swissmedic

Date: 3 December 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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 15 October 2025

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
AESI	Adverse event of special interest
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
BCRP	Breast cancer resistance protein
BID	*Bis in die*, twice a day
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
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)
FDC	Fixed-dose combination
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBE cells	Human bronchial epithelial cells
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
LFT	Liver function test
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
PEx	Pulmonary exacerbation
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PND	Postnatal days
PopPK	Population pharmacokinetics
ppFEV1	Percent predicted forced expiratory volume

PSP	Pediatric study plan (US FDA)
QD	*Quaque die*, once a day
RMP	Risk management plan
SAE	Serious adverse event
SwCl	Sweat chloride
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TEZ	Tezacaftor
TK	Toxicokinetics
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

New active substance status
The applicant requested new active substance status for vanzacaftor in the above-mentioned medicinal product.

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 or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

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).

2.2.3 Requested dosage

Summary of the requested standard dosage:

For patients 6 years and older with a body weight below 40 kg:
Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg once daily.

For patients 6 years and older with a body weight of 40 kg and more:
Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	28 June 2024
Formal control completed	5 July 2024
List of Questions (LoQ)	8 October 2024
Response to LoQ	6 January 2025
Preliminary decision	3 April 2025
Response to preliminary decision	2 June 2025
Labelling corrections and/or other aspects	31 July 2025
Response to labelling corrections and/or other aspects	1 September 2025
Final decision	15 October 2025
Decision	approval

3 Medical context

CF is a multisystem disorder caused by pathogenic mutations of the *CFTR* gene. Deranged 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 1 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 2 disease-causing mutations in the CFTR gene, 1 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. Other treatments in CF have the goal of airway clearance, infection prevention, bronchodilation, anti-inflammation, and the prevention and treatment of acute exacerbations.
In case of advanced lung disease, respiratory support with supplemental oxygen or nocturnal non-invasive positive-pressure ventilation are therapeutic options. The last option for CF patients with advanced lung disease is lung transplantation.

There are 4 CFTR modulators/combinations approved in Switzerland for the treatment of CF for different mutations. Alyftrek contains the new active substances vanzacaftor (VNZ) and deutivacaftor (D-IVA) in combination with the known active substance tezacaftor (TEZ). VNZ and TEZ are so-called CFTR correctors and D-IVA is a CFTR potentiator. Correctors facilitate the cellular processing and trafficking of CFTR to increase the quantity of CFTR protein at the cell surface. Potentiators increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance chloride transport. In combination, the active substances increase the quantity and function of CFTR at the cell surface.

4 Quality aspects

4.1 Drug substance

Drug substance – vanzacaftor

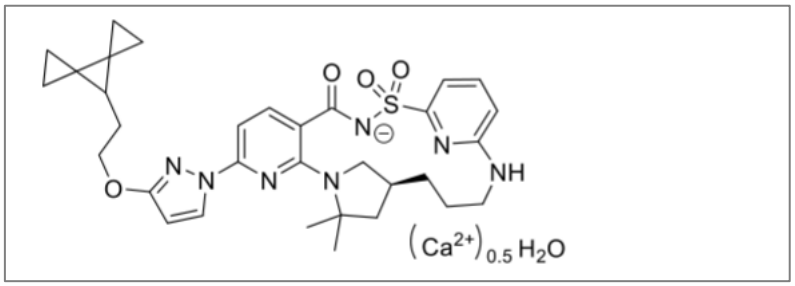
INN: Vanzacaftor

Chemical name: calcium bis((14S)-8-[3-(2-{dispiro[2.0.2⁴.1³] heptan-7-yl}ethoxy)pyrazol-1-yl]-12,12-dimethyl-2,2,4-trioxo-2λ⁶-thia-3,9,11,18,23-pentaazatetracyclo[17.3.1.1¹¹,¹⁴.0⁵,¹⁰]tetracosa-1(23),5,7,9,19,21-hexaen-3-ide) dihydrate

Molecular formula: $C_{32}H_{38}N_7O_4S \bullet Ca_{0.5} \bullet H_2O$

Molecular mass: 654.82 g/m

Molecular structure:



Physicochemical properties: Vanzacaftor is a white to off-white solid, slightly hygroscopic, and practically insoluble under physiological conditions (pH 1.1 to pH 6.8). Calcium salt Form D is used as this is the most thermodynamically stable form.

Synthesis: The drug substance is obtained through a multi-stage synthetic process, involving macrocyclisation, coupling reactions, and slat formation and purification.

Specification: In order to ensure a consistent quality of vanzacaftor drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period. Based on the results, a satisfactory retest period has been established when stored in double low density polyethylene (LDPE) bags placed in a foil bag to protect from light.

