ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 50 mg/20 mg/4 mg film-coated tablets
Alyftrek 125 mg/50 mg/10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

Each film-coated tablet contains 50 mg of deutivacaftor, 20 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 4 mg of vanzacaftor.

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

Each film-coated tablet contains 125 mg of deutivacaftor, 50 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 10 mg of vanzacaftor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

Purple, round-shaped tablet debossed with “V4” on one side and plain on the other (7.35 mm diameter).

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

Purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other (15 mm × 7 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Alyftrek tablets are indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Alyftrek should only be prescribed by healthcare professionals with experience in the treatment of CF. If the person with CF has an unknown genotype, an accurate and validated genotyping method should be performed to confirm the presence of at least one *CFTR* mutation that is responsive based on clinical and/or *in vitro* data (using a genotyping assay) (see section 5.1). Alyftrek should only be used in people diagnosed with CF. A diagnosis of CF should be made based on diagnostic guidelines and clinical judgement.

There are a limited number of people with CF who harbour mutations not listed in Table 4 that may be responsive to treatment. In these cases, treatment can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision. This excludes people with CF with two Class I (null) mutations (mutations that are known not to produce CFTR protein) as they are not expected to respond to modulator therapy (see sections 4.1, 4.4, and 5.1).

Posology

Monitoring of transaminases (ALT and AST) and total bilirubin is recommended for all patients prior to initiating treatment, 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 (see section 4.4).

Adults and paediatrics 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 deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg
	≥ 40 kg	Two tablets of deutivacaftor 125 mg/tezacaftor 50 mg/vanzacaftor 10 mg

Each dose should be taken in its entirety with fat-containing food, once daily at approximately the same time each day (see Method of administration).

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.

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, or clarithromycin), the dose should be reduced as recommended in Table 2 (see sections 4.4 and 4.5).

Table 2: Dosing schedule for concomitant use with moderate or strong CYP3A inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
≥ 6 years	< 40 kg	Two tablets of deutivacaftor 50 mg/tezacaftor 20 mg/ vanzacaftor 4 mg every other day	Two tablets of deutivacaftor 50 mg/ tezacaftor 20 mg/vanzacaftor 4 mg once a week
	≥ 40 kg	One tablet of deutivacaftor 125 mg/tezacaftor 50 mg/ vanzacaftor 10 mg every other day	One tablet of deutivacaftor 125 mg/ tezacaftor 50 mg/vanzacaftor 10 mg once a week

Special populations

Elderly

No dose adjustment is recommended for the elderly patient population (see sections 4.4 and 5.2).

Hepatic impairment

Mild hepatic impairment (Child-Pugh Class A)

No dose adjustment is recommended. Liver function tests should be closely monitored (see sections 4.4, 4.8, and 5.2).

Moderate hepatic impairment (Child-Pugh Class B)

Use not recommended. D-IVA/TEZ/VNZ should only be considered when there is a clear medical need, and the benefit outweighs the risk. If used, no dose adjustment is recommended. Liver function tests should be closely monitored (see sections 4.4, 4.8, and 5.2).

Severe hepatic impairment (Child-Pugh Class C)

Should not be used (see sections 4.4 and 5.2).

Renal impairment

No dose adjustment is recommended for people with CF who have mild or moderate renal impairment. There is no experience in patients with severe renal impairment or end-stage renal disease (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of D-IVA/TEZ/VNZ in children aged less than 6 years have not yet been established. No clinical trial data are available. D-IVA/TEZ/VNZ should not be used in children less than 1 year of age because of safety-related findings in juvenile rat studies with tezacaftor (see section 5.3).

Method of administration

For oral use. People with CF should be instructed to swallow the tablets whole. The tablets should not be chewed, crushed, or broken before swallowing because there are no clinical data currently available to support other methods of administration.

Tablets 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, cheeses, nuts, whole milk, or meats (see section 5.2).

Food or drink containing grapefruit should be avoided during treatment (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 medicinal product containing elexacaftor, tezacaftor, and ivacaftor, which contains one same (tezacaftor) and one similar (ivacaftor) active ingredient as Alyftrek. Elevated transaminases are common in people with CF and have been observed in some people with CF treated with D-IVA/TEZ/VNZ (see section 4.8). In patients taking IVA/TEZ/ELX in combination with IVA, transaminase elevations have sometimes been associated with concomitant elevations in total bilirubin. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all people with CF prior to initiating treatment, 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.

Treatment should be interrupted, and serum transaminases and total bilirubin should be promptly measured 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). Dosing should be interrupted in the event of ALT or AST > 5 × the upper limit of normal (ULN), or ALT or AST > 3 × ULN with bilirubin > 2 × ULN. Laboratory tests should be closely followed until the abnormalities resolve. Following resolution, the benefits and risks of resuming treatment should be considered (see sections 4.2, 4.8, and 5.2). Patients who resume treatment after interruption should be monitored closely.

In people with CF with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension) D-IVA/TEZ/VNZ should be used with caution 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, 4.8, and 5.2).

Patients who discontinued or interrupted a medicinal product containing tezacaftor or ivacaftor due to adverse reactions

There are no available safety data for D-IVA/TEZ/VNZ in patients who previously discontinued or interrupted treatment with a medicinal product containing tezacaftor or ivacaftor due to adverse reactions. The benefits and risks should be considered before using D-IVA/TEZ/VNZ in these patients. If D-IVA/TEZ/VNZ is used in these patients, they should be closely monitored, as clinically appropriate.

Hepatic impairment

Treatment of patients with moderate hepatic impairment is not recommended. For people with CF with moderate hepatic impairment, the use of D-IVA/TEZ/VNZ should only be considered when there is a clear medical need, and the benefits are expected to outweigh the risks. If used, no dose adjustment is needed.

Patients with severe hepatic impairment should not be treated with D-IVA/TEZ/VNZ (see sections 4.2, 4.8, and 5.2).

Depression and other psychiatric disorders

Depression and anxiety have been reported in patients treated with D-IVA/TEZ/VNZ. Cases of behavioural changes and insomnia have been reported in patients taking a medicinal product

containing elexacaftor, tezacaftor, and ivacaftor, which contains one same (tezacaftor) and one similar (ivacaftor) active ingredient as Alyftrek.

In some cases, symptom improvement was reported after treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, sleep disorders, or unusual changes in behaviour and instruct them to notify their physician if these symptoms occur (see section 4.8).

Renal impairment

There is no experience with D-IVA/TEZ/VNZ in people with CF with severe renal impairment/end-stage renal disease therefore caution is recommended in this population (see sections 4.2 and 5.2).

