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg
Purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other (15 mm × 7 mm).

Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
Purple, round-shaped tablet debossed with “V4” on one side and plain on the other (7.35 mm diameter).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alyftrek is indicated for the treatment of those who meet the diagnostic criteria for cystic fibrosis (CF) in people aged 6 years and older who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive based on clinical or *in vitro* evidence (see section 5.1 PHARMACODYNAMIC PROPERTIES, Table 4).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dosage

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

Table 1: Dosing recommendation for people with CF aged 6 years and older

Age	Weight	Daily Dose (once daily)
≥ 6 years	< 40 kg	Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
	≥ 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg

Method of Administration

For oral use. Tablets should be swallowed whole.

Alyftrek should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, peanut butter, cheeses, nuts, whole milk, or meats (see section 5.2 PHARMACOKINETIC PROPERTIES).

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

Missed dose
If 6 hours or less have passed since the missed dose, the missed dose should be taken as soon as possible, and the original schedule should be continued the next day.

If more than 6 hours have passed since the missed dose, the missed dose should be skipped, and the original schedule should be continued the next day.

Dosage adjustment

Concomitant use of CYP3A inhibitors

When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, or clarithromycin), the dose of Alyftrek should be reduced as recommended in Table 2 (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant use of ciprofloxacin is not expected to have a clinically relevant effect on the exposure of Alyftrek; therefore, no dose adjustment is recommended with concomitant use of ciprofloxacin (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Table 2: Dosing schedule for concomitant use of Alyftrek with moderate or strong CYP3A inhibitors			
Age	**Weight**	**Moderate CYP3A Inhibitors**	**Strong CYP3A Inhibitors**
≥ 6 years	< 40 kg	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg every other day	Two tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg once a week
	≥ 40 kg	One tablet of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg every other day	One tablet of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg once a week

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A). Use not recommended in moderate hepatic impairment (Child-Pugh Class B). Alyftrek should only be considered when there is a clear medical need, and the benefit exceeds the risk. Liver function tests should be closely monitored. Patients with severe hepatic impairment (Child-Pugh Class C) should not be treated with Alyftrek (see sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

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

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

- *Mild Hepatic Impairment (Child-Pugh Class A):* No dose adjustment is recommended. Liver function tests should be closely monitored.
- *Moderate Hepatic Impairment (Child-Pugh Class B):* Use not recommended. Alyftrek should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used, no dose adjustment is recommended. Liver function tests should be closely monitored.
- *Severe Hepatic Impairment (Child-Pugh Class C):* Should not be used. Alyftrek has not been studied in patients with severe hepatic impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

Elevated transaminases and hepatic injury

Cases of liver failure leading to transplantation have been reported within the first 6 months of treatment in patients with and without pre-existing advanced liver disease taking a drug containing elexacaftor, tezacaftor and ivacaftor which contains one active ingredient that is the same (tezacaftor)

and one similar (ivacaftor) to Alyftrek. Elevated transaminases are common in people with CF and have been observed in some people with CF treated with Alyftrek.

Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all people with CF prior to initiating Alyftrek, every 3 months during the first year of treatment, and annually thereafter. For people with CF with a history of liver disease or transaminase elevations, more frequent monitoring should be considered.

Interrupt Alyftrek and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms suggestive of liver injury (e.g, jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain or anorexia). Interrupt dosing in the event of ALT or AST > 5 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with total bilirubin > 2 × ULN. Follow laboratory tests closely until the abnormalities resolve.

Following the resolution of transaminase elevations consider the benefits and risks of resuming treatment. Patients who resume treatment after interruption should be monitored closely. (see sections 4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.8 ADVERSE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

In people with CF with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), Alyftrek should be used with caution and only if the benefits are expected to outweigh the risks. If used, they should be closely monitored after the initiation of treatment (4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.8 ADVERSE EFFECTS, and 5.2 PHARMACOKINETIC PROPERTIES).

Patients who discontinued or interrupted treatment with a drug containing tezacaftor or ivacaftor due to adverse reactions

There are no available safety data for Alyftrek in patients who previously discontinued or interrupted treatment with a drug containing tezacaftor or ivacaftor due to adverse reactions. Consider the benefits and risks before using Alyftrek in these patients. If Alyftrek is used in these patients, monitor closely as clinically appropriate.

Interactions with medicinal products

CYP3A inducers
Exposures to vanzacaftor, tezacaftor and deutivacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Alyftrek 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
Exposures to vanzacaftor, tezacaftor and deutivacaftor are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose of Alyftrek should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see sections 4.2 DOSAGE AND METHOD OF ADMINISTRATION and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in people with CF aged less than 18 years, 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. As deutivacaftor is a deuterated isotopolog of ivacaftor,

baseline and follow-up ophthalmological examinations are recommended in people with CF aged less than 18 years initiating treatment with Alyftrek.

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 to ivacaftor and its major metabolites approximately 0.3 times the maximum recommended human dose of ALYFTREK (based on summed AUCs of the ivacaftor component of ALYFTREK). This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown.

Renal impairment

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

Effects on laboratory tests

Refer to section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Elevated transaminases and hepatic injury.

Use in the elderly

Clinical studies of Alyftrek did not include a sufficient number of people with CF aged 65 years and older to determine whether they respond differently from younger people with CF.

Paediatric use

The safety and efficacy of Alyftrek in children aged less than 6 years have not been established (see section 5.1 PHARMACODYNAMIC PROPERTIES).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicinal products affecting the pharmacokinetics of Alyftrek

CYP3A inducers

Vanzacaftor, tezacaftor and deutivacaftor are substrates of CYP3A. Vanzacaftor and deutivacaftor are sensitive substrates of CYP3A. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced Alyftrek efficacy. Co-administration of Alyftrek with moderate or strong CYP3A inducers is not recommended (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Examples of strong CYP3A inducers include:

- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's Wort (*Hypericum perforatum*), and efavirenz.

