swissmedic

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Swiss Public Assessment Report

Extension of therapeutic indication

Alyftrek

International non-proprietary name:	vanzacaftor, tezacaftor, deutivacaftor
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	4 mg/ 20 mg/ 50 mg 10 mg/ 50 mg/ 125 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Vertex Pharmaceuticals (CH) GmbH
Marketing authorisation no.:	69398
Decision and decision date:	approved on 23 September 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
D-IVA	Deutivacaftor
ELX	Elexacaftor
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FRT	Fischer rat thyroid
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IVA	Ivacaftor
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
ppFEV1	Percent predicted forced expiratory volume
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TEZ	Tezacaftor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)

TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VNZ	Vanzacaftor

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 3 August 2023.

2.2 Indication and dosage

2.2.1 Requested indication

Alyftrek is indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data (see "Properties/Effects", Table 4).

[An additional 424 mutations are added to Table 4 "List of *CFTR* gene mutations responsive to Alyftrek" of the Information for healthcare professionals, thereby bringing the total number of Alyftrek-responsive mutations to 727.]

2.2.2 Approved indication

Alyftrek is indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data (see "Properties/Effects", Table 4).

[An additional 424 mutations are added to Table 4 "List of *CFTR* gene mutations responsive to Alyftrek" of the Information for healthcare professionals, thereby bringing the total number of Alyftrek-responsive mutations to 727.]

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	16 February 2026
Formal objection	19 February 2026
Response to formal objection	20 February 2026
Formal control completed	24 February 2026
Preliminary decision	28 May 2026
Response to preliminary decision	27 July 2026
Final decision	23 September 2026
Decision	approval

3 Medical context

CF is a multisystem disorder caused by pathogenic mutations of the *CFTR* gene. Defective transport of chloride and/or other *CFTR*-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions. Typical symptoms and signs include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels. Nowadays, CF testing is part of the newborn screening programme in Switzerland. Diagnosis of CF is based on clinical symptoms in at least one organ system, positive newborn screening, or having a sibling with CF and evidence of *CFTR* dysfunction (any of the following: elevated sweat chloride ≥60 mmol/L, presence of two disease-causing mutations in the *CFTR* gene, one from each parental allele, or abnormal nasal potential difference). The incidence of CF in Switzerland ranges from 2.3 to 4.1 per 10,000 live births. Pulmonary disease remains the leading cause of morbidity and mortality in patients with CF. The mortality rate varies with age and is likely to be about 1–2% per year overall. The median predicted survival in 2020 was 59.0 years (95 percent confidence interval: 56.4–65.1 years). *CFTR* modulators are the only causative treatment of CF; however, they are not able to fix the underlying genetic defect. The goals of other treatments in CF are airway clearance, infection prevention, bronchodilation, anti-inflammation, and the prevention and treatment of acute exacerbations. In Respiratory support with supplemental oxygen or nocturnal non invasive positive-pressure ventilation are therapeutic options for cases of advanced lung disease. The last option for CF patients with advanced lung disease is lung transplantation.

More than 2,000 *CFTR* gene mutations have been identified; however, the vast majority (>80% in the US and EU) of people with CF carry either one or two copies of the *F508del-CFTR* mutation. People with CF who do not carry at least one *F508del* mutation have mutations that are individually rare. The most prevalent of these mutations occur in hundreds of people with CF, and in some cases these mutations are found in as few as one or two people with CF.

Alyftrek (VNZ/TEZ/D-IVA) is a once daily *CFTR* modulator therapy. This application sought to expand the list of *CFTR* gene mutations for which Alyftrek is indicated. The proposed extension includes a total of 424 additional *CFTR* mutations:

- 280 mutations supported by in vitro Fischer rat thyroid (FRT) assay data;
- one mutation (*R334W*) supported by extrapolation from clinical evidence obtained in an investigator-initiated French Compassionate Programme; and
- 143 additional mutations identified through updated FRT assay data

There is currently no approved *CFTR* modulator therapy for patients with many of the mutations proposed for inclusion. Consequently, a significant unmet medical need exists in this population.

4 Nonclinical aspects

The applicant submitted new nonclinical pharmacology data to support the requested extension of the indication. This was considered acceptable. From the nonclinical point of view, there are no objections to the approval of the requested new indication.

5 Clinical aspects

5.1 Clinical pharmacology

No new clinical pharmacology aspects were submitted for this application.

5.2 Dose finding and dose recommendation

No new dose finding and dose recommendation aspects were submitted for this application.

5.3 Efficacy

In vitro FRT data
The majority of the proposed mutations were evaluated using the FRT assay, a standardised and reproducible in vitro system that has been used to assess *CFTR* modulator responsiveness.
For 280 additional mutations, treatment with VNZ/TEZ/D-IVA resulted in a *CFTR*-mediated chloride transport improvement of at least 10 percentage points above baseline, meeting the established threshold for responsiveness.