Drug substance – tezacaftor

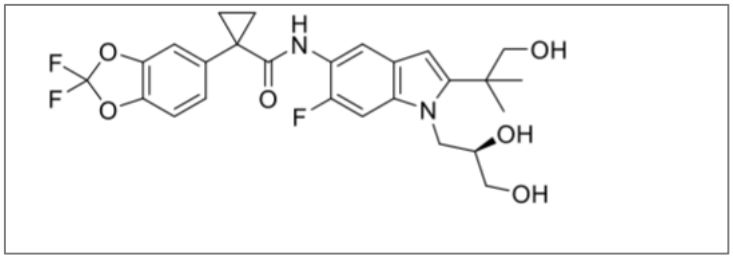
INN: Tezacaftor

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

Molecular formula: 520.50 g/mol

Molecular mass: $C_{26}H_{27}N_2F_3O_6$

Molecular structure:



Physicochemical properties: Tezacaftor is a white to off-white non-hygroscopic solid, practically insoluble under physiological conditions (pH 1.1 to pH 6.8), and very slightly soluble in fed state simulated intestinal fluid.

Synthesis: The drug substance is obtained through a multi-stage synthetic process, involving cross-coupling reaction, intermediate coupling reactions, and multi-crystallisation steps to yield the final drug substance, tezacaftor. The drug substance polymorph A is the thermodynamically stable form.

Specification: In order to ensure a consistent quality of tezacaftor drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period. Based on the results, a satisfactory retest period has been established when stored in double low density polyethylene (LDPE) bags.

Drug substance – deutivacaftor

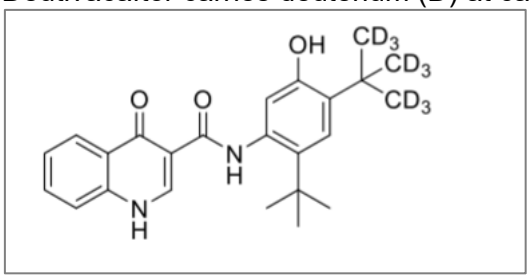
INN: Deutivacaftor

Chemical name: N-(2-(tert-butyl)-5-hydroxy-4-(2-(methyl-d3)propan-2-yl-1,1,1,3,3,3-d6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide

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

Molecular mass: 401.55g/mol

Molecular structure: Deutivacaftor carries deuterium (D) at carbon positions 19, 20, and 21



Physicochemical properties: Deutivacaftor is a white to off-white non-hygroscopic solid, practically insoluble under physiological conditions (pH 1.1 to pH 6.8), and very slightly soluble in fed state simulated intestinal fluid. The drug substance is typically observed as a mixture of 2 major crystalline neat polymorphic forms (B and C).

Synthesis: The drug substance is obtained through a multi-stage synthetic process, involving hydrolysis, coupling reactions, crystallisation, and methonalysis to yield deutivacaftor.

Specification: In order to ensure a consistent quality of deutivacaftor drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability: Appropriate stability data have been generated, resulting in a suitable retest period. Based on the results, a satisfactory retest period has been established when stored in double low density polyethylene (LDPE) bags.

4.2 Drug product

Description and composition: Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) drug product is an immediate-release film-coated tablet for oral administration. Two strengths of Alyftrek are available: Alyftrek 4/20/50 mg and Alyftrek 10/50/125 mg. Both strengths are coated with a purple film and can be differentiated by tablet shape (round and oval) and the characteristic debossing “V4” or “V10” on 1 side of the tablet of the respective strengths.

Manufacture: Manufacturing consists of mixing vanzacaftor drug substance with a spray-dried dispersion of tezacaftor, a spray-dried dispersion of deutivacaftor, and excipients. The mixture is compacted and further mixed and compressed into tablets, which are then film coated.

Specification: Adequate tests and acceptance criteria for release and shelf-life have been established for the control of the finished product. The specifications include relevant physicochemical characteristics, identification of the drug substance, assay, purity, and microbiological tests.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines. The storage recommendation is “Do not store above 30°C. Store in the original package”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

The nonclinical development programme for Alyftrek, containing the active substances vanzacaftor (VNZ), tezacaftor (TEZ), and deutivacaftor (D-IVA), followed relevant ICH guidelines. Nonclinical data for TEZ had already been submitted and assessed in connection with prior approvals (e.g. Symdeko and Trikafta). The toxicology programme for D-IVA was streamlined due to its similar safety profile to ivacaftor (IVA).