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased vanzacaftor AUC by 10.5-fold, tezacaftor AUC by 4.0- to 4.5-fold and deutivacaftor AUC by 11.1-fold. The dose of Alyftrek should be reduced when co-administered with strong CYP3A inhibitors (see sections 4.2 DOSAGE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 vanzacaftor, tezacaftor, and deutivacaftor AUC by approximately 2.4- to 3.9-fold, 2.1-fold, and 2.9- to 4.8-fold, respectively. The dose of Alyftrek should be reduced when co-administered with moderate CYP3A inhibitors (see sections 4.2 DOSAGE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Examples of moderate CYP3A inhibitors include:
- fluconazole
- erythromycin
- verapamil

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

Ciprofloxacin
Vanzacaftor/tezacaftor/deutivacaftor was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to have a clinically relevant effect on the exposure of vanzacaftor or deutivacaftor. Therefore, no dose adjustment is necessary during concomitant administration of Alyftrek with ciprofloxacin.

Medicinal products affected by Alyftrek

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

Breast Cancer Resistance Protein (BCRP) Substrates
Vanzacaftor and deutivacaftor are inhibitors of BCRP in vitro. Concomitant use of Alyftrek with BCRP substrates may increase exposure of these substrates; however, this has not been studied clinically. When administered concomitantly with substrates of BCRP, caution and appropriate monitoring should be used.

Potential for interaction with transporters
Alyftrek was not evaluated for concomitant use with P-glycoprotein (P-gp) substrates. However, co-administration of tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Based on *in vitro* results, vanzacaftor has low potential to inhibit P-gp at clinically relevant concentrations. Administration of Alyftrek 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 cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Based on *in vitro* data, vanzacaftor, tezacaftor, and deutivacaftor have low potential to inhibit OATP1B1 at clinically relevant concentrations. Co-administration of tezacaftor/ivacaftor with pitavastatin, an OATP1B1 substrate, had no clinically relevant effect on the exposure of pitavastatin.

Hormonal contraceptives
Alyftrek is not expected to have an impact on the efficacy of oral contraceptives. Alyftrek was not evaluated for concomitant use with oral contraceptives. Tezacaftor in combination with ivacaftor and ivacaftor alone have been studied with ethinyl estradiol/norethindrone and were found to have no clinically relevant effect on the exposures of the oral contraceptive. Vanzacaftor and deutivacaftor have low potential to induce CYP3A based on *in vitro* data.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Vanzacaftor did not affect fertility or reproductive performance indices in male and female rats at oral doses of 12.5 mg/kg/day and 10 mg/kg/day in the respective sexes (yielding systemic exposure in animals 19–3times greater than that in patients at the maximum recommended human dose [MRHD] based on $AUC_{0\text{-}24h}$).

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 tezacaftor and its pharmacologically active M1 metabolite).

The effects of deutivacaftor on fertility have not been evaluated; however, ivacaftor impaired fertility and reproductive performance indices in male and female rats at an oral dose of 200 mg/kg/day (yielding approximately 11 and 7 times, respectively, the systemic exposure anticipated in patients at the MRHD of 300 mg/day ivacaftor based on summed AUCs of ivacaftor and its major metabolites) when dams were dosed prior to and during early pregnancy. The pregnancy rate was decreased, oestrus cycling was disrupted and preimplantation 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 approximately 8 and 5 times, respectively, the exposure at the MRHD based on summed AUCs of ivacaftor and its metabolites).

Use in pregnancy - Category B3

No adequate and well-controlled studies of Alyftrek in pregnant women have been conducted. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Because animal reproduction studies are not always predictive of human response, Alyftrek should be used during pregnancy only if the potential benefits outweigh the potential risks. Vanzacaftor, tezacaftor, ivacaftor and/or their metabolites were shown to cross the placenta in laboratory animal species (rats and/or rabbits).

Vanzacaftor

Vanzacaftor was not teratogenic in rats at oral doses up to 10 mg/kg/day or up to 40 mg/kg/day in rabbits (yielding systemic exposure approximately 30 and 22 times greater in the respective species than at the MRHD based on $AUC_{0–24\ h}$ of vanzacaftor. Effects on embryofetal development were limited to lower mean fetal body weight (at ≥10 mg/kg/day) in rabbits.

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 ALYFTREK 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 0.2 times greater than that at the MRHD based on summed AUCs of tezacaftor and its M1 metabolite).

Deutivacaftor/Ivacaftor

No developmental toxicity studies have been performed with deutivacaftor.

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 7 and 9 times greater, than that in patients at the MRHD of 300 mg/day ivacaftor based on summed AUCs of ivacaftor 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.

Use in lactation

Vanzacaftor and tezacaftor are excreted into the milk of lactating female rats. The effect of deutivacaftor has not been evaluated; however, ivacaftor is excreted into the milk of lactating female rats. Exposure in rats of ^{14}C-vanzacaftor, ^{14}C-tezacaftor and ^{14}C-ivacaftor in milk was approximately 0.2, 2.0, and 1.5 times, respectively, the value observed in plasma (based on $AUC_{0\text{-}24\ h}$). Because it is not known if vanzacaftor, tezacaftor, deutivacaftor, or their metabolites are excreted in human milk, Alyftrek should be used during breastfeeding only if the potential benefits outweigh the potential risks to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile of Alyftrek is based on data from 480 participants aged 12 years and older in two randomized, elexacaftor/tezacaftor/ivacaftor-controlled, Phase 3 studies (Studies 121-102 and 121-103) with 52 weeks of treatment duration. In both studies, all subjects participated in a 4-week run-in period with elexacaftor/tezacaftor/ivacaftor. In Studies 121-102 and 121-103, the proportion of people with CF who discontinued Alyftrek prematurely due to adverse events was 3.8%.

Serious adverse drug reactions that occurred with Alyftrek in 2 or more participants (≥ 0.4%) were ALT increased (0.4%) and AST increased (0.4%). The most common (≥ 10%) adverse drug reactions in people with CF treated with Alyftrek were headache (15.8%) and diarrhoea (12.1%).

The safety profile of Alyftrek was generally similar across all subgroups of participants, including analysis by age, sex, baseline percent predicted Forced Expiratory Volume in one second ($ppFEV_1$), and geographic regions.

