Date: 28 January 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

TRIKAFTA

International non-proprietary name: elexacaftor, ivacaftor, tezacaftor

Pharmaceutical form: film-coated tablet

Dosage strength(s):

Morning dose: 100 mg of elexacaftor, 50 mg of tezacaftor, and 75 mg of ivacaftor as a fixed-dose combination tablet

Evening dose: 150 mg of ivacaftor

Route(s) of administration: oral

Marketing Authorisation Holder: Vertex Pharmaceuticals (CH) GmbH

Marketing Authorisation No.: 67773

Decision and Decision date: approved on 10 December 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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Table of contents

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body Mass Index
cAMP	3',5'-cyclic adenosine monophosphate
Cmax	Maximum observed plasma/serum concentration of drug
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised (measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production, and difficulty breathing)
CFTR	Cystic fibrosis transmembrane conductance regulator
CYP	Cytochrome P450
ELX	Elexacaftor
ERA	Environmental Risk Assessment
F508del	CFTR gene mutation with deletion of the phenylalanine codon in position 508 of the wild-type protein
F/MF	F508del/minimal function
FEV1	Forced Expiratory Volume in 1 second
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
IVA	Ivacaftor
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MF	minimal function
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SD	Standard Deviation
SwissPAR	Swiss Public Assessment Report
TEZ	Tezacaftor
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance elexacaftor of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a[decies] no. 1 or 2 of the TPA. The Orphan Status was granted on 9 April 2020.

2.2 Indication and Dosage

2.2.1 Requested Indication

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

2.2.2 Approved Indication

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are either homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation (see "Clinical efficacy").

2.2.3 Requested Dosage

Morning dose:	2 fixed-dose combination tablets each containing 100 mg of elexacaftor / 50 mg of tezacaftor / 75 mg of ivacaftor
Evening dose:	1 tablet containing 150 mg of ivacaftor

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	20 March 2020
Formal control completed	24 March 2020
List of Questions (LoQ)	20 May 2020
Answers to LoQ	2 July 2020
Predecision	20 August 2020
Answers to Predecision	19 October 2020

Labelling corrections	4 November 2020
Answers to Labelling corrections:	20 November 2020
Final Decision	10 December 2020
Decision	approval

3 Medical Context

Cystic Fibrosis (CF)

Cystic fibrosis (CF) is a genetic disease caused by a deficiency and/or dysfunction of the “cystic fibrosis transmembrane conductance regulator” (CFTR). The CFTR protein is a pore-forming transmembrane protein and functions as a cAMP-regulated chloride channel. The gene has several mutations/defects, which to some extent can be found simultaneously in the same patient. The most common defect is the lack of coding for phenylalanine (F508del), which leads to a processing disorder and therefore to an obstacle in the transport of CFTR to the cell surface. Approximately 45% of patients with cystic fibrosis have a homozygous defect in this allele, which leads to an extensive CFTR malfunction and therefore to severe forms of disease. In addition, there are a number of other mutations that impair the CFTR function in various ways and to varying extents.

Current Therapeutic Options and Importance of the Requested Combination

In addition to a number of symptomatic treatments (e.g. dornase alpha, inhaled antibiotics …), the following CFTR potentiators have been available for a few years. To date, these are only approved for defined gating mutations (class III), homozygous F508del mutations and heterozygous F508del with “residual function mutations” in the second CFTR gene.

Ivacaftor (IVA): In the presence of cAMP, ivacaftor in vitro improves the chloride transport capacity of CFTR (“by potentiating the channel-open probability or gating”) in both wild-type and various mutations, the extent of this being dependent on the mutation. In order for ivacaftor to have an effect, CFTR proteins must be present on the cell surface. The compound is approved for some defined gating mutations (class III) in the CFTR gene.

Lumacaftor is used only in combination with IVA: chaperone protein, which influences the folding of CFTR and in so doing improves the stability of the conformation and transport to the surface. The combination Lumacaftor/IVA is approved for homozygous F508del mutations in the CFTR gene.

Tezacaftor (TEZ) is used only in combination with IVA. Tezacaftor in vitro improves the processing and transport of normal CFTR and certain mutations, and in so doing leads to an increase in mature surface CFTR. The combination TEZ/IVA is approved for homozygous F508del mutations and heterozygous F508del mutations in combination with certain “residual function” mutations in the second CFTR gene.