Mutations unlikely to respond to modulator therapy

Patients with a genotype consisting of two *CFTR* mutations that are known not to produce CFTR protein (i.e., two Class I mutations) are not expected to respond to treatment.

Clinical studies comparing D-IVA/TEZ/VNZ to TEZ/IVA or IVA

No clinical study has been conducted to directly compare D-IVA/TEZ/VNZ to TEZ/IVA or IVA in patients not harbouring *F508del* variants.

Patients after organ transplantation

D-IVA/TEZ/VNZ has not been studied in people with CF who have undergone organ transplantation. Therefore, use in transplanted patients is not recommended. If used, see section 4.5 for interactions with commonly used immunosuppressants.

Rash events

The incidence of rash events was higher in females than in males, particularly in females taking hormonal contraceptives. A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For people with CF taking hormonal contraceptives who develop rash, interrupting treatment with D-IVA/TEZ/VNZ and hormonal contraceptives should be considered. Following the resolution of rash, it should be considered if resuming D-IVA/TEZ/VNZ without hormonal contraceptives is appropriate. If rash does not recur, resumption of hormonal contraceptives can be considered (see sections 4.5 and 4.8).

Elderly

Clinical studies of D-IVA/TEZ/VNZ did not include sufficient number of people with CF aged 65 years and older to determine whether response in these patients is different from younger adults. Dose recommendations are based on the pharmacokinetic profile and knowledge from studies with tezacaftor/ivacaftor (TEZ/IVA) in combination with ivacaftor (IVA), and ivacaftor (IVA) monotherapy (see sections 4.2 and 5.2).

Interactions with medicinal products

CYP3A inducers

Exposures to vanzacaftor (VNZ), tezacaftor (TEZ) and deutivacaftor (D-IVA) are expected to decrease with the concomitant use of moderate or strong CYP3A inducers, potentially resulting in the reduction of D-IVA/TEZ/VNZ efficacy; therefore, co-administration with moderate or strong CYP3A inducers is not recommended (see section 4.5).

CYP3A inhibitors

Exposure to VNZ, TEZ and D-IVA are increased when co-administered with moderate or strong CYP3A inhibitors. Therefore, the dose should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see sections 4.2 and 4.5).

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 (IVA)-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 IVA cannot be excluded. As D-IVA is a deuterated isotopologue of IVA, baseline and follow-up ophthalmological examinations are recommended in people with CF aged less than 18 years initiating treatment with D-IVA/TEZ/VNZ (see section 5.3).

Excipients with known effect

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products affecting the pharmacokinetics of D-IVA/TEZ/VNZ

CYP3A inducers

VNZ, TEZ and D-IVA are substrates of CYP3A. VNZ and D-IVA are sensitive substrates of CYP3A. Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced D-IVA/TEZ/VNZ efficacy. Co-administration with moderate or strong CYP3A inducers is not recommended (see section 4.4).

Examples of moderate or strong CYP3A inducers include:
- rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*), and efavirenz

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased VNZ AUC by 10.5-fold, TEZ AUC by 4.0- to 4.5-fold and D-IVA AUC by 11.1-fold. The dose of D-IVA/TEZ/VNZ should be reduced when co-administered with strong CYP3A inhibitors (see sections 4.2 and 4.4).

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 VNZ, TEZ, and D-IVA AUC by approximately 2.4- to 3.9-fold, 2.1-fold, and 2.9- to 4.8-fold, respectively. The dose of D-IVA/TEZ/VNZ should be reduced when co-administered with moderate CYP3A inhibitors (see sections 4.2 and 4.4).

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

Co-administration of D-IVA/TEZ/VNZ with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of VNZ, TEZ and D-IVA. Food or drink containing grapefruit should be avoided during treatment (see section 4.2).

Ciprofloxacin

D-IVA/TEZ/VNZ was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of TEZ or IVA and is not expected to have a clinically relevant effect on the exposure of VNZ or D-IVA. Therefore, no dose adjustment is necessary during concomitant administration of D-IVA/TEZ/VNZ with ciprofloxacin.

Medicinal products affected by VNZ, TEZ, and D-IVA

CYP2C9 substrates

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

Potential for interaction with transporters

D-IVA/TEZ/VNZ was not evaluated for concomitant use with P-glycoprotein (P-gp) substrates. However, co-administration of tezacaftor/ivacaftor (TEZ/IVA) with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold. Administration of D-IVA/TEZ/VNZ 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.

Based on *in vitro* data, VNZ, TEZ, and D-IVA have low potential to inhibit OATP1B1 at clinically relevant concentrations. D-IVA has a similar OATP1B1 inhibition potential to IVA *in vitro*. Co-administration of TEZ/IVA with pitavastatin, an OATP1B1 substrate, had no clinically relevant effect on the exposure of pitavastatin.

Breast Cancer Resistance Protein (BCRP) Substrates

VNZ and D-IVA are inhibitors of BCRP *in vitro*. Concomitant use of D-IVA/TEZ/VNZ 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.

Hormonal contraceptives

D-IVA/TEZ/VNZ was not evaluated for concomitant use with oral contraceptives. TEZ in combination with IVA and IVA alone have been studied with ethinyl estradiol/norethindrone and were found to have no clinically relevant effect on the exposures of the oral contraceptive. VNZ, TEZ, and D-IVA have low potential to induce or inhibit CYP3A *in vitro*. D-IVA/TEZ/VNZ is not expected to have an impact on the efficacy of oral contraceptives.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of D-IVA/TEZ/VNZ in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Alyftrek during pregnancy.

Breast-feeding

Limited data show that TEZ is excreted in human milk and has been quantified in plasma of breastfed newborns/infants of treated women. VNZ is excreted into the milk of lactating female rats. The effect of D-IVA has not been evaluated, however, limited data show that IVA is excreted in human milk and has been quantified in plasma of breastfed newborns/infants of treated women.

A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Alyftrek therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of VNZ, TEZ, and D-IVA on fertility in humans. The effects of D-IVA on fertility have not been evaluated in rats; however, IVA had an effect on fertility in female and male rats. VNZ and TEZ had no effects on fertility and reproductive performance indices in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

D-IVA/TEZ/VNZ has a minor influence on the ability to drive or use machines. Dizziness has been reported in people with CF receiving TEZ/IVA in combination with IVA as well as IVA monotherapy (see section 4.8). Patients experiencing dizziness should be advised not to drive or use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions in people with CF aged 12 years and older treated with Alyftrek include headache (15.8%) and diarrhoea (12.1%). The frequency of treatment discontinuation, in clinical trials, due to adverse reactions is 3.8%. The most common adverse reactions leading to treatment discontinuation were alanine aminotransferase increased (1.5%) and aspartate aminotransferase increased (1.3%).