Table 3 shows overall incidence of adverse drug reactions of people with CF treated with Alyftrek. Adverse drug reactions for Alyftrek 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 3: Adverse reactions by preferred term, incidence and frequency

System Organ Class (SOC)	Adverse Drug Reactions (Preferred Term)	Alyftrek N = 480 n (%)	Frequency for Alyftrek
Nervous system disorders	Headache	76 (15.8)	very common
Gastrointestinal disorders	Diarrhoea	58 (12.1)	very common
Skin and subcutaneous tissue disorders	Rash	37 (7.7)	common
Investigations	Blood creatine phosphokinase increased	43 (9.0)	common
	Alanine aminotransferase increased	38 (7.9)	common
	Aspartate aminotransferase increased	33 (6.9)	common

Safety data from the following studies were generally consistent with the safety data observed in Studies 121-102 and 121-103.

- A 24-week, open-label study (Study 121-105, Cohort B1) in 78 people with CF aged 6 to less than 12 years.

Detailed description of selected adverse events

Transaminase elevations

In Studies 121-102 and 121-103, the incidence of maximum transaminase (ALT or AST) > 8 ×, > 5 ×, or > 3 × the ULN was 1.3%, 2.5%, and 6.0% with Alyftrek. The incidence of adverse reactions of transaminase elevations was 9.0% with Alyftrek. Of the Alyftrek-treated participants, 1.5% discontinued treatment for elevated transaminases.

In Study 121-105, Cohort B1 in people with CF aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) > 8 ×, > 5 ×, and > 3 × ULN were 0%, 1.3%, and 3.8%, respectively.

Rash Events

In Studies 121-102 and 121-103, the incidence of rash events (e.g., rash, rash pruritic) was 11.0% with Alyftrek. The rash events were generally mild to moderate in severity. The incidence of rash events was 9.4% in males and 13.0% in females.

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

Increased creatine phosphokinase
In Studies 121-102 and 121-103, the incidence of maximum creatine phosphokinase > 5 × the ULN was 7.9% with Alyftrek. Of the Alyftrek-treated participants, 0.2% discontinued treatment for increased creatine phosphokinase.

Reporting suspected adverse effects

Reporting of suspected adverse reactions after registration of the medicinal product is 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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Vanzacaftor 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 select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Deutivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of vanzacaftor, tezacaftor and deutivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured both by CFTR mediated chloride transport *in vitro* and by sweat chloride (SwCl) in people with CF.

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR

The chloride transport response of mutant CFTR protein to vanzacaftor/tezacaftor/deutivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Vanzacaftor/tezacaftor/deutivacaftor increased chloride transport in FRT cells expressing select *CFTR* mutations.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or can be reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

Clinical outcomes were consistent with *in vitro* results and indicate that a single responsive allele (including the *F508del* mutation) is sufficient to result in a significant clinical response (see Clinical efficacy).

Table 4 lists responsive *CFTR* mutations based on clinical and/or *in vitro* data.

Table 4: List of *CFTR* Gene Mutations that are Responsive to ALYFTREK							
1140-1151dup	*A561E*	*F1052V*	*G628A*	*K522Q*	*P1021T*	*R516G*	*T1057R*
1341G→A	*A566D*	*F1074L*	*G628R*	*K951E*	*P111L*	*R516S*	*T1086A*
1461insGAT	*A613T*	*F1078S*	*G85E*	*L1011S*	*P1372T*	*R553Q*	*T1086I*
1507_1515del9	*A62P*	*F1099L*	*G85V*	*L102R*	*P140S*	*R555G*	*T1246I*
1898+3A→G	*A72D*	*F1107L*	*G91R*	*L102R;F1016S*[*]	*P205S*	*R560S*	*T1299I*
2055del9	*A872E*	*F191V*	*G930E*	*L1065P*	*P439S*	*R560T*	*T1299K*
2183A→G	*c.1367_1369dupTTG*	*F200I*	*G970D*	*L1065R*	*P499A*	*R600S*	*T164P*
2752-26A→G	*C225R*	*F311del*	*G970S*	*L1077P*	*P574H*	*R668C*	*T338I*
2789+2insA	*C491R*	*F311L*	*G970V*	*L1227S*	*P5L*	*R709Q*	*T351I*
2789+5G→A	*C590Y*	*F312del*	*H1054D*	*L1324P*	*P67L*	*R74Q*	*T351S*
2851A/G	*C866Y*	*F433L*	*H1079P*	*L1335P*	*P750L*	*R74Q;R297Q*[*]	*T351S;R851L*[*]
293A→G	*D110E*	*F508C*	*H1085P*	*L137P*	*P798S*	*R74Q;V201M;D1270N*[*]	*T388M*
296+28A→G	*D110H*	*F508C;S1251N*[*]	*H1085R*	*L137R*	*P988R*	*R74W*	*T465I*
3007del6	*D110N*	*F508del*	*H1375N*	*L1388P*	*P99L*	*R74W;D1270N*[*]	*T465N*
3041-15T→G	*D1152A*	*F508del;R1438W*[*]	*H1375P*	*L1480P*	*Q1012P*	*R74W;R1070W;D1270N*[*]	*T501A*
3131del15	*D1152H*	*F575Y*	*H139L*	*L159S*	*Q1100P*	*R74W;S945L*[*]	*T582S*
3132T→G	*D1270N*	*F587I*	*H139R*	*L15P*	*Q1209P*	*R74W;V201M*[*]	*T604I*
3141del9	*D1270Y*	*F587L*	*H146R*	*L15P;L1253F*[*]	*Q1291H*	*R74W;V201M;D1270N*[*]	*T908N*
3143del9	*D1312G*	*F693L(TTG)*	*H147del*	*L165S*	*Q1291R*	*R74W;V201M;L997F*[*]	*T990I*
314del9	*D1377H*	*F87L*	*H147P*	*L167R*	*Q1313K*	*R751L*	*V1008D*
3195del6	*D1445N*	*F932S*	*H199Q*	*L206W*	*Q1352H*	*R75L*	*V1010D*
3199del6	*D192G*	*G1047D*	*H199R*	*L210P*	*Q151K*	*R75Q*	*V1153E*
3272-26A→G	*D192N*	*G1047R*	*H199Y*	*L293P*	*Q179K*	*R75Q;L1065P*[*]	*V11I*
3331del6	*D373N*	*G1061R*	*H609L*	*L320V*	*Q237E*	*R75Q;N1088D*[*]	*V1240G*
3410T→C	*D426N*	*G1069R*	*H609R*	*L327P*	*Q237H*	*R75Q;S549N*[*]	*V1293G*
3523A→G	*D443Y*	*G1123R*	*H620P*	*L32P*	*Q237P*	*R792G*	*V1293I*
3600G→A	*D443Y;G576A;R668C*[*]	*G1173S*	*H620Q*	*L333F*	*Q30P*	*R792Q*	*V1415F*
3601A→C	*D513G*	*G1237V*	*H939R*	*L333H*	*Q359K/T360K*[*]	*R810G*	*V201M*
3761T→G	*D529G*	*G1244E*	*H939R;H949L*[*]	*L346P*	*Q359R*	*R851L*	*V232A*
3791C/T	*D565G*	*G1244R*	*H954P*	*L441P*	*Q372H*	*R933G*	*V232D*
3849+10kbC→T	*D567N*	*G1247R*	*I1023R*	*L453S*	*Q452P*	*S1045Y*	*V317A*
3849+40A→G	*D572N*	*G1249E*	*I1027T*	*L467F*	*Q493L*	*S108F*	*V322M*
3849+4A→G	*D579G*	*G1249R*	*I105N*	*L558F*	*Q493R*	*S1118F*	*V392G*