Elexacaftor (ELX) will be used in the newly-requested treatment in combination with TEZ and IVA. ELX in vitro improves the processing and transport of normal CFTR in certain mutations but binds to other areas of the CFTR protein than TEZ. With the newly-requested combination ELX/TEZ/IVA, a functional improvement for F508del mutations is achieved, which is more pronounced than with TEZ/IVA. It appears to be sufficient to be beneficial, even in the case of heterozygous F508del mutations with complete and therapy-resistant malfunction of the second CFTR gene (“minimal function mutation”).

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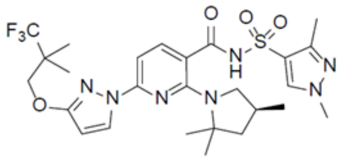
4 Quality Aspects

4.1 Drug Substance

INN: Elexacaftor
Chemical name: N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide
Molecular formula: $C_{26}H_{34}F_3N_7O_4S$
Molecular mass: 597.66 g/mol
Molecular structure:



Physico-chemical properties:
Elexacaftor is a white or almost white crystalline powder. It contains one stereogenic centre and is manufactured as a single stereoisomer. Only one crystalline form of elexacaftor is known. The compound is practically insoluble in aqueous media.

Structure elucidation:
The structure of elexacaftor hydrochloride has been fully elucidated using several spectroscopic techniques such as mass spectroscopy, infrared spectroscopy and nuclear magnetic resonance spectroscopy. In addition, the crystal structure and the absolute configuration have been determined by single crystal X-ray diffraction.

Synthesis:
The drug substance is manufactured by a multi-step chemical synthesis with a final crystallisation. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification:
In order to ensure a consistent quality of elexacaftor, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability:
The bulk drug substance is packaged in LDPE (low density polyethylene) bags. A stability study was carried out according to the current guideline recommendations. Based on the results of this study, a satisfactory retest period was established.

4.2 Drug Product

Description and composition:
Elexacaftor/tezacaftor/ivacaftor tablet is a new fixed dose combination (FDC) immediate-release film-coated tablet containing the new active substance elexacaftor (100 mg) and the known active substances tezacaftor (50 mg), and ivacaftor (75 mg). It is an orange film-coated tablet, debossed with “T100” on one face and plain on the other face. The tablet core consists of the pharmaceutical excipients hypromellose, hypromellose acetate, sodium lauryl sulphate, croscarmellose sodium, microcrystalline cellulose and magnesium stearate. The tablets are film-coated with a film coating mixture consisting of hypromellose, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow and iron oxide red.

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Pharmaceutical Development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a QbD (Quality by Design) approach.

Manufacture:
The tablets are manufactured by a continuous manufacturing process, including each of the following steps : blending, granulation and compression, followed by the film-coating process. Adequate in-process controls are established in order to ensure a consistent manufacturing process.

Specification:
The drug product specifications cover relevant physicochemical characteristics as well as identification, assay and purity tests. The analytical procedures are validated according to the recommendations of international guidelines.

Container Closure System:
The container closure system for Trikafta tablets is a thermoformed blister consisting of clear Aclar (PCTFE – polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The stability study included three primary stability batches. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

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

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Trikafta, Swissmedic conducted an abridged evaluation that was based on the FDA assessment report provided by the applicant (Multidisciplinary Review dated 21 October 2019). Studies with the new active substance elexacaftor and impurities that were not discussed in the FDA report (e.g. juvenile toxicity studies) were reviewed in detail.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Trikafta in the proposed indication. Pharmacology and the toxicological profile of elexacaftor were sufficiently characterised. The main target organs of elexacaftor identified in the nonclinical species (rats and dogs) were glandular stomach (rats), bone marrow (rats), and male reproductive organs (both species). Additionally, increases in serum transaminases and bilirubin without related microscopic changes in liver were frequently observed in rats treated with elexacaftor; similar changes in clinical pathology were also observed in the clinical studies. Systemic exposure (AUC) at the NOAELs in the chronic toxicity studies was about 3-fold (male rats), 11-fold (female rats), and 14-fold (dogs) the clinical exposure. In rats, elexacaftor also induced changes in lung (alveolar macrophage aggregation) and pancreas (single cell necrosis) at clinically relevant exposures. Given the low severity grade of these findings and absence of respiratory clinical signs in the studies, these changes were considered non-adverse. In the clinical trials, there were no findings indicative of treatment-related effects on pancreas and lung. In combination toxicity studies, no new toxicities or significant exacerbation of elexacaftor-related effects were observed when combined with tezacaftor and ivacaftor.
In line with the PIP, juvenile toxicity studies in rats were conducted with elexacaftor with treatment from postnatal day (PND) 7 up to PND 70. No adverse effects were observed up to the highest dose levels, which corresponded to a systemic exposure (AUC) on PND 70 of about 3-fold (males) and 5-fold (females), respectively, the clinical AUC in patients aged 12 years and older.
Impurities are considered adequately controlled. There are no concerns with regard to excipients.
Based on the ERAs submitted for the individual active substances, the risk for the environment resulting from the introduction of Trikafta to the market is considered low.
All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The clinical-pharmacology documentation for the now-requested combination and dose recommendation essentially comprises six studies in subjects and three studies in CF patients:

Study Number	Study Description
Studies in Healthy Subjects	
Study 001 (Parts A, B, and C)	Single-dose and multiple-dose escalation study and BA study of VX-445 monotherapy, or VX-445/TEZ/IVA
Study 001 (Part A QT)	Cardiodynamic analysis of the effect of VX-445 on QTc interval
Study 002	DDI study of the effect of VX-445/TEZ/IVA on the PK of oral contraceptives
Study 003	Mass balance study to investigate the absorption, distribution, metabolism, and excretion of VX-445
Study 005	BA study of VX-445/TEZ/D-IVA and VX-445/TEZ/IVA FDC tablets and food effect of VX-445/TEZ/D-IVA FDC tablet
Study 006	DDI study of the effect of itraconazole on the PK of VX-445/TEZ/D-IVA
Study 009	Thorough QT/QTc study of VX-445
Studies in Subjects With CF	
Study 001 (Parts D, E, and F)	Safety and efficacy of VX-445/TEZ/IVA and VX-445/TEZ/D-IVA (F/MF and F/F subjects)
Study 102	Efficacy and safety of VX-445/TEZ/IVA (F/MF subjects)
Study 103	Efficacy and safety of VX-445/TEZ/IVA (F/F subjects)

Source: submitted documentation

Pharmacokinetics:

During twice-daily treatment with the requested dose regimen, for elexacaftor a steady-state of plasma concentrations was achieved in CF patients within approximately 14 days, for tezacaftor this was achieved within 8 days and, for ivacaftor, within 3-5 days. The most important pharmacokinetic parameters of elexacaftor, tezacaftor, and ivacaftor at steady state in CF patients aged 12 years and older are listed in the following table:

Pharmacokinetic Parameters of Trikafta Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
General Information			
AUC (SD), µg·h/mL[a]	162 (47.5)[b]	89.3 (23.2)[b]	11.7 (4.01)[c]
C_{max}, (SD), µg/mL[a]	9.2 (2.1)	7.7 (1.7)	1.2 (0.3)
Time to Steady State, days	Within 7 days	Within 8 days	Within 3-5 days
Accumulation Ratio	2.2	2.07	2.4
Absorption			
Absolute Bioavailability	80%	Not determined	Not determined
Median T_{max} (range), hours	6 (4 to 12)	3 (2 to 4)	4 (3 to 6)
Effect of Food	AUC increases 1.9- to 2.5-fold (moderate-fat meal)	No clinically significant effect	Exposure increases 2.5- to 4-fold
Distribution			

Pharmacokinetic Parameters of Trikafta Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
Mean (SD) Apparent Volume of Distribution, L[d]	53.7 (17.7)	82.0 (22.3)	293 (89.8)
Protein Binding[e]	> 99%	approximately 99%	approximately 99%
Elimination			
Mean (SD) Effective Half-Life, hours[f]	27.4 (9.31)	25.1 (4.93)	15.0 (3.92)
Mean (SD) Apparent Clearance, L/hours	1.18 (0.29)	0.79 (0.10)	10.2 (3.13)
Metabolism			
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active Metabolites	M23-ELX	M1-TEZ	M1-IVA
Metabolite Potency Relative to Parent	Similar	Similar	approximately 1/6th of parent
Excretion[g]			
Primary Pathway	• Faeces: 87.3% (primarily as metabolites) • Urine: 0.23%	• Faeces: 72% (unchanged or as M2-TEZ) • Urine: 14% (0.79% unchanged)	• Faeces: 87.8% • Urine: 6.6%

[a] Based on elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours at steady state in patients with CF aged 12 years and older.
[b] AUC_{0-24h}.
[c] AUC_{0-12h}.
[d] Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.
[e] Elexacaftor and tezacaftor bind primarily to albumin. Ivacaftor primarily binds to albumin, alpha 1-acid glycoprotein and human gamma-globulin.
[f] Mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.
[g] Following radiolabelled doses.