Extrapolation from clinical data: *R334W*
The applicant also proposed the inclusion of the *R334W* mutation based on clinical evidence demonstrating responsiveness to elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA).
Although *R334W* did not reach the predefined FRT responsiveness threshold for VNZ/TEZ/D-IVA, showing an improvement of nine percentage points compared with the required threshold of 10 percentage points, clinical evidence supports its responsiveness. Data from a French compassionate-use programme demonstrated clinically meaningful improvements in sweat chloride concentration and percent predicted forced expiratory volume in one second (ppFEV1) in 14 patients carrying the *R334W* mutation and a non-responsive mutation on the second allele.
The extrapolation of these findings to VNZ/TEZ/D-IVA is considered justified for the following reasons: All ELX/TEZ/IVA-responsive mutations tested to date have also demonstrated responsiveness to VNZ/TEZ/D-IVA in the FRT assay, VNZ and ELX share the same binding site and mechanism of action, and clinical development data for VNZ/TEZ/D-IVA demonstrated clinical benefit across patients carrying *F508del* and 25 other ELX/TEZ/IVA-responsive mutations, involving a total of more than 1,100 subjects.
Given the absence of alternative *CFTR* modulator treatment options for patients with the *R334W* mutation and the observed clinical benefit, the inclusion of *R334W* is considered acceptable.

Additional 143 mutations
Updated study U015 (Version 3.0) was included in the submission, identifying an additional 143 *CFTR* mutations as responsive to VNZ/TEZ/D-IVA based on FRT assay data.
These mutations have been incorporated into the proposed list of responsive mutations.

5.4 Safety

The safety profile of VNZ/TEZ/D-IVA was established through the clinical development programme and post-marketing experience with *CFTR* modulators.
The most commonly observed adverse drug reactions include headache, diarrhoea, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased blood creatine phosphokinase, and rash.
These adverse reactions were generally mild to moderate in severity, and treatment discontinuations due to adverse events were uncommon.
The provided data do not suggest that patients carrying the newly proposed mutations would experience a different safety profile compared with patients carrying currently approved mutations.

Therefore, the established safety profile of VNZ/TEZ/D-IVA is considered applicable to the additional responsive mutations.

5.5 Final clinical benefit risk assessment

Overall, the benefit-risk balance of Alyftrek remains positive and unchanged. The evidence supports the inclusion of the additional *CFTR* mutations based on established FRT responsiveness criteria and, for *R334W*, supportive clinical evidence. No new safety concerns were identified.

The indication extension will provide access to *CFTR* modulator therapy for patients with rare *CFTR* mutations who currently lack approved disease-modifying treatment options, thereby addressing an important unmet medical need in cystic fibrosis.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Alyftrek was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo-pro.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting adverse of reactions.

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

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

Composition

Active substances

Vanzacaftor (as vanzacaftor hemicalcium monohydrate), tezacaftor, deutivacaftor.

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).
Each 4 mg/20 mg/50 mg film-coated tablet contains maximum 0.86 mg sodium.
Each 10 mg/50 mg/125 mg film-coated tablet contains maximum 2.16 mg sodium.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet (tablet)

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

Each film-coated tablet contains vanzacaftor calcium dihydrate equivalent to 4 mg of vanzacaftor, 20 mg of tezacaftor, and 50 mg of deutivacaftor as a fixed-dose combination.
Purple, round-shaped tablet debossed with “V4” on one side and plain on the other (7.35 mm diameter).

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

Each film-coated tablet contains vanzacaftor calcium dihydrate equivalent to 10 mg of vanzacaftor, 50 mg of tezacaftor, and 125 mg of deutivacaftor as a fixed-dose combination.
Purple, capsule-shaped tablet debossed with “V10” on one side and plain on the other (15 mm × 7 mm).

Indications/Uses

Alyftrek is indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data (see “Properties/Effects”, Table 4).

Dosage/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 *F508del* mutation or another responsive mutation (see “Properties/Effects”).
Monitoring of transaminases (ALT and AST) and total bilirubin is recommended for all patients prior to initiating treatment every month during the first 6 months of treatment, every 3 months during the next 6 months, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered (see “Warnings and precautions”).

Usual dosage

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	20 kg - < 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

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

Delayed administration

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) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, or clarithromycin), the dose should be reduced as recommended in Table 2 (see “Warnings and precautions” and “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 “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	20 kg - < 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

Special dosage instructions

Patients with hepatic disorders

- Mild Hepatic Impairment (Child-Pugh Class A): No dose adjustment is recommended. Liver function tests should be closely monitored (see “Warnings and precautions”, “Undesirable effects”, and “Pharmacokinetics”).
- 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 (see “Warnings and precautions”, “Undesirable effects”, and “Pharmacokinetics”).
- Severe Hepatic Impairment (Child-Pugh Class C): Should not be used. Alyftrek has not been studied in people with CF with severe hepatic impairment (see “Pharmacokinetics”).