5.1 Pharmacology

The pharmacological profiles of VNZ and the VNZ/TEZ/D-IVA combination were evaluated exclusively *in vitro*. VNZ was assessed through biochemical and functional studies, both as a single agent and in combination with clinically relevant concentrations of TEZ and/or D-IVA. These studies utilised human bronchial epithelial (HBE) cells from CF patients who were homozygous for F508del-CFTR (F/F HBE) or heterozygous for F508del-CFTR with a minimal function mutation (F/MF HBE). Western blot analyses revealed that VNZ (220 nM), in combination with TEZ (18 µM) and/or D-IVA (1 µM), increased steady-state levels of mature, glycosylated CFTR compared to TEZ/D-IVA or vehicle-treated cells. Chamber electrophysiology studies demonstrated that 320 nM VNZ, either alone or in combination with TEZ and/or D-IVA, enhanced CFTR-mediated chloride transport in both F/F and F/MF CF-HBE cells. The triple combination of VNZ, TEZ, and D-IVA exhibited greater potency than single or dual therapies, supporting its clinical utility. Cross-study comparisons indicated a consistent response in CFTR-expressing cells. In the Fischer rat thyroid cell model, the combination significantly increased chloride transport and improved CFTR processing for F508del-CFTR and 134 additional mutations. VNZ demonstrated efficacy as a CFTR corrector, enhancing F508del-CFTR processing and trafficking, with its potency further augmented in combination with TEZ and D-IVA.

Regarding secondary pharmacodynamics, VNZ, TEZ, and D-IVA exhibited no significant off-target activity across a range of receptors, channels, and enzymes, indicating a low potential for off-target effects. Consequently, no secondary pharmacological effects for Alyftrek are anticipated in humans.

VNZ was evaluated in a core battery of *in vitro* and *in vivo* studies to assess its effects on cardiovascular, respiratory, and central nervous system (CNS) function in accordance with ICH S7A/B guidelines. At clinically relevant concentrations and exposures, VNZ did not raise any safety concerns related to cardiac function in dogs or respiratory and CNS function in rats. Similarly, safety pharmacology studies conducted with TEZ and D-IVA demonstrated a low potential for adverse effects.

5.2 Pharmacokinetics

The pharmacokinetics of VNZ in rats and dogs were well characterised, demonstrating overall comparability to humans. In rats, VNZ exhibited a half-life of approximately 19-22 hours and a bioavailability of 77%. In dogs, the half-life was shorter (11-12 hours), with a bioavailability of approximately 50%. While the half-life of VNZ in humans (92 hours) differs between from that in nonclinical species, the overall pharmacokinetic profiles are consistent.

Single-dose oral and intravenous pharmacokinetic (PK) studies in rats and dogs and a repeat-dose toxicokinetic (TK) study in rats revealed that the PK / TK profiles of D-IVA were comparable to that of IVA. In repeat-dose studies, VNZ exposure in rats and dogs increased more than dose-proportionally, whereas TEZ and D-IVA exhibited dose-proportional increases at lower doses but less than dose-proportional increases at higher doses. VNZ and D-IVA accumulated 2- to 6-fold in rats and dogs, while TEZ showed no significant accumulation.

VNZ, TEZ, and D-IVA exhibited high plasma protein binding (≥ 98%) across species. VNZ had no major metabolites, whereas the major metabolites of TEZ (M1-TEZ, M2-TEZ, and M5-TEZ) and D-IVA (M1-D-IVA and M6-D-IVA) also displayed high plasma protein binding, primarily to human serum albumin.

Tissue distribution studies in rats using ^{14}C-labelled compounds indicated widespread distribution, particularly in the gastrointestinal tract, liver, adrenal glands, kidney, pancreas, heart, and placenta, with limited penetration into the brain, eyes, and testes. Placental transfer of VNZ and TEZ was observed in pregnant rats. The distribution patterns of D-IVA were consistent with, or are expected to be similar to, those of IVA. No significant binding to melanin-containing tissues was observed.

VNZ, TEZ, and D-IVA underwent oxidative metabolism in rats, dogs, and humans. TEZ and its major human plasma metabolites (M1-TEZ, M2-TEZ, and M5-TEZ) accounted for most of the systemic exposure, with M2-TEZ identified as a disproportionate human metabolite. The metabolic pathways of VNZ and D-IVA were similar across species, with no human-specific metabolites identified for either substance.

In rats, excretion of drug-related material primarily occurred via faeces, with biliary excretion playing a significant role.

VNZ, TEZ, and D-IVA were detected in the milk of lactating rats at concentrations 0.2, 3.0, and 1.5 times the plasma exposure (based on AUC). Although milk transfer of D-IVA was not studied, it is anticipated to behave similarly to IVA. No data are available regarding the presence of VNZ, TEZ, and D-IVA in human milk. Consequently, the Information for healthcare professionals advises discontinuing breastfeeding or abstaining from therapy due to the potential risk to infants.

5.3 Toxicology

The nonclinical studies for VNZ, TEZ, and D-IVA, conducted individually and in combination, adequately addressed all relevant toxicological aspects. The toxicological profiles of these substances were evaluated in rats, rabbits, and dogs. The selection of rats and dogs for the safety assessment of VNZ was justified with the similar metabolic profiles and comparable PK profiles to those in humans. Furthermore, the use of the oral route of administration and once-daily dosing in the nonclinical studies is consistent with the proposed clinical regimen.