The most common serious adverse reactions that occurred with Alyftrek are ALT increased (0.4%) and AST increased (0.4%).

Tabulated list of adverse reactions

Table 3 reflects adverse reactions observed with D-IVA/TEZ/VNZ, TEZ/IVA in combination with IVA, and IVA monotherapy. Adverse reactions 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); not known (cannot be estimated from the available data).

Table 3: Adverse Drug Reactions by Preferred Term, Incidence and Frequency		
System organ class	**Adverse reactions**	**Frequency**
Infections and infestations	Upper respiratory tract infection	very common
	Nasopharyngitis	very common
	Influenza*	very common
	Rhinitis	common
Psychiatric disorders	Depression*	common
	Anxiety*	common
Nervous system disorders	Headache*	very common
	Dizziness	very common
Ear and labyrinth disorders	Ear pain	common
	Ear discomfort	common
	Tinnitus	common
	Tympanic membrane hyperaemia	common
	Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	very common
	Nasal congestion	very common
	Sinus congestion	common
	Pharyngeal erythema	common
Gastrointestinal disorders	Abdominal pain	very common
	Diarrhoea*	very common
	Nausea	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*	common
	Aspartate aminotransferase increased*	common
Skin and subcutaneous tissue disorders	Rash*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation	uncommon
	Gynaecomastia	uncommon
	Nipple disorder	uncommon
	Nipple pain	uncommon
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase increased*	common

* Adverse reactions observed during clinical studies with deutivacaftor/tezacaftor/vanzacaftor.

Description of selected adverse reactions

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 D-IVA/TEZ/VNZ. The incidence of adverse reactions of transaminase elevations was 9.0% with D-IVA/TEZ/VNZ. Of the D-IVA/TEZ/VNZ-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 D-IVA/TEZ/VNZ. 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 (see sections 4.4 and 4.5).

Increased creatine phosphokinase

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

Paediatric population

The safety data of D-IVA/TEZ/VNZ in study 121-105, Cohort B1 was evaluated in 78 people with CF aged 6 to less than 12 years. The safety data of D-IVA/TEZ/VNZ in study 121-102 and study 121-103 was evaluated in 67 people with CF aged 12 to less than 18 years. The safety profile is generally consistent among paediatric and adult patients.

Transaminase elevations

During 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 was 0.0%, 1.3%, and 3.8%, respectively. No Alyftrek-treated patients had transaminase elevation > 3 × ULN associated with elevated total bilirubin > 2 × ULN or discontinued treatment due to transaminase elevations (see section 4.4).

Rash

During study 121-105 in patients aged 6 to less than 12 years, 4 (5.1%) subjects had at least 1 rash event. The rash events were mild in severity. These rashes did not lead to discontinuation or interruption of treatment.

Lenticular opacity

During study 121-105 in patients aged 6 to less than 12 years, 1 (1.3%) person with CF had an event of lenticular opacity.

Other special populations

The safety profile of D-IVA/TEZ/VNZ was generally similar across all subgroups of patients, including analysis by age, gender, baseline percent predicted Forced Expiratory Volume in one second ($ppFEV_1$) and geographic regions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code: R07AX33

Mechanism of action

VNZ and TEZ 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. D-IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of VNZ, TEZ and D-IVA 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 D-IVA/TEZ/VNZ was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. D-IVA/TEZ/VNZ 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 reasonably expected to predict clinical response. 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.

In CF, the presence of one *CFTR* mutation responsive to D-IVA/TEZ/VNZ based on *in vitro* data in FRT cells, will likely result in a clinical response.

Table 4 lists *CFTR* mutations included in the indication for treatment with Alyftrek. The occurrence of *CFTR* mutations listed in this table should not be used in lieu of a diagnosis of cystic fibrosis, nor as a sole determinant for prescribing purposes.

Table 4: *CFTR* mutations identified to be responsive to D-IVA/TEZ/VNZ based on clinical and/or *in vitro* data

1140-1151dup	E116Q	H147del	N1088D	S1118F
1461insGAT	E1221V	H147P	N1195T	S1159F*
1507_1515del9	E1228K	H199Q	N1303I	S1159P[#]
2055del9	E1409K	H199R	N1303K[¶]	S1188L
2183A→G	E1433K	H199Y	N186K	S1251N*
2789+5G→A[†]	E193K[#]	H609L	N187K	S1255P
2851A/G	E217G	H609R	N396Y	S13F
293A→G	E264V	H620P	N418S	S13P
3007del6	E282D	H620Q	N900K	S158N
3131del15	E292K	H939R[#]	P1013H	S182R
3132T→G	E384K	H939R;H949L[‡]	P1013L	S18I
3141del9	E403D[#]	H954P	P1021L	S18N
3143del9	E474K	I1023R	P1021T	S308P
314del9	E527G	I105N	P111L	S341P
3195del6	E56K[#]	I1139V[#]	P1372T	S364P