Patients with renal disorders

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 “Pharmacokinetics”).

Elderly population

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.

Children and adolescents

The safety and efficacy of Alyftrek in children aged less than 6 years have not yet been established. No data are available.

Mode 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 modes of administration.
Alyftrek 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 “Pharmacokinetics”).
Food or drink containing grapefruit should be avoided during treatment with Alyftrek (see “Interactions”).

Contraindications

Hypersensitivity to the active substances or to any of the excipients (see “Composition”).

Warnings and precautions

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 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 Alyftrek. Assessments of transaminases (ALT and AST) and total bilirubin are recommended for all people with CF prior to initiating Alyftrek, every month during the first 6 months of treatment, every 3 months during the next 6 months, 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 bilirubin > 2 × ULN. Follow laboratory tests closely until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment (see “Dosage/Administration”, “Undesirable effects”, and “Pharmacokinetics”). 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), 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 (see “Dosage/Administration”, “Undesirable effects”, and “Pharmacokinetics”).

Patients who discontinued or interrupted 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.

Depression

Depression has been reported in patients treated with 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, unusual changes in behaviour, anxiety, or insomnia, and to seek medical advice immediately if these symptoms present.

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 Alyftrek efficacy; therefore, co-administration with moderate or strong CYP3A inducers is not recommended (see “Interactions”).

CYP3A inhibitors

Exposure to VNZ, TEZ and D-IVA 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 “Dosage/Administration” and “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 (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 Alyftrek (see “Preclinical data”).

Patients after organ transplantation

Alyftrek has not been studied in CF patients after organ transplantation. Therefore, its use is not recommended in patients with organ transplants. See “Interactions” for information on interactions with cyclosporine or tacrolimus.

Sodium

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

Interactions

Effect of other agents on the pharmacokinetics of Alyftrek

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 Alyftrek efficacy. Co-administration of Alyftrek with moderate or strong CYP3A inducers is not recommended (see “Warnings and precautions”).
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 Alyftrek should be reduced when co-administered with strong CYP3A inhibitors (see “Dosage/Administration” and “Warnings and precautions”).
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 Alyftrek should be reduced when co-administered with moderate CYP3A inhibitors (see “Dosage/Administration” and “Warnings and precautions”).
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 VNZ, TEZ and D-IVA. Food or drink containing grapefruit should be avoided during treatment with Alyftrek (see “Dosage/Administration”).

Ciprofloxacin

Alyftrek 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 Alyftrek with ciprofloxacin.

Effect of VNZ, TEZ, and D-IVA on other medicinal products

CYP2C9 substrates

D-IVA 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.

Potential for interaction with transporters

Alyftrek 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 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, 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 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.

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. 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 based on *in vitro* data.

Paediatric population

Interaction studies have only been performed in adults.

Pregnancy, lactation

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) in pregnant women. Animal studies with the single active substances do not indicate direct reproductive toxicity (see “Preclinical data”). As a precautionary measure, use of Alyftrek should be avoided during pregnancy.

Lactation

Limited data show that TEZ and IVA are excreted in human milk. The excretion of D-IVA in the milk has not been investigated. However, in animal studies VNZ, TEZ and IVA passed into the milk (see “Preclinical data”). 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

The effect of VNZ, TEZ, and D-IVA on fertility was not investigated in humans. Animal studies showed no effect of VNZ and TEZ on fertility. In animal studies the effect of D-IVA on fertility has not been evaluated; however, IVA showed an effect on fertility in rats (see “Preclinical data”).

Effects on ability to drive and use machines

The influence of Alyftrek on the ability to drive and use machines has not been specifically investigated.

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 (ELX/TEZ/IVA)-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 ELX/TEZ/IVA. 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%).

Tabulated list of adverse reactions

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); not known (frequency cannot be estimated from the available data).

Table 3: Adverse reactions by preferred term, frequency

System Organ Class (SOC)	**Adverse Drug Reactions (Preferred Term)**	**Frequency for Alyftrek**
Infections and infestations	Influenza	very common
Psychiatric disorders	Depression	common
	Behavioural changes, anxiety, insomnia	not known
Nervous system disorders	Headache	very common
Gastrointestinal disorders	Diarrhoea	very common
Hepatobiliary disorders	Alanine aminotransferase increased	common
	Aspartate aminotransferase increased	common
Skin and subcutaneous tissue disorders	Rash	common
Investigations	Blood creatine phosphokinase increased	common

Safety data from the following study 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.

Description of specific adverse reactions and additional information

Patients who have discontinued or interrupted treatment due to undesirable effects with drugs containing TEZ or IVA were excluded from the two studies. Therefore, safety data on undesirable effects with Alyftrek in patients who have previously discontinued or interrupted drugs containing TEZ or IVA due to undesirable effects are not available.