The general toxicology of VNZ was evaluated in rats and dogs over 26 and 39 weeks, with 6-week recovery periods. Male rats received doses of 5, 12, 25, and 125 mg/kg/day, while females were dosed at 2.5, 6, 12.5, and 30 mg/kg/day. Dogs were administered 1.5, 4, and 10 mg/kg/day. D-IVA was assessed in 4-week studies in rats and dogs, as well as in a 13-week bridging study in rats with IVA and D-IVA. VNZ was not tolerated at the highest doses in rats, with males terminated early at 125 mg/kg/day due to VNZ-related mortality and adverse clinical signs. Females experienced unscheduled deaths at 30 mg/kg/day. Other toxicities with VNZ included hepatocellular vacuolar degeneration, stomach erosions, increased leukocyte counts, and body weight loss, all of which were reversible following the recovery period. The NOAEL for VNZ was determined to be 12 mg/kg/day in males and 12.5 mg/kg/day in females, corresponding to approximately 21- and 60-fold the clinical exposure at 20 mg/day, respectively (based on AUC). In dogs, VNZ was well tolerated, with a NOAEL of 10 mg/kg/day, representing a 105-fold margin over clinical exposure. D-IVA was not tolerated in rats at doses of ≥ 100 mg/kg/day, with pathology findings observed at doses of ≥ 50 mg/kg/day. Dose-related effects included decreased thymus weight in males and increased liver weight in females, although no microscopic correlates were identified. Minimal, non-adverse lung changes, such as dark foci and histopathological alterations, were observed but resolved after recovery. The NOAEL for D-IVA was established at 35 mg/kg/day, corresponding to a 12-fold margin over the clinical exposure based on AUC. In dogs, D-IVA was well tolerated, with a NOAEL of 20 mg/kg/day, representing 18- and 14-fold the clinical exposure in males and females, respectively. A repeat-dose toxicity study of the VNZ/TEZ/D-IVA combination in rats confirmed the safety profile. The administered doses of VNZ (2.5 mg/kg/day), TEZ (45 mg/kg/day), and D-IVA (17.5 mg/kg/day) were well tolerated individually and in combination, with no adverse effects. The AUC values in the triple combination group corresponded to 4-, 1.2-, and 1.4-fold the clinical exposure at the maximum recommended human dose (MRHD). Although exposure margins were relatively low, they were deemed acceptable based on the comprehensive repeat-dose toxicity data for the individual compounds.

VNZ, tezacaftor, and D-IVA tested negative for genotoxic potential in both *in vitro* and *in vivo* genotoxic assays conducted in accordance with ICH S2 (R1).

VNZ demonstrated no evidence of carcinogenic potential in rasH2 transgenic mice up to the highest dose level tested (30 mg/kg/day, corresponding to a plasma exposure margin of 27-fold). A 2-year carcinogenicity study in rats is ongoing and will be submitted to Swissmedic as a post-approval requirement. TEZ and IVA were found to be non-carcinogenic. The carcinogenicity of D-IVA was not assessed, which is considered acceptable.

The reproductive and developmental toxicity of VNZ was assessed in compliance with the ICH S5 guideline. A fertility study in rats showed no effects on reproductive performance, sperm parameters, or intrauterine survival at doses up to 19 times the exposure at the MRHD in males. In animal embryo fetal development studies, oral administration of VNZ to pregnant rats and rabbits during organogenesis demonstrated no adverse developmental effects at doses that produced maternal exposures up to approximately 30 times the exposure at the MRHD in rats and 22 times the MRHD in rabbits. In a pre- and postnatal study in rats, no adverse effects were observed on maternal or offspring development. The NOAEL was 10 mg/kg/day, associated with a plasma exposure 18-fold the clinical exposure. TEZ and IVA did not demonstrate adverse developmental effects at doses resulting in low maternal exposure at the MRHD. Specific reproductive studies were not conducted for D-IVA; however, this is considered acceptable due to its structural and functional similarity to IVA.

Juvenile animal studies for VNZ and TEZ were conducted in accordance with the EMA Paediatric Investigation Plan. VNZ was well tolerated in both male and female juvenile rats from postnatal days (PND) 7 to 70. However, in juvenile toxicity studies, convulsions and mortality were observed in rats administered TEZ at a dose of 100 mg/kg/day (approximately 1.9 times the MRHD) during the treatment periods of PND 7 to 35 and PND 21

to 49. Cataracts were observed in juvenile rats treated with IVA at doses of ≥ 10 mg/kg/day (0.21 times the MRHD from PND 7 to 35. As juvenile toxicity studies have already been conducted for IVA, no additional studies were performed for D-IVA.

At the NOAEL, VNZ demonstrated good local tolerance with no evidence of gastrointestinal toxicity in repeat-dose oral studies. It also showed no phototoxicity in pigmented rats. TEZ exhibited no phototoxicity *in vitro*. Phototoxicity testing was not conducted for IVA or D-IVA due to their lack of significant partitioning or binding to melanin-containing tissues, a decision deemed acceptable. Consequently, the potential for phototoxicity with the VNZ/TEZ/D-IVA combination is considered low.