3850-3T→G	*D58H*	*G1265V*	*I1139V*	*L594P*	*Q552P*	*S1159F*	*V456A*
3850G→A	*D58V*	*G126D*	*I1203V*	*L610S*	*Q98P*	*S1159P*	*V456F*
3978G→C	*D614G*	*G1298V*	*I1234L*	*L619S*	*Q98R*	*S1188L*	*V520F*
4005+2T→C	*D651H*	*G1349D*	*I1234Vdel6aa*	*L633P*	*R1048G*	*S1235R*	*V520I*
4193T→G	*D651N*	*G149R*	*I125T*	*L636P*	*R1066C*	*S1251N*	*V562I*
546insCTA	*D806G*	*G149R;G576A;R668C*[*]	*I1269N*	*L88S*	*R1066G*	*S1255P*	*V562I;A1006E*[*]
548insTAC	*D836Y*	*G178E*	*I1366N*	*L927P*	*R1066H*	*S13F*	*V562L*
5T;TG12	*D924N*	*G178R*	*I1366T*	*L967F;L1096R*[*]	*R1066L*	*S13P*	*V591A*
5T;TG13	*D979A*	*G194R*	*I1398S*	*L967S*	*R1066M*	*S158N*	*V603F*
621+3A→G	*D979V*	*G194V*	*I148L*	*L973F*	*R1070P*	*S182R*	*V754M*
711+3A→G	*D985H*	*G213E*	*I148N*	*L997F*	*R1070Q*	*S18I*	*V920L*
A1006E	*D985Y*	*G213E;R668C*[*]	*I148T*	*M1101K*	*R1070W*	*S18N*	*V920M*
A1025D	*D993A*	*G213V*	*I148T;H609R*[*]	*M1101R*	*R1162L*	*S308P*	*V93D*
A1067P	*D993G*	*G226R*	*I175V*	*M1137R*	*R1162Q*	*S341P*	*W1098C*
A1067T	*D993Y*	*G239R*	*I331N*	*M1137V*	*R117C*	*S364P*	*W1282G*
A1067V	*E1104K*	*G253R*	*I336K*	*M1210K*	*R117C;G576A;R668C*[*]	*S434P*	*W1282R*
A107G	*E1104V*	*G27E*	*I336L*	*M150K*	*R117G*	*S492F*	*W202C*
A1081V	*E1126K*	*G27R*	*I444S*	*M150R*	*R117H*	*S50P*	*W361R*
A1087P	*E116K*	*G314E*	*I497S*	*M152L*	*R117L*	*S519G*	*W496R*
A120T	*E116Q*	*G314R*	*I502T*	*M152V*	*R117L;L997F*[*]	*S531P*	*Y1014C*
A1319E	*E1221V*	*G424S*	*I506L*	*M265R*	*R117P*	*S549I*	*Y1032C*
A1374D	*E1228K*	*G437D*	*I506T*	*M348K*	*R1239S*	*S549N*	*Y1032N*
A141D	*E1409K*	*G451V*	*I506V*	*M394L*	*R1283G*	*S549R*	*Y1073C*
A1466S	*E1433K*	*G461R*	*I506V;D1168G*[*]	*M469V*	*R1283M*	*S557F*	*Y1092H*
A155P	*E193K*	*G461V*	*I521S*	*M498I*	*R1283S*	*S589I*	*Y109C*
A234D	*E217G*	*G463V*	*I530N*	*M952I*	*R1438W*	*S589N*	*Y109H*
A234V	*E264V*	*G480C*	*I556V*	*M952T*	*R170H*	*S624R*	*Y109N*
A238V	*E282D*	*G480D*	*I586V*	*M961L*	*R248K*	*S686Y*	*Y122C*
A309D	*E292K*	*G480S*	*I601F*	*N1088D*	*R258G*	*S737F*	*Y1381H*
A349V	*E384K*	*G500D*	*I601T*	*N1195T*	*R297Q*	*S821G*	*Y161C*
A357T	*E403D*	*G545R*	*I618N*	*N1303I*	*R31C*	*S898R*	*Y161D*
A455E	*E474K*	*G551A*	*I618T*	*N1303K*	*R31L*	*S912L*	*Y161S*
A455V	*E527G*	*G551D*	*I807M*	*N186K*	*R334L*	*S912L;G1244V*[*]	*Y301C*
A457T	*E56K*	*G551R*	*I86M*	*N187K*	*R334Q*	*S912T*	*Y517C*
A462P	*E588V*	*G551S*	*I980K*	*N396Y*	*R334W*	*S945L*	*Y563N*
A46D	*E60K*	*G576A*	*K1060T*	*N418S*	*R347H*	*S955P*	*Y569C*
A534E	*E822K*	*G576A;R668C*[*]	*K162E*	*N900K*	*R347L*	*S977F*	*Y89C*
A554E	*E831X*	*G576A;S1359Y*[*]	*K464E*	*P1013H*	*R347P*	*S977F;R1438W*[*]	*Y913C*
A559T	*E92K*	*G622D*	*K464N*	*P1013L*	*R352Q*	*T1036N*	*Y913S*
A559V	*F1016S*	*G622V*	*K522E*	*P1021L*	*R352W*	*T1053I*	*Y919C*

[*] Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

There may be patients with mutations not listed in Table 4. Provided they do not harbour two Class I mutations, ALYFTREK can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.