Studies 121-102 and 121-103 were not designed to evaluate meaningful comparisons of the incidence of adverse reactions between the Alyftrek and ELX/TEZ/IVA treatment groups. For additional information regarding ELX/TEZ/IVA adverse reactions, refer to ELX/TEZ/IVA Prescribing Information.

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 and 0.2%, 1.2% and 3.1% with ELX/TEZ/IVA. The incidence of adverse reactions of transaminase elevations was 9.0% with Alyftrek and 7.1% with ELX/TEZ/IVA. Of the Alyftrek-treated participants, 1.5% and 0.6% ELX/TEZ/IVA treated participants discontinued treatment for elevated transaminases.

Rash events

In Studies 121-102 and 121-103, the incidence of rash events (e.g., rash, rash pruritic) was 11.0% with Alyftrek and 7.7% in ELX/TEZ/IVA. 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 with Alyftrek treatment and 7.6% in males and 7.9% in females with ELX/TEZ/IVA treatment.
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 and 6.5% with ELX/TEZ/IVA treatment. Discontinuation due to increased creatine phosphokinase was 0.2% for Alyftrek-treated patients and 0.2% for ELX/TEZ/IVA-treated patients.

Paediatric population

The safety data of Alyftrek in study 121-105, Cohort B1 was evaluated in 78 people with CF aged 6 to less than 12 years. The safety profile is generally consistent among adolescents and adult patients.

Transaminase elevations (patients age 6-12 years)

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 “Warnings and precautions”).

Rash events (patients age 6-12 years)

During study 121-105, Cohort B1, 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. No Alyftrek-treated patients interrupted or discontinued treatment for rash events.

Increased creatine phosphokinase (patients age 6-12 years)

During study 121-105 in patients aged 6 to less than 12 years, 2 (2.6%) subjects had any creatine kinase (CK) elevation event. Both events were mild in severity. No Alyftrek-treated patients interrupted or discontinued treatment for creatine phosphokinase elevation event.

Specific populations

The safety profile of Alyftrek was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted Forced Expiratory Volume in one second (ppFEV$_1$) and geographic regions.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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 VNZ/TEZ/D-IVA was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. VNZ/TEZ/D-IVA 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 of 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 data and/or on *in vitro* data or extrapolation in FRT cells indicating that VNZ/TEZ/D-IVA increases chloride transport to at least 10% of normal over baseline.

The presence of the *CFTR* mutations listed in Table 4 should not be used in place of a diagnosis of cystic fibrosis nor as the sole factor for prescription purposes.

Table 4: List of *CFTR* Gene Mutations Responsive to Alyftrek						
Based on Clinical Data*						
A455E	*G551D*†	*L1077P*†	*R352Q*	*S1251N*	*S945L*	*W1098C*†
D1152H	*G85E*†	*L206W*	*R75Q*	*S549N*	*V562I*	*W1282R*
F508del†	*H1054D*	*M1101K*†	*S1159F*	*S549R*	*V754M*	*Y563N*†
G1244E	*I336K*	*R1066H*				
Based on *in vitro* Data‡						
1140-1151dup	*D192N*	*G1249R*	*I203M*	*M150K*	*R1283G*	*S977F*
1461insGAT	*D249Y*	*G1265V*	*I331N*	*M150R*	*R1283M*	*S977F;R1438W*§
1507_1515del9	*D373N*	*G126D*	*I336L*	*M152L*	*R1283S*	*T1036I*
1650C/G	*D426N*	*G1298V*	*I444S*	*M152V*	*R1422W*	*T1036N*
2055del9	*D443Y*	*G1349D*	*I444T*	*M265R*	*R1438W*	*T1053I*
2183A→G	*D44G*	*G149R*	*I497S*	*M348K*	*R1453W*	*T1057R*
2851A/G	*D443Y;G576A;R668C*§	*G149R;G576A;R668C*§	*I502N*	*M394L*	*R170C*	*T1086A*
293A→G	*D513G*	*G178E*	*I502T*	*M469V*	*R170H*	*T1086I*
3007del6	*D529G*	*G178R*	*I506L*	*M498I*	*R248K*	*T1246I*
3131del15	*D537N*	*G194R*	*I506T*	*M595V*	*R248T*	*T1299I*
3132T→G	*D565G*	*G194V*	*I506V*	*M952I*	*R258G*	*T1299K*
3141del9	*D567N*	*G213E*	*I506V;D1168G*§	*M952T*	*R297Q*	*T1396P*