Impurities are controlled in compliance with ICH Q3A/B(R2) and ICH M7(R2). There are no concerns regarding excipients.

The RMP adequately summarises the results of the nonclinical studies and their relevance to human use.

Based on the ERA, TEZ does not pose a risk to the environment. Since IVA has been shown to pose no environmental risk, a similar outcome is expected for D-IVA. However, environmental risks cannot be excluded for VNZ based on the Phase 1 ERA. The final environmental risk assessment for Alyftrek will be submitted to Swissmedic as a post-approval requirement.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profiles of VNZ, TEZ, and D-IVA are considered sufficiently characterised. The submitted nonclinical data support the approval of Alyftrek for the proposed indication, and all relevant information is included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The proposed commercial formulation of VNZ/TEZ/D-IVA is a fixed-dose combination (FDC) in 2 dose strengths: VNZ 4-mg/TEZ 20-mg/D-IVA 50-mg for patients < 40 kg and VNZ 10-mg /TEZ 50-mg/D-IVA 125-mg for patients ≥ 40 kg.
The FDC is to be taken once daily with a fat-containing meal. The posology is based on body weight bands for patients from 6 years, with dose adjustments in case of interactions.
The clinical pharmacology was described in 15 clinical studies, in addition to studies from the previous programmes including IVA and TEZ.

The PopPK models for VNZ, TEZ, M1-TEZ, D-IVA, M1-D-IVA, and M6-D-IVA described the data in all included age and weight groups sufficiently well to be suitable for simulations. Apart from patient status, none of the covariates investigated had a major impact on VNZ exposures. Similar to IVA, only body weight had a relevant impact on the exposures of D-IVA and its metabolites.

Simulations with the final PopPK models indicated that the exposures of all analytes were within the adult reference ranges in children between 6 and 11 years of age after the proposed dosing recommendations. Based on the current data, a lower weight limit of 20 kg is specified until more paediatric data become available. The proposed weight cut-off of 40 kg is suitable based on the results of the VNZ and D-IVA PopPK models.
The half-life of D-IVA is sufficiently long to allow QD dosing, in contrast to IVA, which requires BID dosing.

VNZ/TEZ/D-IVA must be taken with a fat-containing meal because of the low bioavailability of VNZ and D-IVA after fasted administration. Absorption is highly dependent on fatty meals and is further influenced by significant drug-drug interactions (CYP3A4 inhibitors); warnings in this regard are included in the Information for healthcare professionals.

VNZ, TEZ, and D-IVA are almost exclusively metabolised by CYP3A4, requiring dose adjustments for the co-administration of strong or moderate CYP3A4 inhibitors. The current triple combination includes 2 sensitive CYP3A4 substrates: VNZ and D-IVA. The long half-life of VNZ and the QD dosing of D-IVA made it challenging to identify dose adjustments for the co-administration of moderate or strong CYP3A4 inhibitors. In some cases, the proposed recommendations result in very low exposures of TEZ, its active metabolite M1-TEZ, and the active metabolite of D-IVA, M1-D-IVA. Simulations of active moieties indicated lower exposures, mainly of the TEZ active moiety. Alternative scenarios did not provide better exposure matching. Sensitivity analyses of exposure vs SwCl and exposure vs ppFEV1 indicated that the difference in exposure after the dose adjustments with strong or moderate CYP3A4 inhibitors was of limited clinical consequence (due to reaching a plateau of the exposure vs efficacy curve), and thus the proposed dose adjustments were accepted.

The applicant committed to conducting a clinical study (VX25-121-014) to investigate the inhibition of BCRP by VNZ with a sensitive BCRP substrate (rosuvastatin) as a post-approval requirement. Completion of the study is expected in January 2027.

The exposure-response analyses for efficacy indicated that all VNZ doses investigated (5 mg, 10 mg, and 20 mg QD) were close to or at the plateau of the exposure-response curve for ppFEV1 and SwCl. For ppFEV1, VNZ/TEZ/D-IVA maintained the effect of ELX/TEZ/IVA administered in the run-in phase of the pivotal paediatric study but did not provide any additional improvement.

There was no apparent relationship between VNZ or D-IVA exposure and the incidence of AEs.