Clinical trials

Pharmacodynamic effects

Effects on sweat chloride
In Study 121-102 (people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor [minimal function mutation]) the treatment difference of Alyftrek compared to elexacaftor/tezacaftor/ivacaftor for mean absolute change in SwCl from baseline through Week 24 was -8.4 mmol/L (95% CI: -10.5, -6.3; $P < 0.0001$).

In Study 121-103 (people with CF homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation), the treatment difference of Alyftrek compared to elexacaftor/tezacaftor/ivacaftor for mean absolute change in SwCl from baseline through Week 24 was -2.8 mmol/L (95% CI: -4.7, -0.9; $P = 0.0034$).

In Study 121-105, Cohort B1 (people with CF aged 6 to less than 12 years with at least one mutation that is responsive to elexacaftor/tezacaftor/ivacaftor), the mean absolute change in SwCl from baseline through Week 24 was -8.6 mmol/L (95% CI: -11.0, -6.3).

Cardiovascular effects

Effect on QT interval
At exposures corresponding up to 6 times over those observed with the vanzacaftor maximum recommended dose, and doses up to 3 times over the tezacaftor and deutivacaftor maximum recommended doses, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Clinical efficacy

The efficacy of Alyftrek in people with CF aged 12 years and older was evaluated in two, Phase 3, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled studies (Study 121-102 and Study 121-103). The pharmacokinetic profile, safety, and efficacy of Alyftrek in people with CF aged 6 to less than 12 years are supported with evidence from studies of Alyftrek in people with CF aged 12 years and older (Studies 121-102 and 121-103), and additional data from an open-label, Phase 3 study (Study 121-105, Cohort B1).

Studies 121-102 and 121-103
Study 121-102 was a 52-week, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to ivacaftor or tezacaftor/ivacaftor (minimal function mutation). A total of 398 people with CF aged 12 years and older (mean age 30.8 years) received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive Alyftrek or elexacaftor/tezacaftor/ivacaftor during the 52-week treatment period. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 67.1 percentage points (range: 28.0, 108.6) and the mean SwCl at baseline was 53.9 mmol/L (range: 10.0 mmol/L, 113.5 mmol/L).

Study 121-103 was a 52-week, randomized, double-blind, elexacaftor/tezacaftor/ivacaftor-controlled study in people with CF who had one of the following genotypes: homozygous for the *F508del* mutation, heterozygous for the *F508del* mutation and either a gating or a residual function mutation, or at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor with no *F508del* mutation. A total of 573 people with CF aged 12 years and older (mean age 33.7 years) received elexacaftor/tezacaftor/ivacaftor during a 4-week run-in period and were then randomized to receive Alyftrek or elexacaftor/tezacaftor/ivacaftor during the 52-week treatment period. After the 4-week

run-in, the mean $ppFEV_1$ at baseline was 66.8 percentage points (range: 36.4, 112.5) and the mean SwCl at baseline was 42.8 mmol/L (range: 10.0 mmol/L, 113.3 mmol/L)**.**

In both studies, the primary endpoint evaluated non-inferiority in mean absolute change from baseline in $ppFEV_1$ through Week 24. Key secondary endpoints evaluated superiority in mean absolute change from baseline in SwCl through Week 24, and the proportion of participants achieving SwCl < 60 mmol/L and SwCl < 30 mmol/L through Week 24.

In Study 121-102, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.7, 1.1) in absolute change in $ppFEV_1$ from baseline through Week 24 compared to elexacaftor/tezacaftor/ivacaftor. In Study 121-103, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (1-sided $P < 0.0001$ for non-inferiority; 95% CI: -0.5, 0.9) in absolute change in $ppFEV_1$ from baseline through Week 24 compared to elexacaftor/tezacaftor/ivacaftor. In Studies 121-102 and 121-103, mean absolute change from baseline in $ppFEV_1$ through Week 24 was maintained through Week 52.

As the lower bounds of the 95% CI of the LS mean difference in absolute change in $ppFEV_1$ from baseline through Week 24 was greater than -3.0 percentage points (the pre-specified non-inferiority margin) in Study 121-102 and Study 121-103, these results demonstrate non-inferiority of Alyftrek compared to elexacaftor/tezacaftor/ivacaftor.

In Studies 121-102 and 121-103, Alyftrek was superior to elexacaftor/tezacaftor/ivacaftor on all key secondary endpoints. On the first key secondary endpoint, when compared to elexacaftor/tezacaftor/ivacaftor, treatment with Alyftrek resulted in a reduction of -8.4 mmol/L (95% CI: -10.5, -6.3; $P < 0.0001$) and -2.8 mmol/L (95% CI: -4.7, -0.9; $P = 0.0034$) in SwCl through Week 24, in Studies 121-102 and 121-103, respectively. Absolute change from baseline in SwCl through Week 24 was maintained through Week 52 in both trials. On the remaining key secondary endpoints, treatment with Alyftrek resulted in 86% of people with CF achieving a SwCl level below 60 mmol/L through Week 24, compared to 77% of people treated with elexacaftor/tezacaftor/ivacaftor (odds ratio 2.21; 95% CI: 1.55, 3.15; $P < 0.0001$), and 31% of people with CF achieving a SwCl level below 30 mmol/L through Week 24, compared to 23% of people treated with elexacaftor/tezacaftor/ivacaftor (odds ratio 2.87; 95% CI: 2.00, 4.12; $P < 0.0001$).

Other secondary endpoints (pulmonary exacerbation rate, change in CFQ-R RD score from baseline) demonstrated consistent benefit between Alyftrek and elexacaftor/tezacaftor/ivacaftor.

See Table 5 for a summary of key efficacy outcomes for Studies 121-102 and 121-103.