3143del9	D572N	G213E;R668C[§]	I521S	M961L	R31C	T164P
314del9	D579G	G213V	I530N	N1088D	R31L	T338I
3195del6	D58H	G226R	I539T	N1195T	R334L	T351I
3199del6	D58V	G239R	I556V	N1303I	R334Q	T351S
3331del6	D614G	G241W	I586V	N1303K[‡]	R347H	T351S;R851L[§]
3410T→C	D651H	G253R	I601F	N186K	R347L	T388M
3523A→G	D651N	G27E	I601T	N187K	R347P	T465I
3601A→C	D806G	G27R	I616T	N287K	R352G	T465N
3761T→G	D828G	G314A	I618N	N287Y	R352W	T501A
3791C/T	D836Y	G314E	I618T	N396Y	R3M	T582I
3850G→A	D891G	G314R	I807M	N418S	R516G	T582S
3978G→C	D924N	G424S	I86M	N847S	R516S	T604I
4193T→G	D979A	G437D	I980K	N900K	R553Q	T896I
546insCTA	D979V	G451V	I982M	P1013H	R555G	T908N
548insTAC	D985H	G461R	I991M	P1013L	R55K	T990I
A1006E	D985Y	G461V	K1060T	P1021L	R560S	V1008D
A1018E	D993A	G463D	K1080Q	P1021T	R560T	V1010D
A1025D	D993G	G463V	K162E	P1050A	R600S	V1108L
A1067P	D993Y	G480C	K464E	P111A	R668C	V1114L
A1067T	deltaM1140	G480D	K464N	P111L	R709Q	V1153E
A1067V	E1104K	G480S	K481E	P1372T	R74Q	V11I
A107G	E1104V	G500D	K522E	P140S	R74Q;R297Q[§]	V1240G
A1081V	E1123del	G544S	K522Q	P205S	R74Q;V201M;D1270N[§]	V1293G
A1087P	E1126K	G545R	K536E	P355L	R74W	V1293I
A1136T	E116K	G551A	K564E	P41R	R74W;D1270N[§]	V1318A
A120T	E116Q	G551R	K598E	P439S	R74W;R1070W;D1270N[§]	V1415F
A1285G	E1221V	G551S	K68E	P477S	R74W;S945L[§]	V201M
A1285V	E1228K	G576A	K951E	P499A	R74W;V201M[§]	V232A
A1319E	E1401G	G576A;R668C[§]	L100V	P499S	R74W;V201M;D1270N[§]	V232D
A1364V	E1409K	G576A;S1359Y[§]	L1011S	P574H	R74W;V201M;L997F[§]	V317A
A1374D	E1433K	G622D	L102R	P5L	R74W;V201M;Q1268R[§]	V322M
A141D	E193K	G622V	L102R;F1016S[§]	P67L	R751L	V392G
A1466S	E217G	G628A	L1040F	P731L	R75L	V393L
A155P	E257G	G628R	L1065P	P750L	R75Q;L1065P[§]	V456A
A209S	E264V	G723V	L1065R	P798S	R75Q;N1088D[§]	V456F
A234D	E279D	G85V	L1227S	P988R	R75Q;S549N[§]	V520F
A234V	E282D	G91R	L1260P	P99L	R765S	V520I
A238V	E292K	G930E	L1324P	P99R	R766K	V562I;A1006E[§]
A300D	E384K	G970D	L1335F	Q1012P	R792G	V562L
A309D	E403D	G970S	L1335P	Q1100P	R792Q	V591A
A349V	E474K	G970V	L1339F	Q1209P	R810G	V603F
A357T	E479D	H1054Y	L137P	Q1238R	R851L	V855I
A455V	E527G	H1079P	L137R	Q1291H	R933G	V915L
A457P	E528A	H1085P	L1388P	Q1291R	S1045Y	V920L
A457T	E56K	H1085R	L145H	Q1309H	S108F	V920M
A462P	E588K	H1197L	L145V	Q1313K	S1118F	V938G
A46D	E588V	H1375N	L1480P	Q1352H	S1141N	V93D
A46V	E60K	H1375P	L159S	Q151K	S1159P	V93G
A534E	E725K	H1375R	L15P	Q179K	S1188L	W1282G
A554E	E822K	H139L	L15P;L1253F[§]	Q237E	S1188P	W202C
A559T	E826K	H139R	L165S	Q237H	S1235R	W361R
A559V	E92K	H139Y	L167R	Q237P	S1255P	W496R
A561E	F1016S	H146R	L183I	Q2X	S1362N	W79R
A566D	F1052V	H147del	L210P	Q30P	S13F	Y1014C