3199del6	E588V[#]	I1203V	P140S	S434P
3272-26A→G[†]	E60K[#]	I1234L	P205S[#]	S492F
3331del6	E822K[#]	I1234Vdel6aa	P439S	S50P
3410T→C	E831X[†]	I125T	P499A	S519G
3523A→G	E92K[#]	I1269N[#]	P574H	S531P
3601A→C	F1016S[#]	I1366N[#]	P5L[#]	S549I
3761T→G	F1052V[#]	I1366T	P67L[#]	S549N*
3791C/T	F1074L[#]	I1398S	P750L	S549R*
3849+10kbC→T[†]	F1078S	I148L	P798S	S557F
3850G→A	F1099L[#]	I148N	P988R	S589I
3978G→C	F1107L	I148T;H609R[‡]	P99L	S589N[#]
4193T→G	F191V[#]	I175V[#]	Q1012P	S624R
546insCTA[#]	F200I	I331N	Q1100P	S686Y
548insTAC	F311del[#]	I336K*	Q1209P	S737F[#]
711+3A→G[†]	F311L[#]	I336L	Q1291H	S821G
A1006E[#]	F312del	I444S	Q1291R[#]	S898R
A1025D	F433L	I497S	Q1313K	S912L[#]
A1067P	F508C;S1251N[‡ #]	I502T*	Q1352H	S912L;G124
A1067T[#]	F508del*	I506L	Q151K	4V[‡]
A1067V	F508del;R1438W[‡]	I506T	Q179K	S912T
A107G	F575Y[#]	I506V	Q237E[#]	S945L*
A1081V	F587I	I506V;D1168G[‡]	Q237H[#]	S955P
A1087P	F587L	I521S	Q237P	S977F[#]
A120T[#]	F693L(TTG)	I530N	Q30P	S977F;R1438
A1319E	F87L	I556V	Q359K/T360K[‡]	W[‡]
A1374D	F932S	I586V	Q359R[#]	T1036N[#]
A141D	G1047D	I601F[#]	Q372H	T1057R
A1466S	G1047R	I601T	Q452P	T1086A
A155P	G1061R	I618N	Q493L	T1086I
A234D[#]	G1069R[#]	I618T[#]	Q493R	T1246I
A234V	G1123R	I86M	Q552P	T1299I
A238V	G1173S	I980K[#]	Q98P	T1299K
A309D	G1237V	K1060T[#]	Q98R[#]	T164P
A349V[#]	G1244E*	K162E	R1048G	T338I[#]
A357T	G1244R	K464E	R1066C	T351I
A455E*	G1247R	K464N	R1066G	T351S
A455V	G1249E	K522E	R1066H*	T351S;R851
A457T	G1249R[#]	K522Q	R1066L	L[‡]
A462P	G1265V	K951E	R1066M	T388M
A46D	G126D[#]	L1011S	R1070P	T465I
A534E	G1298V	L102R	R1070Q[#]	T465N
A554E[#]	G1349D[#]	L102R;F1016S[‡]	R1070W[#]	T501A
A559T	G149R	L1065P	R1162Q	T582S
A559V	G149R;G576A;R668	L1065R	R117C	T604I
A561E	C[‡]	L1077P*	R117C;G576A;R66	T908N
A566D	G178E[#]	L1227S	8C[‡]	T990I
A613T	G178R[#]	L1324P[#]	R117G[#]	V1008D
A62P	G194R[#]	L1335P[#]	R117H	V1010D
A72D	G194V[#]	L137P	R117L[#]	V1153E[#]
A872E	G213E	L137R	R117L;L997F[‡]	V11I
c.1367_1369dupTT	G213E;R668C[‡]	L1388P	R117P[#]	V1240G[#]
G	G213V	L1480P[#]	R1239S	V1293G[#]
C225R	G226R	L159S	R1283G	V1293I
C491R	G239R	L15P[#]	R1283M[#]	V1415F
C590Y	G253R	L15P;L1253F[‡]	R1283S[#]	V201M[#]

C866Y	G27E	L165S	R1438W	V232A
D110E[#]	G27R	L167R	R248K	V232D[#]
D110H[#]	G314E[#]	L206W*	R258G[#]	V317A
D110N	G314R	L210P	R297Q	V322M
D1152A	G424S	L293P	R31L[#]	V392G
D1152H*	G437D	L327P	R334L[#]	V456A
D1270N[#]	G451V	L32P	R334Q[#]	V456F
D1270Y	G461R	L333F	R347H[#]	V520F
D1312G	G461V	L333H	R347L[#]	V520I
D1377H	G463V	L346P[#]	R347P*	V562I;A1006
D1445N	G480C	L441P	R352Q*	E[‡]
D192G[#]	G480D	L453S	R352W[#]	V562L
D192N	G480S	L467F	R516G	V591A
D373N	G500D	L558F	R516S	V603F
D426N	G545R	L594P	R553Q[#]	V920L
D443Y[#]	G551A	L610S	R555G	V920M
D443Y;G576A;R6	G551D*	L619S	R560S	V93D
68C[‡ #]	G551R	L633P	R560T	W1098C*
D513G	G551S[#]	L636P	R600S	W1282G
D529G	G576A;R668C[‡ #]	L88S	R709Q	W1282R*
D565G	G576A;S1359Y[‡]	L927P	R74Q[#]	W202C
D567N	G622D[#]	L967F;L1096R[‡]	R74Q;R297Q[‡]	W361R
D572N	G622V	L973F	R74Q;V201M;D12	W496R
D579G[#]	G628A	M1101K*	70N[‡]	Y1014C[#]
D58H	G628R	M1101R	R74W[#]	Y1032C[#]
D58V	G85E*	M1137R	R74W;D1270N[‡#]	Y1032N
D614G[#]	G85V	M1137V	R74W;R1070W;D1	Y1073C
D651H	G91R	M1210K	270N[‡]	Y1092H
D651N	G930E	M150K	R74W;S945L[‡]	Y109C
D806G	G970D[#]	M150R	R74W;V201M[‡#]	Y109H
D924N[#]	G970S	M152L	R74W;V201M;D12	Y109N[#]
D979A	G970V	M152V[#]	70N[‡#]	Y122C
D979V[#]	H1054D*	M265R[#]	R74W;V201M;L99	Y1381H
D985H	H1079P	M348K	7F[‡]	Y161C
D985Y	H1085P	M394L	R751L[#]	Y161D
D993A	H1085R	M469V	R75L	Y161S[#]
D993G	H1375N	M498I	R75Q;L1065P[‡]	Y301C
D993Y	H1375P[#]	M952I[#]	R75Q;N1088D[‡]	Y517C
E1104K	H139L	M952T[#]	R75Q;S549N[‡]	Y563N*
E1104V	H139R	M961L	R792G[#]	Y569C
E1126K	H146R		R792Q	Y89C
E116K[#]			R810G	Y913C
			R851L	Y913S
			R933G[#]	Y919C
			S1045Y	
			S108F	

There are people with CF harbouring two rare, non-*F508del CFTR* mutations not listed in Table 4. Provided that they do not harbour two Class I (null) mutations (mutations that are known not to produce CFTR protein) (see section 4.1), they may respond to treatment. In these cases, Alyftrek can be considered when the physician deems the potential benefits outweigh the potential risks and under close medical supervision.

The individual diagnosis of CF should be based on diagnostic guidelines and clinical judgement as considerable variability exists in phenotype for patients harbouring the same genotype.

* Mutations supported by clinical data.
† Non-canonical splice mutations where efficacy is extrapolated from clinical data from other CFTR modulators because these mutations are not amenable to FRT assay.
‡ 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.
¶ N1303K is extrapolated from clinical data from IVA/TEZ/ELX in combination with IVA and supported by Human Bronchial Epithelial (HBE) assay data.
# Mutations are extrapolated from FRT data with TEZ/IVA or IVA monotherapy in which a positive response is indicative of a clinical response.