Table 5: Efficacy analyses from Study 121-102 and Study 121-103					
Analysis*	**Statistic**	**Study 121-102**		**Study 121-103**	
		Alyftrek N = 196	**elexacaftor/tezacaftor/ivacaftor N = 202**	**Alyftrek N = 284**	**elexacaftor/tezacaftor/ivacaftor N = 289**
Primary					
Baseline $ppFEV_1$	Mean (SD)	67.0 (15.3)	67.2 (14.6)	67.2 (14.6)	66.4 (14.9)
Absolute change from baseline in $ppFEV_1$ through Week 24 (percentage points)	n	187	193	268	276
	LS mean (SE)	0.5 (0.3)	0.3 (0.3)	0.2 (0.3)	0.0 (0.2)
	LS mean difference, 95% CI	0.2 (-0.7, 1.1)		0.2 (-0.5, 0.9)	
	P-value (1-sided) for Non-Inferiority#	< 0.0001		< 0.0001	
Key Secondary					
Baseline SwCl	Mean (SD)	53.6 (17.0)	54.3 (18.2)	43.4 (18.5)	42.1 (17.9)
Absolute change from baseline in SwCl through Week 24 (mmol/L)	n	185	194	270	276
	LS mean (SE)	-7.5 (0.8)	0.9 (0.8)	-5.1 (0.7)	-2.3 (0.7)
	LS mean difference, 95% CI	-8.4 (-10.5, -6.3)		-2.8 (-4.7, -0.9)	
	P-value (2-sided)	< 0.0001		0.0034	
Proportion of participants with SwCl < 60 mmol/L† through Week 24	n	**465 Alyftrek**	**vs**	**479 elexacaftor/tezacaftor/ivacaftor**	
	Proportion (%)	86 Alyftrek	vs	77 elexacaftor/tezacaftor/ivacaftor	
	Odds Ratio, 95% CI¶	2.21 (1.55, 3.15)			
	P-value (2-sided)	< 0.0001			
Proportion of participants with SwCl < 30 mmol/L§ through Week 24	n	**465 Alyftrek**	**vs**	**479 elexacaftor/tezacaftor/ivacaftor**	
	Proportion (%)	31 Alyftrek	vs	23 elexacaftor/tezacaftor/ivacaftor	
	Odds Ratio, 95% CI¶	2.87 (2.00, 4.12)			
	P-value (2-sided)	< 0.0001			
Other Secondary Þ					
Number of pulmonary exacerbations through Week 52	Number of events	67	90	86	79
	Event rate per year	0.32	0.42	0.29	0.26
	Rate difference, 95% CI	-0.10 (-0.24, 0.04)		0.03 (-0.07, 0.13)	
Absolute change from baseline in CFQ-R RD score through Week 24 (points)	n	186	192	268	270
	LS mean (SE)	0.5 (1.1)	-1.7 (1.0)	-1.2 (0.8)	-1.2 (0.8)
	LS mean difference, 95% CI	2.3 (-0.6, 5.2)		-0.1 (-2.3, 2.1)	

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SE: Standard Error; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised (respiratory domain); SwCl: Sweat Chloride

Note: Analyses were based on the full analysis set (FAS) unless otherwise noted. FAS was defined as all randomized subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug.

* A 4-week elexacaftor/tezacaftor/ivacaftor run-in-period was performed to establish an on-treatment baseline.

† SwCl ≥ 60 mmol/L meets the diagnostic threshold for CF as evidence of CFTR dysfunction.

§ Normal SwCl levels are considered < 30 mmol/L.

¶ Odds ratio > 1 favors Alyftrek.

The pre-specified non-inferiority margin was -3.0 percentage points.

Þ Not controlled for multiplicity.

Study 121-105

Study 121-105 was a multicohort, open-label study in people with CF with at least one mutation responsive to elexacaftor/tezacaftor/ivacaftor. Cohort A1 evaluated pharmacokinetic and safety parameters of Alyftrek during a 22-day treatment period in a total of 17 people with CF aged 6 to less than 12 years. Cohort B1 evaluated the safety, tolerability, and efficacy of Alyftrek in a total of 78 people with CF aged 6 to less than 12 years (mean age 9.1 years) during a 24-week treatment period. In Cohort B1, all participants were on elexacaftor/tezacaftor/ivacaftor at baseline. The mean $ppFEV_1$ at baseline, on elexacaftor/tezacaftor/ivacaftor, was 99.7 percentage points (range: 29.3, 146.0) and the mean SwCl at baseline, on elexacaftor/tezacaftor/ivacaftor, was 40.4 mmol/L (range: 11.5 mmol/L, 109.5 mmol/L).

In Study 121-105, Cohort B1, safety and tolerability were the primary endpoints. Efficacy endpoints included absolute change in $ppFEV_1$, absolute change in SwCl, proportion of participants with SwCl of < 60 mmol/L, proportion of participants with SwCl of < 30 mmol/L, absolute change in CFQ-R respiratory domain score, and number of PEx through Week 24.

See Table 6 for a summary of efficacy outcomes.

Table 6: Efficacy analyses from Study 121-105, (Cohort B1)

Analysis	Statistic	Alyftrek N = 78
Secondary Efficacy		
Baseline $ppFEV_1$	Mean (SD)	99.7 (15.1)
Baseline SwCl	Mean (SD)	40.4 (20.9)
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	LS mean (95% CI)	0.0 (-2.0, 1.9)
Absolute change in SwCl from baseline through Week 24 (mmol/L)	LS mean (95% CI)	-8.6 (-11.0, -6.3)
Proportion of participants with SwCl < 60 mmol/L* through Week 24	Proportion (95% CI)	95% (87%, 99%)
Proportion of participants with SwCl < 30 mmol/L† through Week 24	Proportion (95% CI)	53% (41%, 64%)
Absolute change in CFQ-R Respiratory Domain score from baseline through Week 24 (points)	LS mean (95% CI)	3.9 (1.5, 6.3)
Number of pulmonary exacerbations through Week 24	Event rate per year	0.15

CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CFQ-R: Cystic Fibrosis Questionnaire-Revised

* SwCl ≥ 60 mmol/L meets the diagnostic threshold for CF as evidence of CFTR dysfunction.

† Normal SwCl levels are considered < 30 mmol/L.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of vanzacaftor, tezacaftor and deutivacaftor are similar between healthy adult subjects and people with CF. Following initiation of once-daily dosing vanzacaftor/tezacaftor/deutivacaftor plasma concentrations reach steady state within 20 days for vanzacaftor, within 8 days for tezacaftor, and within 8 days for deutivacaftor.