6.2 Dose finding and dose recommendation

There were 2 studies supporting the dose selection and providing proof-of-concept for this triple combination.
Study 101 established proof of concept for VNZ and provided data to support dose selection to achieve maximum CFTR functional restoration in the Phase 3 studies.
Part 1 had a randomised, double-blind, placebo-controlled, parallel-group design that evaluated 3 different VNZ doses (5 mg, 10 mg, or 20 mg) in VNZ/TEZ/D-IVA compared to placebo. Part 2 had a randomised, double-blind, TEZ/IVA-controlled, parallel-group design that evaluated VNZ (20 mg)/TEZ/D-IVA. The study included adult CF patients who are heterozygous for F508del and a minimal function mutation (Part 1) or who are homozygous for F508del (Part 2). In Part 1, the change in ppFEV1 was highest in the TC-10 mg group. However, the changes in SwCl and CFQ-R RD score were greater in the TC-20 mg group. In Part 2, the TC-20 mg group showed a greater improvement in ppFEV1 and CFQ-R RD score and a larger reduction in SwCl compared to the TEZ/IVA group. No dose-dependent safety issues were observed. Although the 10mg VNZ dose would also have been a reasonable option, due to the highest change in SwCl, selection of the 20 mg VNZ dose for the Phase 3 studies can be understood.
Study 561-101 established safety and efficacy of D-IVA monotherapy compared to IVA monotherapy and supported D-IVA dose selection for the Phase 3 studies. The study evaluated 2 dose levels (150 vs 250 mg) of D-IVA in adult CF participants who have a gating mutation and were previously taking a stable dose of IVA. Overall, the absolute change in ppFEV1 was similar between the 3 treatment arms. However, the absolute change in SwCl was greater in the D-IVA 250 mg qd group compared to the other 2 groups. No concerning safety issues between the groups were observed.
Consequently, the dose of 250 mg D-IVA was selected for the Phase 3 studies.
The TEZ dose of 100 mg qd is the same as for already approved CFTR modulators. Therefore, no specific dose-finding studies were conducted in this submission for TEZ.
Taken together, the selection of the VNZ 20mg/TEZ 100mg/D-IVA 250 mg dose can be understood.

6.3 Efficacy

Two pivotal studies were submitted: Study 102 and Study 103. These were similar in design, the main difference being the inclusion criterion of different CF genotypes.
Study 102 was a Phase 3, randomised, double-blind, ELX/TEZ/IVA-controlled, parallel-group, 52-week, multicentre study in F/MF (heterozygous for F508del and a minimal function mutation) participants ≥12 years of age.
Study 103 had the same study design but included F/F (homozygous for F508del), F/G (heterozygous for F508del and a gating mutation), F/RF (heterozygous for F508del and a residual function mutation), and TCR/non-F (heterozygous for a triple combination responsive mutation and no F508del mutation) participants ≥12 years of age.
In both studies, participants entered a run-in period for 4 weeks, receiving ELX/TEZ/IVA. Following completion of the run-in period, participants were randomised 1:1 to the VNZ/TEZ/D-IVA group or ELX/TEZ/IVA group for 52 weeks.
The primary endpoint was to demonstrate non-inferiority for ppFEV1 between the 2 treatment groups (with a non-inferiority margin of 3 percentage points). Change in SwCl and the pooled proportion of participants with SwCl <60 mmol/L and <30 mmol/L through Week 24 were the key secondary endpoints.

The baseline demographics and disease characteristics were well balanced between the treatment arms and represented the intended population well.
Both studies met the primary endpoint of non-inferiority for ppFEV1 for VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA.
The secondary endpoint of change in SwCl demonstrated a greater change for the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group in both studies.

Therefore, non-inferiority to ELX/TEZ/IVA was convincingly demonstrated. However, despite the stronger effect of VNZ/TEZ/D-IVA on SwCl, it cannot be concluded that VNZ/TEZ/D-IVA would be more effective than ELX/TEZ/IVA.

The proportion of participants with SwCl <60 and <30 mmol/l through Week 24 (analysed in the pooled FAS for both pivotal studies) was larger in the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group. However, the difference between the 2 groups was small, and as these cut-offs are not validated endpoints, they can only be considered supportive.

Through Week 52, there were slightly more PEx in the ELX/TEZ/IVA group (169) compared to the VNZ/TEZ/D-IVA group (153) when pooling the PEx of Studies 102 and 103.

In addition to participants with at least 1 F508del mutation, participants with TCR/non-F genotypes were included in Study 103. Inclusion of additional genotypes based on *in vitro* data was also proposed in the submitted indication. It is agreed that not all rare mutations can be included and extensively studied in clinical trials. For the mutations based on *in vitro* data, correlation between the *in vitro* data and the *in vivo* data was demonstrated by the applicant. Therefore, efficacy can be extrapolated to these mutations.
However, for the requested 19 non-canonical splice mutations, efficacy is mainly based on extrapolation due to the mechanism of VNZ/TEZ/D-IVA. Due to the unmet medical need in this population and the fact that it is not considered feasible to include all rare mutations in clinical studies, the inclusion of these 19 non-canonical splice mutations is considered acceptable. As the data underlying the effect of VNZ/TEZ/D-IVA in various mutations affect the level of uncertainty on its exact effect, this is specified in the Information for healthcare professionals.