A613T	*F1074L*	*H147P*	*L227P*	*Q359K/T360K*§	*S13P*	*Y1014DEL*
A62P	*F1078S*	*H199Q*	*L293P*	*Q359R*	*S1426F*	*Y1032C*
A72D	*F1099L*	*H199R*	*L320V*	*Q372H*	*S158G*	*Y1032N*
A872E	*F1107L*	*H199Y*	*L327P*	*Q452P*	*S158N*	*Y1073C*
A959V	*F1286S*	*H609L*	*L32P*	*Q493L*	*S158R*	*Y1092H*
A9V	*F191V*	*H609R*	*L333F*	*Q493R*	*S158T*	*Y109C*
C128R	*F200I*	*H620P*	*L333H*	*Q552P*	*S182R*	*Y109H*
C1355F	*F311del*	*H620Q*	*L346P*	*Q715H*	*S18I*	*Y109N*
c.1367_1369dupTTG	*F311L*	*H939R*	*L365P*	*Q799K*	*S18N*	*Y122C*
C225R	*F312del*	*H939R;H949L*§	*L441P*	*Q890R*	*S308P*	*Y1381H*
C225Y	*F433L*	*H949L*	*L453S*	*Q98P*	*S341P*	*Y161C*
C491R	*F508C*	*H954P*	*L467F*	*Q98R*	*S364P*	*Y161D*
C590Y	*F508C;S1251N*§	*I1023R*	*L558F*	*R1048G*	*S42F*	*Y161S*
C76W	*F508del;R1438W*§	*I1027T*	*L568F*	*R1066C*	*S434P*	*Y301C*
C866W	*F575Y*	*I105N*	*L594P*	*R1066G*	*S485C*	*Y517C*
C866Y	*F587I*	*I1051V*	*L610S*	*R1066L*	*S492F*	*Y569C*
CFTRdup22,23	*F587L*	*I1139V*	*L619S*	*R1066M*	*S50P*	*Y569H*
CFTRdup1-3	*F693L(TTG)*	*I119M*	*L633P*	*R1066P*	*S519G*	*Y577F*
D110E	*F834L*	*I119V*	*L636P*	*R1070P*	*S531P*	*Y84H*
D110H	*F87L*	*I1203V*	*L88S*	*R1070Q*	*S549I*	*Y89C*
D110N	*F932S*	*I1230T*	*L927P*	*R1070W*	*S557F*	*Y913C*
D112N	*F994C*	*I1234L*	*L967F;L1096R*§	*R1097H*	*S589I*	*Y913S*
D1152A	*G1047D*	*I1234Vdel6aa*	*L967S*	*R1128G*	*S589N*	*Y919C*
D1154G	*G1047R*	*I125T*	*L973F*	*R1162L*	*S624R*	
D1154N	*G1061R*	*I1269N*	*L986P*	*R1162Q*	*S686Y*	
D1168G	*G1069R*	*I1366N*	*L997F*	*R117C*	*S737F*	
D1270N	*G1123R*	*I1366T*	*M1028R*	*R117C;G576A;R668C*§	*S821G*	
D1270Y	*G1127E*	*I1398S*	*M1101R*	*R117G*	*S898R*	
D1305E	*G1173S*	*I148L*	*M1137R*	*R117H*	*S912L*	
D1312G	*G1237V*	*I148N*	*M1137V*	*R117L*	*S912L;G1244V*§	
D1377H	*G1244R*	*I148T*	*M1157I*	*R117L;L997F*§	*S912T*	
D1445N	*G1247R*	*I148T;H609R*§	*M1210K*	*R117P*	*S912W*	
D192G	*G1249E*	*I175V*	*M1354T*	*R1239S*	*S955P*	
Based on Extrapolation						
1341G→A¶	*2789+2insA*¶	*3041-15T→G*¶	*3849+10kbC→T*¶	*3850-3T→G*¶	*5T;TG13*¶	*R334W*#
1898+3A→G¶	*2789+5G→A*¶	*3272-26A→G*¶	*3849+4A→G*¶	*4005+2T→C*¶	*621+3A→G*¶	*E831X*¶
2752-26A→G¶	*296+28A→G*¶	*3600G→A*¶	*3849+40A→G*¶	*5T;TG12*¶	*711+3A→G*¶	

* Clinical data is obtained from Studies 121-102 and 121-103.

† This mutation is also predicted to be responsive by FRT assay with Alyftrek.

‡ The *N1303K* mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by 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.

¶ Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

The *R334W* mutation is predicted to be responsive by extrapolation of clinical data from published literature with ELX/TEZ/IVA.

Pharmacodynamics

Effects on sweat chloride

In study 121-102 (people with CF heterozygous for a *F508del* and a *CFTR* mutation that results in a protein that is not responsive to IVA or TEZ/IVA [minimal function mutation]) the treatment difference of Alyftrek compared to ELX/TEZ/IVA 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 ELX/TEZ/IVA with no *F508del* mutation), the treatment difference of Alyftrek compared to ELX/TEZ/IVA 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 ELX/TEZ/IVA), 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

After an exposure corresponding up to 6 times compared to exposure after administration of the VNZ maximum recommended dose, and of doses up to 3 times over the TEZ and D-IVA maximum recommended doses, no clinically relevant QT/QTc interval prolongation in healthy subjects was observed.