Upon dosing vanzacaftor/tezacaftor/deutivacaftor to steady state, the accumulation ratio based on AUC is approximately 6.09 for vanzacaftor, 1.92 for tezacaftor and 1.74 for deutivacaftor. Key pharmacokinetic parameters for vanzacaftor/tezacaftor/deutivacaftor at steady state in people with CF aged 12 years and older are shown in Table 7.

Table 7: Mean (SD) pharmacokinetic parameters of vanzacaftor, tezacaftor and deutivacaftor at steady state in people with CF aged 12 years and older			
Dose	**Active Substance**	**C_{max} (mcg/mL)**	**AUC_{0-24h} (mcg·h/mL)**
vanzacaftor 20 mg/tezacaftor 100 mg /deutivacaftor 250 mg	vanzacaftor	0.812 (0.344)	18.6 (8.08)
	tezacaftor	6.77 (1.24)	89.5 (28.0)
	deutivacaftor	2.33 (0.637)	39.0 (15.3)
SD: Standard Deviation; C_{max}: maximum observed concentration; AUC_{0-24h}: Area Under the Concentration versus time curve at steady state.			

Absorption

Vanzacaftor, tezacaftor, and deutivacaftor are absorbed with a median (range) time to maximum concentration (t_{max}) of approximately 7.80 hours (3.70 to 11.9 hours), 1.60 hours (1.40 to 1.70 hours), and 3.7 hours (2.7 to 11.4 hours), respectively.

Vanzacaftor exposure (AUC) increases approximately 4- to 6-fold when administered with fat-containing meals relative to fasted conditions. deutivacaftor exposure increases approximately 3- to 4-fold when administered with fat-containing meals relative to fasted conditions, while food has no clinically significant effect on the exposure of tezacaftor (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Distribution

Vanzacaftor and deutivacaftor are > 99% bound to plasma protein, primarily to albumin and alpha 1-acid glycoprotein. Tezacaftor is approximately 99% bound to plasma proteins, primarily to albumin.

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent volume of distribution of vanzacaftor, tezacaftor and deutivacaftor was 90.4 L (31.3), 123 L (43.2) and 157 L (47.3), respectively. Vanzacaftor, tezacaftor and deutivacaftor do not partition preferentially into human red blood cells.

Metabolism

Vanzacaftor is metabolized extensively in humans, mainly by CYP3A4/5. Vanzacaftor has no major circulating metabolites.

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-tezacaftor, M2-tezacaftor and M5-tezacaftor were the three major circulating metabolites of tezacaftor in humans. M1-tezacaftor has similar apparent potency to that of tezacaftor and is considered pharmacologically active. M2-tezacaftor is much less pharmacologically active than tezacaftor or M1-tezacaftor, and M5-tezacaftor is not considered pharmacologically active. Another minor circulating metabolite, M3-tezacaftor, is formed by direct glucuronidation of tezacaftor.

Deutivacaftor is primarily metabolized by CYP3A4/5 to form the 2 major circulating metabolites, M1-deutivacaftor and M6-deutivacaftor. Relative to ivacaftor, deutivacaftor exhibited more metabolic stability and formed less M1-deutivacaftor, the deuterated-equivalent of M1-ivacaftor. M1-deutivacaftor has approximately one-fifth the potency of deutivacaftor and is considered pharmacologically active. M6-deutivacaftor is the other major metabolite of deutivacaftor, the deuterated-equivalent of M6-ivacaftor, and is not considered pharmacologically active.

Elimination

After oral administration of vanzacaftor/tezacaftor/deutivacaftor, the mean (SD) apparent clearance values of vanzacaftor, tezacaftor and deutivacaftor were 1.18 (0.455) L/h, 0.937 (0.338) L/h and 6.52 (2.77) L/h, respectively. The mean (SD) terminal half-lives of vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor fixed-dose combination tablets are approximately 54.0 (10.1) hours, 92.4 (23.1) hours and 17.3 (2.67) hours, respectively. The mean (SD) effective half-lives of vanzacaftor, tezacaftor and deutivacaftor following administration of the vanzacaftor/tezacaftor/deutivacaftor fixed-dose combination tablets are approximately 92.8 (30.2) hours, 22.5 (5.85) hours and 19.2 (8.71) hours, respectively.

Excretion

Following oral administration of ^{14}C-vanzacaftor alone (91.6%), the majority of radioactivity was eliminated in faeces primarily as metabolites in the faeces.

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

Preclinical data indicate that the majority of ^{14}C-deutivacaftor and ^{14}C-ivacaftor are excreted in the faeces. Major excreted metabolites of deutivacaftor were M1-deutivacaftor and M6-deutivacaftor and major excreted metabolites for ivacaftor were M1-ivacaftor and M6-ivacaftor. The excretion of deutivacaftor in humans is expected to be similar to that of ivacaftor, based on similar structure (deuterated isotopolog) and nonclinical data.

After oral administration of ^{14}C-ivacaftor alone, the majority of ivacaftor (87.8%) was eliminated in faeces after metabolic conversion. There was minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of ivacaftor was recovered in the urine).

Hepatic impairment

Vanzacaftor/tezacaftor/deutivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C). Following a single dose of vanzacaftor/tezacaftor/deutivacaftor, subjects with moderate hepatic impairment had approximately 30% lower total vanzacaftor exposures, comparable total tezacaftor exposures, and 20% lower total deutivacaftor exposures compared to healthy subjects matched for demographics.

Renal impairment

Urinary excretion of vanzacaftor, tezacaftor, and deutivacaftor is negligible (see Elimination).

Vanzacaftor alone or in combination with tezacaftor and deutivacaftor has not been studied in people with CF with severe renal impairment (eGFR less than 30 mL/min) or in people with CF with end-stage renal disease. Based on population pharmacokinetic (PK) analysis, exposure of vanzacaftor was similar in patients with mild renal impairment (N = 126; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 580; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of tezacaftor was similar in patients with 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) relative to those with normal renal function (N = 637; eGFR 90 mL/min/1.73 m^2 or greater).

Based on population PK analysis, exposure of deutivacaftor was similar in patients with mild (N = 132; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N = 2; eGFR 30 to less than 60 mL/min/1.73 m^2) relative to those with normal renal function (N = 577; eGFR 90 mL/min/1.73 m^2 or greater) (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Gender

Based on population PK analysis, there are no clinically relevant differences in exposures of vanzacaftor, tezacaftor and deutivacaftor between males and females.