Study 105 is a supportive, ongoing Phase 3, open-label, 2-part, multicohort, multicentre study in participants with a triple combination responsive mutation (TCR/any) aged 1 to 11 years. Only an interim analysis report including the final data from participants aged 6 to 11 years enrolled in Cohorts A1 and B1 was submitted. Cohorts A2 and B2 will evaluate participants aged 2 to 5 years, and Cohorts A3 and B3 will evaluate participants aged 1 to less than 2 years. Data from these cohorts were not yet included in the submission package.
Participants who were not on stable ELX/TEZ/IVA treatment entered the 4-week run-in period and received ELX/TEZ/IVA. Participants who were receiving stable ELX/TEZ/IVA treatment had the run-in period waived and entered the treatment period within 28 days of the screening visit. Participants in Cohort A1 received VNZ 10 mg qd/TEZ 50 mg qd/D-IVA 125 mg qd for 22 days.
In Cohort B1, all participants received VNZ/TEZ/D-IVA for approximately 24 weeks. Participants <40 kg received VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd and participants ≥40 kg received VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd.
The study design is similar to the design of other CFTR modulator trials in younger age groups that take extrapolation of efficacy from older age groups into account.
There was a further reduction of SwCl with VNZ/TEZ/D-IVA and no change in ppFEV1 after 24 weeks compared to the results after the run-in treatment period with ELX/TEZ/IVA. A high proportion of participants reached the SwCl threshold of <60 mmol/L (94.9%) and 52.6% reached the SwCl threshold of <30 mmol/L. However, at baseline (although measured after a 4-week run in on ELX/TEX/IVA), 83.3% were already below the threshold of <60 mmol/L and 38.5% were already below the SwCl threshold of <30 mmol/L, somewhat attenuating this high percentage of participants reaching these endpoints. Therefore, the efficacy results were similar compared to the older age groups.

One advantage for patients over ELX/TEZ/IVA is that VNZ/TEZ/D-IVA only has to be taken once daily and not twice.

6.4 Safety

The core safety analysis included the pooled safety data from the 2 pivotal Studies 102 and 103. In addition, safety data from Study 105 was presented.
The core safety analysis included 971 participants (491 in the ELX/TEX/IVA group and 480 in the VNZ/TEZ/D-IVA group). The mean exposure duration was 49.5 weeks in the VNZ/TEZ/D-IVA group and 49.9 weeks in the ELX/TEZ/IVA group. Overall, 303 participants received ≥52 weeks of VNZ/TEZ/D-IVA in Studies 102 and 103. The size of this safety database is considered adequate for this rare disease.

A high percentage of patients in both treatment groups had AEs (95.5% in the ELX/TEZ/IVA and 95.6% in the VNZ/TEZ/D-IVA group). However, most of the AEs were moderate or mild.
The most common AE was PEx, with a higher percentage in the ELX/TEZ/IVA group (32.2%) compared to the VNZ/TEZ/D-IVA group (27.7%).
Other common AEs were cough, COVID-19, nasopharyngitis, headache, upper respiratory tract infection, oropharyngeal pain, and diarrhoea, all with similar percentages in both treatment groups. A difference in the percentages between the treatment groups was observed for influenza, with 5.3% in the ELX/TEZ/IVA group compared to 10.8% in the VNZ/TEZ/D-IVA group.

There were no deaths reported in the VNZ/TEZ/D-IVA clinical development programme during the treatment-emergent period. Two participants in the Study 103 ELX/TEZ/IVA group died after the treatment-emergent period. Both deaths are considered as not related to ELX/TEZ/IVA.

The overall percentage of participants with SAEs was slightly higher in the ELX/TEZ/IVA group (16.5%) compared to the VNZ/TEZ/D-IVA group (14.2%). SAEs that occurred in 2 or more participants in any treatment group included influenza, AST increase, γ-GT increase, depression, and syncope. However, the differences in the numbers were very small.

A higher percentage of participants had AESIs of elevated transaminase events in the VNZ/TEZ/D-IVA group (9.0%) compared to the ELX/TEZ/IVA group (7.1%). There was even 1 participant with ALT/AST >20 x ULN in the VNZ/TEZ/D-IVA group compared to none in the ELX/TEZ/IVA group. Although the overall percentages of elevated transaminase events were lower compared to the pooled pivotal ELX/TEZ/IVA studies, comparisons between different studies always have to be interpreted with caution due to different settings.
Nevertheless, as LFT elevations were slightly higher for VNZ/TEZ/D-IVA in the pivotal studies compared to ELX/TEZ/IVA but smaller than in the ELX/TEZ/IVA pivotal studies, this is considered acceptable with the appropriate warnings and recommendations for liver enzyme monitoring in the Information for healthcare professionals.

Taken together, the safety profile of VNZ/TEZ/D-IVA is acceptable. However, in line with the study design, the main safety data for VNZ/TEZ/D-IVA were only generated in a population who were already on ELX/TEZ/IVA treatment. The Information for healthcare professionals therefore states that safety data are only available from a selected patient population.

6.5 Final clinical benefit-risk assessment

With the demonstrated non-inferiority for ppFEV1 of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA and the acceptable safety profile, the overall benefit-risk is considered positive for participants with CF aged 6 years and older who have at least 1 F508del mutation or another responsive mutation in the CFTR gene.

7 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.