Non-annotated mutations are included based on the FRT assay with D-IVA/TEZ/VNZ in which a positive response is indicative of a clinical response.

Pharmacodynamic effects

Effects on sweat chloride

In study 121-102 (people with CF heterozygous for a *F508del* and a *CFTR* mutation that predicts either no production of a CFTR protein or a CFTR protein that does not transport chloride and is not responsive to other CFTR modulators (IVA and TEZ/IVA) *in vitro),* the treatment difference of D-IVA/TEZ/VNZ compared to IVA/TEZ/ELX 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 IVA/TEZ/ELX with no *F508del* mutation), the treatment difference of D-IVA/TEZ/VNZ compared to IVA/TEZ/ELX 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 IVA/TEZ/ELX), 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 VNZ maximum recommended dose, and doses up to 3 times over the TEZ and D-IVA maximum recommended doses, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

Clinical efficacy and safety

The efficacy of D-IVA/TEZ/VNZ in people with CF aged 12 years and older was evaluated in two, phase 3, randomised, double-blind, IVA/TEZ/ELX-controlled studies (Studies 121-102 and 121-103). The pharmacokinetic profile, safety, and efficacy of D-IVA/TEZ/VNZ in people with CF aged 6 to less than 12 years are supported with evidence from studies of D-IVA/TEZ/VNZ 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, randomised, double-blind, IVA/TEZ/ELX-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation that predicts either no production of a CFTR protein or a CFTR protein that does not transport chloride and is not responsive to other CFTR

modulators (IVA and TEZ/IVA) *in vitro* A total of 398 people with CF aged 12 years and older received IVA/TEZ/ELX during a 4-week run-in period and were then randomised to receive D-IVA/TEZ/VNZ or IVA/TEZ/ELX during the 52-week treatment period. The mean age was 30.8 years (range 12.2 years, 71.6 years; 14.3% aged under 18 years) and 41% female and 59% male. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 67.1 percentage points (range: 28.0, 108.6), the mean CFQ-R RD score at baseline was 84.4 (range 22.2, 100), 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, randomised, double-blind, IVA/TEZ/ELX-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 IVA/TEZ/ELX with no *F508del* mutation. A total of 573 people with CF aged 12 years and older received IVA/TEZ/ELX during a 4-week run-in period and were then randomised to receive D-IVA/TEZ/VNZ or IVA/TEZ/ELX during the 52-week treatment period. The mean age was 33.7 years (range 12.2 years, 71.2 years; 13.8% aged under 18 years) and 48.9% female and 51.1% male. After the 4-week run-in, the mean $ppFEV_1$ at baseline was 66.8 percentage points (range: 36.4, 112.5), the mean CFQ-R RD score at baseline was 85.7 (range 27.8, 100), 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. The key secondary endpoint evaluated superiority in mean absolute change from baseline in SwCl through week 24.

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**	
		D-IVA/TEZ/ VNZ N = 196	**IVA/TEZ/ELX N = 202**	**D-IVA/TEZ/ VNZ N = 284**	**IVA/TEZ/ELX N = 289**
Primary					
Baseline $ppFEV_1$ (percentage points)	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 (mmol/L)	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	
Other Secondary §					
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; SD: Standard Deviation; 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). FAS was defined as all randomised subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study treatment.
* A 4-week IVA/TEZ/ELX run-in-period was performed to establish an on-treatment baseline.
† The pre-specified non-inferiority margin was -3.0 percentage points.
§ Not controlled for multiplicity.

In Studies 121-102 and 121-103, mean absolute change from baseline in $ppFEV_1$ and absolute change from baseline in sweat chloride through week 24 was maintained through week 52.

Study 121-105

Study 121-105 was an open-label study in people with CF with at least one mutation responsive to IVA/TEZ/ELX. Cohort B1 evaluated the safety, tolerability, and efficacy of D-IVA/TEZ/VNZ in a total of 78 people with CF aged 6 to less than 12 years (mean age 9.1 years (range 6.2 years to 12.0 years), 43.6% female, 56.4% male) during a 24-week treatment period. In Cohort B1, all participants were on IVA/TEZ/ELX at baseline. The mean $ppFEV_1$ at baseline on IVA/TEZ/ELX was 99.7 percentage points (range: 29.3, 146.0), the mean CFQ-R RD score at baseline on IVA/TEZ/ELX was

84.8 (range 16.7, 100), and the mean SwCl at baseline, on IVA/TEZ/ELX, 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, absolute change in CFQ-R respiratory domain score, and number of pulmonary exacerbations (PEx) through week 24.

See Table 6 for a summary of efficacy outcomes.

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

Analysis	Statistic	D-IVA/TEZ/VNZ 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)
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; SD: Standard Deviation; CFQ-R: Cystic Fibrosis Questionnaire-Revised

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with D-IVA/TEZ/VNZ in one or more subset of the paediatric population in cystic fibrosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

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

Table 7: Mean (SD) pharmacokinetic parameters of VNZ, TEZ and D-IVA 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)**
D-IVA 250 mg /TEZ 100 mg /VNZ 20 mg	VNZ	0.812 (0.344)	18.6 (8.08)
	TEZ	6.77 (1.24)	89.5 (28.0)
	D-IVA	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

VNZ, TEZ, and D-IVA 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.

VNZ exposure (AUC) increases approximately 4- to 6-fold when administered with fat-containing meals relative to fasted conditions. D-IVA 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 TEZ (see section 4.2).

Distribution

VNZ and D-IVA are > 99% bound to plasma protein primarily to albumin and alpha 1-acid glycoprotein. TEZ is approximately 99% bound to plasma proteins, primarily to albumin.

After oral administration of D-IVA/TEZ/VNZ, the mean (SD) apparent volume of distribution of VNZ, TEZ and D-IVA was 90.4 L (31.3), 123 L (43.2) and 157 L (47.3), respectively. VNZ, TEZ and D-IVA do not partition preferentially into human red blood cells.

Biotransformation

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

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

D-IVA is primarily metabolized by CYP3A4/5 to form the two major circulating metabolites, M1-D-IVA and M6-D-IVA. M1-D-IVA has approximately one-fifth the potency of D-IVA and is considered pharmacologically active. M6-D-IVA is not considered pharmacologically active.