People with CF 6 to less than 18 years of age

Vanzacaftor, tezacaftor and deutivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 8. Exposure of vanzacaftor, tezacaftor and deutivacaftor in people 6 to less than 18 years of age are within the range observed in adults with CF.

Table 8: Mean (SD) vanzacaftor, tezacaftor and deutivacaftor exposures by age group

Age group	Weight (N)	Dose	vanzacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)	tezacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)	deutivacaftor $AUC_{0\text{-}24h}$ (mcg·h/mL)
6 to < 12 years	< 40 kg (N = 70)	vanzacaftor 12 mg qd/ tezacaftor 60 mg qd/ deutivacaftor 150 mg qd	13.0 (4.90)	69.1 (20.7)	30.2 (11.6)
	≥ 40 kg (N = 8)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 250 mg qd	18.6 (7.49)	101 (33.7)	48.5 (18.7)
12 to < 18 years	(N = 66)	vanzacaftor 20 mg qd/ tezacaftor 100 mg qd/ deutivacaftor 250 mg qd	15.8 (6.52)	93.0 (32.5)	37.1 (15.3)
≥ 18 years	(N = 414)		19.0 (8.22)	89.0 (27.2)	39.3 (15.3)

SD: Standard Deviation; $AUC_{0\text{-}24h}$: area under the concentration versus time curve at steady state; qd: once daily

5.3 PRECLINICAL SAFETY DATA

Effects in non-clinical studies were observed at exposures greater than the maximum human exposure, indicating little relevance to clinical use.

Genotoxicity
Vanzacaftor, tezacaftor and deutivacaftor 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 vanzacaftor and deutivacaftor, and in Chinese hamster ovary cells for tezacaftor), and *in vivo* bone marrow micronucleus test (performed in mice for tezacaftor, and in rats with vanzacaftor and deutivacaftor).

Carcinogenicity
Vanzacaftor was not carcinogenic in a 6-month study in transgenic (Tg.rasH2) mice, involving oral administration at doses up to 30 mg/kg/day (yielding systemic exposure 27-fold higher than in patients at the MRHD based on $AUC_{0\text{–}24\ h}$ for vanzacaftor).

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 1.8 fold higher in mice, 1.5-fold higher in male rats, and 2.5-fold higher in female rats than in patients at the MRHD (based on summed AUCs).

Deutivacaftor is a deuterated isotopolog of ivacaftor with a toxicity profile similar to ivacaftor. 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 noncarcinogenic dosage (200 mg/kg/day, the highest dosage tested) were approximately 3- to 5-fold higher than the plasma levels measured in humans following daily therapy with 20 mg vanzacaftor + 100 mg tezacaftor + 250 mg D-ivacaftor, and at least 1.7- to 3-fold higher with respect to the summed AUCs 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 12- to 22-fold higher than the plasma levels measured in humans following daily therapy with vanzacaftor + tezacaftor + D-ivacaftor, and 9- to 13-fold higher with respect to the summed AUCs for ivacaftor and its major metabolites.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Alyftrek vanzacaftor/tezacaftor/deutivacaftor film-coated tablets:
Croscarmellose sodium
Hypromellose
Hypromellose acetate succinate
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate

Tablet film coat:
Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg
OPADRY II complete film coating system 20A100021 Purple (ARTG PI No: 147682)

Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg
OPADRY II complete film coating system 20A100025 Purple (ARTG PI No: 147679)

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Film-coated tablets
Thermoform blister consisting of PCTFE (polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding.

Pack sizes
Alyftrek 10/50/125 vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets: Pack size of 56 tablets

Alyftrek 4/20/50 vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets: Pack size of 84 tablets

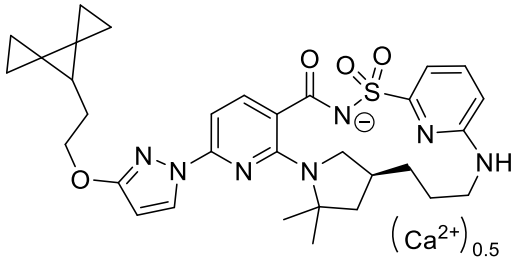
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

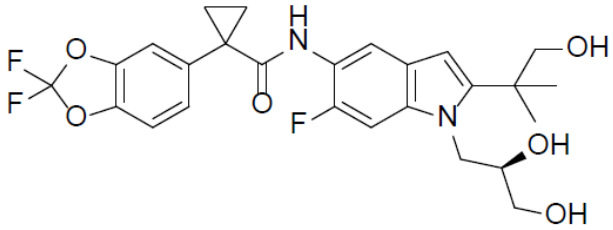
Chemical structure

Vanzacaftor: calcium bis((14*S*)-8-[3-(2-{dispiro[2.0.2^4.1^3]heptan-7-yl}ethoxy)pyrazol-1-yl]-12,12-dimethyl-2,2,4-trioxo-2λ^6-thia-3,9,11,18,23-pentaazatetracyclo[17.3.1.1^{11,14}.0^{5,10}]tetracosa-1(23),5,7,9,19,21-hexaen-3-ide)



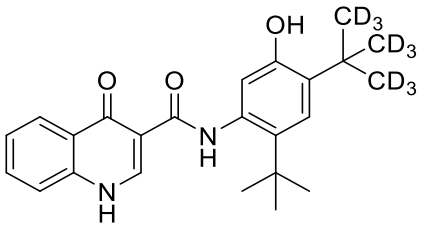
Molecular formula: $C_{32}H_{38}N_7O_4S•Ca_{0.5}$

Tezacaftor: 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide



Molecular formula: $C_{26}H_{27}F_3N_2O_6$

Deutivacaftor: *N*-(2-(*tert*-butyl)-5-hydroxy-4-(2-(methyl-d_3)propan-2-yl-1,1,1,3,3,3-d_6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide



Molecular formula: $C_{24}H_{19}D_9N_2O_3$

CAS number
Vanzacaftor: 2374124-50-0
Tezacaftor: 1152311-62-0
Deutivacaftor: 1413431-07-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

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Australia
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9 DATE OF FIRST APPROVAL

18 NOV 2025

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
	New PI