Clinical efficacy

The efficacy of Alyftrek in people with CF aged 12 years and older was evaluated in two, phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled studies (studies 121-102 and 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, ELX/TEZ/IVA-controlled study in people with CF heterozygous for *F508del* and a *CFTR* mutation that results in a protein that is not responsive to IVA or TEZ/IVA (minimal function mutation). A total of 398 people with CF aged 12 years and older (mean age 30.8 years) received ELX/TEZ/IVA during a 4-week run-in period and were then randomized to receive Alyftrek or ELX/TEZ/IVA 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, ELX/TEZ/IVA-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 ELX/TEZ/IVA with no *F508del* mutation. A total of 573 people with CF aged 12 years and older (mean age 33.7 years) received ELX/TEZ/IVA during a 4-week run-in period and were then randomized to receive Alyftrek or ELX/TEZ/IVA 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. The key secondary endpoint evaluated superiority in mean absolute change from baseline in SwCl through week 24.

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 ELX/TEZ/IVA.

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[Fehler! Textmarke nicht definiert.Fehler! Textmarke nicht definiert.]

Analysis*	Statistic	Study 121-102		Study 121-103	
		Alyftrek N = 196	ELX/TEZ/IVA N = 202	Alyftrek N = 284	ELX/TEZ/IVA 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	

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; SE: Standard Error; 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 ELX/TEZ/IVA run-in-period was performed to establish an on-treatment baseline.
# The pre-specified non-inferiority margin was -3.0 percentage points.

In study 121-102 and study 121-103, the rate of pulmonary exacerbations up to week 52 and the absolute change in CFQ-R RD (Cystic Fibrosis Questionnaire-Revised respiratory domain) up to week 24 from baseline were similar in patients treated with ALYFTREK and ELX/TEZ/IVA. The statistical significance of these results were not provided as they were not included in the pre-specified multiple testing procedure.

Study 121-105

Study 121-105 was multicohort, open-label study in people with CF with at least one mutation responsive to ELX/TEZ/IVA. 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 of age. 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 ELX/TEZ/IVA at baseline. The mean $ppFEV_1$ at baseline on ELX/TEZ/IVA was 99.7 percentage points (range: 29.3, 146.0) and the mean SwCl at baseline, on ELX/TEZ/IVA, 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. Secondary efficacy endpoints included absolute change in $ppFEV_1$, and absolute change in SwCl, through week 24.

See Table 6 for a summary of efficacy outcomes.

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

Analysis	Statistic	VNZ/TEZ/D-IVA 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)

CI: Confidence Interval; $ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second.

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Pharmacokinetics

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 VNZ/TEZ/D-IVA plasma concentrations reach steady state within 20 days for VNZ, within 8 days for TEZ, and within 8 days for D-IVA.

Upon dosing VNZ/TEZ/D-IVA 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 VNZ/TEZ/D-IVA 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)
VNZ 20 mg/TEZ 100 mg/D-IVA 250 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 “Dosage/Administration”).

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 VNZ/TEZ/D-IVA, 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.

Metabolism

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. Relative to IVA, D-IVA exhibited more metabolic stability and formed less M1-D-IVA, the deuterated-equivalent of M1-IVA. M1-D-IVA has approximately one-fifth the potency of D-IVA and is considered pharmacologically active. M6-D-IVA is the other major metabolite of D-IVA, the deuterated-equivalent of M6-IVA, and is not considered pharmacologically active.

Elimination

After oral administration of VNZ/TEZ/D-IVA, 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 VNZ/TEZ/D-IVA 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 VNZ, TEZ and D-IVA following administration of the VNZ/TEZ/D-IVA 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-VNZ alone (91.6%), the majority of radioactivity 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 and ^{14}C-IVA are excreted in the faeces. Major excreted metabolites of D-IVA were M1-D-IVA and M6-D-IVA and major excreted metabolites for IVA were M1-IVA and M6-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.)

Kinetics in specific patient groups

Hepatic impairment

VNZ/TEZ/D-IVA has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C). Following a single dose of VNZ/TEZ/D-IVA, 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 “Excretion”).
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/1.73 m^2) or in people with CF with end-stage renal disease. Based on population pharmacokinetic (PK) analysis, VNZ exposures were 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 “Dosage/Administration”).

Elderly patients

Clinical studies of VNZ/TEZ/D-IVA 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 (see “Dosage/Administration”).

Children and adolescents 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)**	**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-IVA150 mg qd	13.0 (4.90)	69.1 (20.7)	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)	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)	37.1 (15.3)
≥ 18 years	- (N = 414)		19.0 (8.22)	89.0 (27.2)	39.3 (15.3)
SD: Standard Deviation; AUC_{0-24h}: Area Under the Concentration versus time curve at steady state; qd: once daily.					

Race

Race had no clinically meaningful effect on VNZ exposure based on population PK analysis in whites (N = 664 and non-whites (N = 43). 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 16 not collected.
Very limited 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, TEZ, and D-IVA between males and females.

Preclinical data

Vanzacaftor/tezacaftor/deutivacaftor

The toxicity study after repeated dosing with the drug combination in rats to assess the potential for additive and/or synergistic toxicity did not produce any unexpected toxicities or interactions. No safety pharmacology, genotoxicity, carcinogenicity, fertility, reproductive or developmental studies have been conducted with Alyftrek. However, studies with the individual substances and a toxicity study after repeated administration are available.

Vanzacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, reproductive or developmental toxicity, and carcinogenic potential (based on a 6 month study in Tg.rasH2 mice and a 2 year study in Sprague Dawley rats). Placental transfer of VNZ was observed in pregnant rats.

Juvenile toxicity

No adverse effects were observed in juvenile rats treated with VNZ doses up to 25 mg/kg/day (28 times the MRHD for female rats and, 35 times the MRHD for male rats based on the AUC of VNZ) from 7 to 70 days after birth.

Tezacaftor

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

Reproductive toxicity

Tezacaftor did not cause reproductive system toxicity in male and female rats at 100 mg/kg/day, the highest dose evaluated (approximately 3 times the MRHD based on summed AUCs of tezacaftor and M1-TEZ). Tezacaftor had no effect on the fertility and reproductive performance indices of male and female rats at doses up to 100 mg/kg/day (approximately 3 times the MRHD based on the summed AUCs of tezacaftor and M1-TEZ). Tezacaftor was not teratogenic in pregnant rats and rabbits at doses approximately 3 times and 0.2 times, respectively, the tezacaftor exposure in humans at the therapeutic dose. In a pre-and post-natal development study, tezacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally at 25 mg/kg/day (approximately 1 time the MRHD based on summed AUCs for tezacaftor and M1-TEZ). At maternally toxic doses (≥50 mg/kg/day), tezacaftor produced lower foetal body weights, a lower fertility index, and effects on estrous cyclicity (increased cycle length and decrease in number of cycles). At the highest dose (100 mg/kg/day), tezacaftor related effects in offspring included poor pup survival to weaning, preweaning developmental effects, and sexual maturation delays. Placental transfer of TEZ was observed in pregnant rats.

Toxicity tests with juvenile animals

Studies in rats exposed from 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 6 years of age and older, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.

Deutivacaftor

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

D-IVA is a deuterated isotopologue of IVA with an established toxicity profile similar to IVA based on a 13-week single-agent repeat dose toxicity study; therefore, reproductive toxicity data and data on the carcinogenic potential of IVA are expected to be equivalent to D-IVA.

Carcinogenicity

No carcinogenicity studies have been conducted with D-IVA. Based on conventional studies on the carcinogenic potential with ivacaftor, the preclinical data do not indicate any particular hazards for humans.

Reproductive toxicity

With D-IVA no reproductive toxicity studies have been conducted. Ivacaftor affected the fertility and reproductive performance indices of male and female rats at doses of 200 mg/kg/day (approximately 11 and 7 times the MRHD for D-IVA, respectively, based on the summated AUCs of ivacaftor and its metabolites). Among the female animals ivacaftor was associated with a reduction in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the oestrous cycle. Ivacaftor also increased the number of females in which all embryos were not viable and reduced the number of viable embryos. Slight decreases of the seminal vesicle weights were observed in males. These impairments of fertility and reproductive performance in rats under a dose of 200 mg/kg/day were attributed to severe toxicity. No effects on male or female fertility and reproductive performance indices were observed after doses of ≤ 100 mg/kg/day (approximately 8 times and 5 times, respectively, the MRHD for D-IVA based on the summated AUCs of ivacaftor and its metabolites).
Ivacaftor was not teratogenic in rats after 200 mg/kg/day and in rabbits after 100 mg/kg/day (approximately 7 and 9 times the MRHD for D-IVA, respectively, based on the sum of AUCs of ivacaftor and its metabolites for rat and ivacaftor alone for rabbit). Effects on foetal body weight and slight increases in common variations in skeletal development were found in rats at doses that were associated with significant toxicity in the dam.
In a pre- and post-natal development study in pregnant rats at Ivacaftor-doses above 100 mg/kg/day (approximately 7 times the MRHD for D-IVA based on the sum of AUCs of IVA and its metabolites), IVA resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights. Placental transfer of IVA was observed in pregnant rats and rabbits.

Toxicity tests with 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 “Warnings and precautions”).

Lactation in animal studies

The excretion of D-IVA in the milk has not been evaluated; however, IVA is excreted into the milk of lactating female rats. Exposure in rats of ^{14}C-VNZ, ^{14}C-TEZ and ^{14}C-IVA in milk was approximately 0.2, 3.0, and 1.5 times, respectively, the value observed in plasma (based on AUC).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging.
Keep out of the reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69398 (Swissmedic)

Packs

Alyftrek, film-coated tablets

- *Vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg film-coated tablets*
  Alyftrek Pack size of 84 tablets (4 foil blisters, each with 21 tablets) [A]
- *Vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg film-coated tablets*
  Alyftrek Pack size of 56 tablets (4 foil blisters, each with 14 tablets) [A]

Marketing authorisation holder

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