Elimination

After oral administration of D-IVA/TEZ/VNZ, the mean (SD) apparent clearance values of VNZ, TEZ and D-IVA 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 VNZ, TEZ and D-IVA following administration of the D-IVA/TEZ/VNZ fixed-dose combination tablets are approximately 54.0 (10.1) hours, 92.4 (23.1) hours and 17.3 (2.67) hours, respectively. Based on population pharmacokinetic analysis, the mean (SD) effective half-lives of VNZ, TEZ and D-IVA following administration of the D-IVA/TEZ/VNZ fixed-dose

combination tablets in people with CF 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-VNZ alone, the majority of radioactivity (91.6%) was eliminated in faeces, primarily as metabolites.

Following oral administration of ^{14}C-TEZ 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.

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

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

Hepatic impairment

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

Renal impairment

Urinary excretion of VNZ, TEZ, and D-IVA is negligible (see Elimination).

VNZ alone or in combination with TEZ and D-IVA 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, VNZ exposures appear similar in patients with mild (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 TEZ 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 D-IVA 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).

Race

Race had no clinically meaningful effect on VNZ exposure based on population PK analysis in whites (N = 664) and non-whites (N = 44). The non-white races consisted of 9 Black or African Americans, 7 Asians, 7 with multiple racial background, 2 American Indian or Alaska Native, 2 with other ethnic background, and 17 not collected.

Very limited population PK data indicate comparable exposure of TEZ in whites (N = 652) and non-whites (N = 8). The non-white races consisted of 5 Blacks or African Americans and 3 Native Hawaiians or other Pacific Islanders.

Race had no clinically meaningful effect on the PK of D-IVA in whites (N = 670) and non-whites (N = 41) based on a population PK analysis. The non-white races consisted of 18 Black or African Americans, 2 Asians, 3 with multiple racial background, 1 with other ethnic background, and 17 not collected.

Gender

Based on population PK analysis, there are no clinically relevant differences in exposures of VNZ (433 males compared to 275 females), TEZ, and D-IVA between males and females.

Elderly

Clinical studies of D-IVA/TEZ/VNZ included 2 people with CF aged 65 years and older. This number is not sufficient to determine whether they respond differently from younger people with CF (see sections 4.2 and 4.4).

Paediatric people with CF 6 to less than 18 years of age

VNZ, TEZ, and D-IVA exposures observed in phase 3 studies as determined using population PK analysis are presented by age group in Table 8. VNZ, TEZ, and D-IVA exposures in the 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	Dose	VNZ $AUC_{0\text{-}24h}$ (mcg·h/mL)	TEZ $AUC_{0\text{-}24h}$ (mcg·h/mL)	M1-TEZ $AUC_{0\text{-}24h,\ ss}$ (µg·h/mL)	D-IVA $AUC_{0\text{-}24h}$ (mcg·h/mL)
6 to < 12 years	< 40 kg (N = 70)	VNZ 12 mg qd/ TEZ 60 mg qd/ D-IVA 150 mg qd	13.0 (4.90)	69.1 (20.7)	163 (42.2)	30.2 (11.6)
	≥ 40 kg (N = 8)	VNZ 20 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd	18.6 (7.49)	101 (33.7)	162 (51.5)	48.5 (18.7)
12 to < 18 years	- (N = 66)	VNZ 20 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd	15.8 (6.52)	93.0 (32.5)	149 (41.2)	37.1 (15.3)
≥ 18 years	- (N = 414)		19.0 (8.22)	89.0 (27.2)	130 (35.2)	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

Vanzacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and Pregnancy

VNZ was not teratogenic in rats at 10 mg/kg/day and at 40 mg/kg/day in rabbits (approximately 30 and 22 times, respectively, the MRHD based on AUCs of VNZ).

VNZ had no effects on fertility and early embryonic development in rats at oral doses up to 12.5 mg/kg/day in males and 10 mg/kg/day for females (approximately 19 times for males and 30 times for females the MRHD based on AUC of vanzacaftor). Placental transfer of VNZ was observed in pregnant rats.

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Placental transfer of TEZ was observed in pregnant rats.

Juvenile toxicity studies in rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity, even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are likely not relevant for the indicated paediatric population of 6 years of age and older, for whom P-glycoprotein expression levels are equivalent to levels observed in adults.

Fertility and Pregnancy

TEZ had no effects on fertility and early embryonic development in rats at oral doses up to 200 mg/kg/day in males and 100 mg/kg/day for females (approximately 3 times for males and 3 times for females the MRHD based on AUC of tezacaftor).

Deutivacaftor

D-IVA is a deuterated isotopologue of IVA, with a bridge between their toxicity profiles established through a 13-week rat toxicity study. No additional toxicity studies were conducted for D-IVA, as toxicity data from IVA studies are considered sufficient to demonstrate the toxicity profile of D-IVA.

As for IVA, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility and pregnancy (IVA)

The NOAEL for fertility findings was 100 mg/kg/day (8 times the MRHD based on summed AUCs of IVA and its metabolites) in male rats and 100 mg/kg/day (5 times the MRHD based on summed AUCs of IVA and its metabolites) in female rats.

In the pre- and post-natal study IVA decreased survival and lactation indices and caused a reduction in pup body weights. The NOAEL for viability and growth in the offspring provides an exposure level of approximately 5 times the systemic exposure of IVA and its metabolites in adult humans at the MRHD. Placental transfer of IVA was observed in pregnant rats and rabbits.

Juvenile animals

Findings of cataracts were observed in juvenile rats dosed from postnatal day 7 through 35 with IVA dose levels of 10 mg/kg/day and higher (0.3 times the MRHD based on systemic exposure of IVA and its metabolites). This finding has not been observed in foetuses derived from rat dams treated with IVA on gestation days 7 to 17, in rat pups exposed to IVA to a certain extent through milk ingestion

up to postnatal day 20, in 7-week-old rats, or in 3.5- to 5-month-old dogs treated with IVA. The potential relevance of these findings in humans is unknown (see section 4.4).