8 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.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, or unusual changes in behaviour 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
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*	*S549N*	*V754M*	
D1152H	*G85E*†	*L206W*	*R75Q*	*S549R*	*W1098C*†	
F508del†	*H1054D*	*M1101K*†	*S1159F*	*S945L*	*W1282R*	
G1244E	*I336K*	*R1066H*	*S1251N*	*V562I*	*Y563N*†	
Based on *in vitro* Data‡						
1507_1515del9	*E116Q*	*G424S*	*I556V*	*P140S*	*R334L*	*T1053I*
2183A→G	*E193K*	*G463V*	*I601F*	*P205S*	*R334Q*	*T1086I*
3141del9	*E292K*	*G480C*	*I618T*	*P499A*	*R347H*	*T1246I*
3195del6	*E403D*	*G480S*	*I807M*	*P5L*	*R347L*	*T1299I*

3199del6	*E474K*	*G551A*	*I980K*	*P574H*	*R347P*	*T338I*
546insCTA	*E56K*	*G551S*	*K1060T*	*P67L*	*R352W*	*T351I*
A1006E	*E588V*	*G576A*	*K162E*	*P750L*	*R516G*	*T604I*
A1067P	*E60K*	*G576A;R668C*[§]	*K464E*	*P99L*	*R516S*	*V1153E*
A1067T	*E822K*	*G622D*	*L1011S*	*Q1100P*	*R553Q*	*V1240G*
A107G	*E92K*	*G628R*	*L102R*	*Q1291R*	*R555G*	*V1293G*
A120T	*F1016S*	*G91R*	*L1065P*	*Q1313K*	*R560S*	*V201M*
A234D	*F1052V*	*G970D*	*L1324P*	*Q237E*	*R560T*	*V232D*
A309D	*F1074L*	*G970S*	*L1335P*	*Q237H*	*R668C*	*V392G*
A349V	*F1099L*	*H1085P*	*L137P*	*Q359R*	*R709Q*	*V456A*
A46D	*F1107L*	*H1085R*	*L1480P*	*Q372H*	*R74Q*	*V456F*
A554E	*F191V*	*H1375P*	*L15P*	*Q452P*	*R74W*	*V520F*
A559T	*F200I*	*H139R*	*L165S*	*Q493R*	*R74W;D1270N*[§]	*V603F*
A559V	*F311del*	*H199R*	*L320V*	*Q552P*	*R74W;V201M*[§]	*W361R*
A561E	*F311L*	*H199Y*	*L333F*	*Q98R*	*R74W;V201M;D1270N*[§]	*Y1014C*
A613T	*F508C*	*H609R*	*L333H*	*R1048G*	*R75L*	*Y1032C*
A62P	*F508C;S1251N*[§]	*H620P*	*L346P*	*R1066C*	*R751L*	*Y109N*
A72D	*F575Y*	*H620Q*	*L441P*	*R1066L*	*R792G*	*Y161D*
C491R	*F587I*	*H939R*	*L453S*	*R1066M*	*R933G*	*Y161S*
D110E	*G1047R*	*H939R;H949L*[§]	*L619S*	*R1070Q*	*S1045Y*	*Y301C*
D110H	*G1061R*	*I1027T*	*L967S*	*R1070W*	*S108F*	*Y569C*
D1270N	*G1069R*	*I105N*	*L997F*	*R1162L*	*S1118F*	*Y913C*
D1445N	*G1123R*	*I1139V*	*M1101R*	*R117C*	*S1159P*	
D192G	*G1247R*	*I1234Vdel6aa*	*M1137V*	*R117C;G576A;R668C*[§]	*S1235R*	
D443Y	*G1249R*	*I125T*	*M150K*	*R117G*	*S1255P*	
D443Y;G576A;R668C[§]	*G126D*	*I1269N*	*M152V*	*R117H*	*S13F*	
D513G	*G1349D*	*I331N*	*M265R*	*R117L*	*S341P*	
D565G	*G149R*	*I1366N*	*M952I*	*R117P*	*S364P*	

D579G	*G178E*	*I1398S*	*M952T*	*R1283M*	*S492F*	
D614G	*G178R*	*I148N*	*N1088D*	*R1283S*	*S549I*	
D836Y	*G194R*	*I148T*	*N1303I*	*R170H*	*S589N*	
D924N	*G194V*	*I175V*	*N1303K*‡	*R258G*	*S737F*	
D979V	*G27E*	*I502T*	*N186K*	*R297Q*	*S912L*	
D993Y	*G27R*	*I506L*	*N187K*	*R31C*	*S977F*	
E116K	*G314E*	*I506T*	*N418S*	*R31L*	*T1036N*	
Based on Extrapolation¶						
1341G→A	*2789+2insA*	*3041-15T→G*	*3849+10kb C→T*	*3850-3T→G*	*5T;TG13*	*711+3A→G*
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*		

* 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.

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 SwCI 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). Long term assessment of

carcinogenic potential of VNZ is currently being conducted. 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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