Deutivacaftor/tezacaftor/vanzacaftor

Combination repeat-dose toxicity studies in rats involving the co-administration of VNZ, TEZ and D-IVA to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium (E468)
Hypromellose (E464)
Hypromellose acetate succinate
Magnesium stearate (E470b)
Microcrystalline cellulose (E460(i))
Sodium laurilsulfate (E487)

Tablet film coat

Carmine (E120)
Brilliant Blue FCF aluminium lake (E133)
Hydroxypropyl cellulose (E463)
Hypromellose (E464)
Iron oxide red (E172)
Talc (E553b)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Pack sizes

Deutivacaftor 125 mg/tezacaftor 50 mg/vanzacaftor 10 mg film-coated tablets

Alyftrek Pack size of 56 tablets (4 blister foils, each with 14 tablets)

Deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg film-coated tablets

Alyftrek Pack size of 84 tablets (4 blister foils, each with 21 tablets)

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland
Tel: +353 (0)1 761 7299

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1943/001
EU/1/25/1943/002

9. DATE OF FIRST AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu/en.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES) (VX24-121-107) : In order to further characterise the efficacy and safety of deutivacaftor/tezacaftor/vanzacaftor in the treatment of cystic fibrosis in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene including people who have two non-*F508del* mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data), the MAH should conduct and submit the results of a non-interventional study based on data from a patient registry, according to an agreed protocol.	Final CSR December 2030

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 125 mg/50 mg/10 mg film-coated tablets
deutivacaftor/tezacaftor/vanzacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 125 mg of deutivacaftor, 50 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 10 mg vanzacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Swallow the tablets whole.

Take the tablets with fat-containing food.

Take two tablets once a day

Open

Insert tab below to close

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1943/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alyftrek 125 mg/50 mg/10 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 125 mg/50 mg/10 mg tablets
deutivacaftor/tezacaftor/vanzacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 50 mg/20 mg/4 mg film-coated tablets
deutivacaftor/tezacaftor/vanzacaftor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 50 mg of deutivacaftor, 20 mg of tezacaftor, and vanzacaftor calcium dihydrate equivalent to 4 mg of vanzacaftor.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

84 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

Swallow the tablets whole.

Take the tablets with fat-containing food.

Take three tablets once a day

Open

Insert tab below to close

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1943/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Alyftrek 50 mg/20 mg/4 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

Alyftrek 50 mg/20 mg/4 mg
tablets
deutivacaftor/tezacaftor/vanzacaftor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Vertex

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alyftrek 50 mg/20 mg/4 mg film-coated tablets
Alyftrek 125 mg/50 mg/10 mg film-coated tablets
deutivacaftor/tezacaftor/vanzacaftor

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alyftrek is and what it is used for

Alyftrek is a tablet that contains three active substances: deutivacaftor, tezacaftor, and vanzacaftor.

Alyftrek **is for people aged 6 years and over who have CF with at least one mutation** in the *CFTR* (*cystic fibrosis transmembrane conductance regulator*) gene that is responsive to Alyftrek. Cystic fibrosis (CF) is an inherited condition in which the lungs and the digestive system can become clogged with thick, sticky mucus. Alyftrek is intended as a long-term treatment.

Alyftrek works on a protein called CFTR. The protein is damaged in some people with CF, if they have a mutation in the *CFTR* gene. Vanzacaftor and tezacaftor increase the amount of CFTR protein at the cell surface, while deutivacaftor causes the protein to work better.

Alyftrek helps your breathing by improving your lung function. You may also notice that you do not get ill as often, or that it is easier to gain weight.

2. What you need to know before you take Alyftrek

Do not take Alyftrek
- **If you are allergic** to deutivacaftor, tezacaftor, vanzacaftor or any of the other ingredients of this medicine (listed in section 6).

Talk to your doctor and do not take the tablets if this applies to you.

Warnings and precautions

- **Liver damage and worsening liver function in people with and without liver disease has been seen** in some patients taking ivacaftor/tezacaftor/elexacaftor, a medicine that has the same

or similar ingredients as Alyftrek. The worsening of liver function can be serious and may require transplantation.

- **Talk to your doctor if you have liver problems**, or have had them previously.

  Your doctor will do some **blood tests to check your liver** before and during treatment with Alyftrek, especially if your blood tests showed high liver enzymes in the past. Increased liver enzymes in the blood are common in patients with CF, and those taking Alyftrek.

  Tell your doctor right away if you have any signs of liver problems. These are listed in section 4.

- Depression and anxiety have been reported in patients while taking Alyftrek. Changes in behaviour and sleep disorders have been reported in some patients taking ivacaftor/tezacaftor/elexacaftor, a medicine that has the same or similar ingredients as Alyftrek. **Talk to your doctor straight away if you (or someone taking this medicine) experience any of the following symptoms which may be signs of depression or other psychiatric disorders**: sad or altered mood, anxiety, feelings of emotional discomfort or thoughts of harming or killing yourself, sleep difficulties, and/or abnormal behaviour (see section 4).

- **Talk to your doctor if you have kidney problems**, or you have previously had them.

- **If you have two Class I mutations** (mutations known not to make CFTR protein), you should not take Alyftrek, as you are not expected to respond to this medicine.

- **Talk to your doctor** before starting treatment with Alyftrek if you have received **an organ transplant**.

- **Talk to your doctor if you have taken another product with tezacaftor or ivacaftor before and temporarily or permanently stopped because of side effects**. Your doctor may want to see you more often.

- **Talk to your doctor if you are using hormonal contraception** (birth control) – for example, women using the contraceptive pill. This may mean you are more likely to get a rash while taking Alyftrek. Talk to your doctor if you develop a rash while taking Alyftrek.

- **Your doctor may do eye examinations** before and during treatment with Alyftrek. Cloudiness of the eye lens (cataract) without any effect on vision has occurred in some children and adolescents receiving ivacaftor which is similar to deutivacaftor, one of the active substances in Alyftrek.

Children under 6 years of age
Do not give this medicine to children under the age of 6 years because it is not known if Alyftrek is safe and effective in this age group.

Other medicines and Alyftrek
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines can affect how Alyftrek works or may make side effects more likely. In particular, tell your doctor if you take any of the medicines listed below. Your doctor may change the dose of one of these medicines if you take any of these.

- **Antifungal medicines** (used for the treatment of fungal infections). These include fluconazole, itraconazole, ketoconazole, posaconazole and voriconazole.
- **Antibiotic medicines** (used for the treatment of bacterial infections). These include clarithromycin, erythromycin, rifampicin, rifabutin and telithromycin.
- **Seizure medicines** (used for the treatment of epileptic seizures or fits). These include carbamazepine, phenobarbital and phenytoin.

- **Herbal medicines.** These include St. John's wort (*Hypericum perforatum*).
- **Immunosuppressants** (used after an organ transplantation). These include ciclosporin, everolimus, sirolimus and tacrolimus.
- **Cardiac glycosides** (used for the treatment of some heart conditions). These include digoxin.
- **Anticoagulant medicines** (used to prevent blood clots). These include warfarin.
- **Medicines for diabetes**. These include glimepiride and glipizide.
- **Medicines for lowering blood pressure**. These include verapamil.

Alyftrek with food and drink
Avoid food or drinks containing grapefruit during treatment as these may increase the side effects of Alyftrek by increasing the amount of Alyftrek in your body.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before taking this medicine.
- **Pregnancy:** Your doctor will help you decide what is best for you and your child.
- **Breast-feeding:** Tezacaftor has been detected in breastfed babies. There is insufficient information to determine if vanzacaftor or deutivacaftor passes into breast milk; however, ivacaftor has been detected in breastfed babies. Your doctor will consider the benefit of breast-feeding for your baby and the benefit of treatment for you to help you decide whether to stop breast-feeding or to stop treatment.

Driving and using machines
Alyftrek can make you dizzy. If you feel dizzy, do not drive, cycle, or use machines unless you are not affected.

Alyftrek contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

3. How to take Alyftrek

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Alyftrek tablets come in two different strengths. Your doctor will determine the correct dose for you.

Recommended dose for people aged 6 years and older:

Weight	Dose per day	Tablet strength
Less than 40 kg	**Three round-shaped tablets**, once a day	deutivacaftor 50 mg/tezacaftor 20 mg/vanzacaftor 4 mg
40 kg or more	**Two capsule-shaped tablets**, once a day	deutivacaftor 125 mg/tezacaftor 50 mg/ vanzacaftor 10 mg

Take Alyftrek tablets with food that contains fat. Meals or snacks that contain fat include those prepared with butter or oils or those containing eggs. Other fat-containing foods are:
- Cheese, whole milk, whole milk dairy products, yogurt, chocolate
- Meats, oily fish
- Avocados, hummus, soy-based products (tofu)
- Nuts, fat-containing nutritional bars or drinks

Avoid food and drink containing grapefruit while you are taking Alyftrek. See Alyftrek with food and drink in section 2 for more details.

Swallow the tablets whole. Do not chew, crush, or break the tablets before swallowing.

Take at approximately the same time each day. The tablets are for oral use.

You must keep using all your other medicines unless your doctor tells you to stop.

If you have moderate liver problems, this medicine is not recommended but your doctor will decide if it is appropriate for you to take this medicine.

If you have severe liver problems, you should not be taking this medicine. See also *Warnings and precautions* in section 2.

If you take more Alyftrek than you should
Contact your doctor or pharmacist for advice. If possible, take your medicine and this leaflet with you. You may get side effects, including those mentioned in section 4 below.

If you forget to take Alyftrek
If you forget a dose, work out how long it is since the dose you missed.
- **If less than 6 hours** have passed since you missed a dose, take the forgotten tablets as soon as possible. Then go back to your usual schedule.
- **If more than 6 hours** have passed since the missed dose, skip the missed dose, and continue on the original schedule the next day.

Do not take a double dose to make up for any missed tablets.

If you stop taking Alyftrek
Your doctor will tell you how long you need to keep taking Alyftrek. It is important to take this medicine regularly. Do not make changes unless your doctor tells you.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Possible signs of liver problems
Increased liver enzymes in the blood are common in people with CF, and those taking Alyftrek. These may be signs of liver problems:
- Pain or discomfort in the upper right area of the stomach (abdominal) area
- Yellowing of the skin or the white part of the eyes
- Loss of appetite
- Nausea or vomiting
- Dark urine

Depression. Signs of this include sad or altered mood, anxiety, feelings of emotional discomfort.

Tell your doctor straight away if you have any of these symptoms.

Other side effects

Very common (may affect more than 1 in 10 people)
- Increase in liver enzymes (signs of stress on the liver)
- Headache
- Diarrhoea

- Belly (abdominal) pain
- Blocked nose (nasal congestion)
- Upper respiratory tract (nose and throat) infection
- Flu (influenza)
- Redness or soreness in the throat (oropharyngeal pain)
- Dizziness
- Bacteria in sputum

Common (may affect up to 1 in 10 people)
- Depression
- Rash
- Increase creatine phosphokinase (sign of muscle breakdown) seen in blood tests
- Anxiety
- Runny nose (rhinitis)
- Ear pain
- Ear discomfort
- Redness of the throat (pharyngeal erythema)
- Ringing or buzzing in the ears (tinnitus)
- Increased blood flow to the eardrum which can cause redness and inflammation (tympanic membrane hyperaemia)
- Problems with the nerves in the inner ear which can affect hearing and balance (vestibular disorder)
- Sinus problems (sinus congestion)
- Nausea (feeling sick)
- Breast lumps (breast mass)

Uncommon (may affect up to 1 in 100 people)
- Breast inflammation
- Blocked ear (ear congestion)
- Enlargement of the breast in men (gynaecomastia)
- Problems with the nipple
- Nipple pain

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alyftrek

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alyftrek contains
- The active substances are deutivacaftor, tezacaftor and vanzacaftor.

Alyftrek 50 mg/20 mg/4 mg film-coated tablets

Each film-coated tablet contains 50 mg of deutivacaftor, 20 mg of tezacaftor and vanzacaftor calcium dihydrate equivalent to 4 mg of vanzacaftor.

Alyftrek 125 mg/50 mg/10 mg film-coated tablets

Each film-coated tablet contains 125 mg of deutivacaftor, 50 mg of tezacaftor and vanzacaftor calcium dihydrate equivalent to 10 mg of vanzacaftor.

The other ingredients are:
- Tablet core: croscarmellose sodium (E468), hypromellose (E464), hypromellose acetate succinate, magnesium stearate (E470b), microcrystalline cellulose (E460(i)) and sodium laurilsulfate (E487).
- Tablet film coat: Carmine (E120), Brilliant Blue FCF aluminum lake (E133), hydroxypropyl cellulose (E463), hypromellose (E464), iron oxide red (E172), talc (E553b) and titanium dioxide (E171).

See the end of section 2 for important information about the contents of Alyftrek.

What Alyftrek looks like and contents of the pack
Alyftrek 50 mg/20 mg/4 mg film-coated tablets are purple, round-shaped tablet debossed with “V4” on one side and plain on the other.

Alyftrek 125 mg/50 mg/10 mg film-coated tablets are purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other.

Marketing Authorisation Holder
Vertex Pharmaceuticals (Ireland) Limited
Unit 49, Block 5, Northwood Court, Northwood Crescent,
Dublin 9, D09 T665,
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Manufacturer
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Co. Louth
A91 P9KD
Ireland

Almac Pharma Services Limited
Seagoe Industrial Estate
Craigavon
Northern Ireland
BT63 5UA
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/en. There are also links to other websites about rare diseases and treatments.