Source: information for healthcare professionals

Special populations

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been specifically examined in patients with liver function and kidney function disorders. According to population-based pharmacokinetic analyses, in the event of mild and moderate kidney insufficiency and for adolescents aged 12-18 years, a similar exposure is expected as for adults with healthy kidneys.

Interaction

In vitro assessments showed that elexacaftor (as well as the previously approved active substances, tezacaftor and ivacaftor) is a substrate of CYP3A. Conversely, elexacaftor (as well as tezacaftor) is a mild inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 P-gp transporters OATP1B1 and OATP1B3. Interaction studies revealed the following impacts on exposure to concomitantly administered medications:

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Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor				
Dose and Schedule		Effect on ELX, TEZ and/or IVA PK	Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0	
			AUC	C_{max}
Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd	TEZ 25 mg qd + IVA 50 mg qd	↑ Tezacaftor	4.02 (3.71, 4.63)	2.83 (2.62, 3.07)
		↑ Ivacaftor	15.6 (13.4, 18.1)	8.60 (7.41, 9.98)
Itraconazole 200 mg qd	ELX 20 mg + TEZ 50 mg single dose	↑ Elexacaftor	2.83 (2.59, 3.10)	1.05 (0.977, 1.13)
		↑ Tezacaftor	4.51 (3.85, 5.29)	1.48 (1.33, 1.65)
Ketoconazole 400 mg qd	IVA 150 mg single dose	↑ Ivacaftor	8.45 (7.14, 10.0)	2.65 (2.21, 3.18)
Ciprofloxacin 750 mg q12h	TEZ 50 mg q12h + IVA 150 mg q12h	↔ Tezacaftor	1.08 (1.03, 1.13)	1.05 (0.99, 1.11)
		↑ Ivacaftor*	1.17 (1.06, 1.30)	1.18 (1.06, 1.31)
Rifampicin 600 mg qd	IVA 150 mg single dose	↓ Ivacaftor	0.114 (0.097, 0.136)	0.200 (0.168, 0.239)
Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd	IVA 150 mg q12h	↑ Ivacaftor	2.95 (2.27, 3.82)	2.47 (1.93, 3.17)
↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics * Effect is not clinically significant				

Impact of Elexacaftor, Tezacaftor and/or Ivacaftor on Other Drugs				
Dose and Schedule		Effect on Other Drug PK	Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0	
			AUC	C_{max}
Midazolam 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol*	1.33 (1.20, 1.49)	1.26 (1.14, 1.39)
		↑ Levonorgestrel*	1.23 (1.10, 1.37)	1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939; 1.07)
↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics * Effect not clinically significant.				

Source: information for healthcare professionals

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6.2 Dose Finding and Dose Recommendation

Part D of Study 001 describes additional effects concerning sweat chloride concentrations and forced expiratory volume in 1 second (FEV1) for a total of 65 CF patients with heterozygous F508del mutation for the adjuvant therapy with various doses of ELX with regard to the previously approved combination treatment with TEZ/IVA. These additional effects were revealed to be numerically highest for the highest ELX dose examined (200 mg). In the absence of evidence for relevant toxicity, and since it was well tolerated, only this dose was chosen, in combination with the previously approved tezacaftor/ivacaftor regimen, in the continued clinical development in the pivotal studies.

6.3 Efficacy

The documentation of efficacy is based mainly on two pivotal, randomised, controlled, double-blind studies. The first study (102) is a 1:1 parallel-group comparison of the approved treatment versus placebo over 24 weeks in a total of approximately 400 heterozygous CF patients aged 12 years and older with a F508del mutation on the one hand and, on the other, with a CFTR mutation that leads to a lack of CFTR protein or to a lack of response to TEZ/IVA.
The second study (103) is a 1:1 parallel-group comparison of TEZ/IVA treatments with/without ELX (as approved) over four weeks in a total of approximately 100 CF patients with homozygous F508del mutation.
The primary endpoint in both studies was absolute Δ-FEV1 baseline - week 4; secondary endpoints in both studies were the absolute Δ after four weeks relating to sweat chloride concentration and Cystic Fibrosis Questionnaire – Revised (CFQ-R: measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production, and difficulty breathing); in Study 102, the absolute Δ after 24 weeks relating to FEV1, sweat chloride concentration and CFQ-R, as well as relating to BMI change and the pulmonary exacerbation rate, were additionally examined.
Relating to the primary and secondary endpoints, both studies consistently showed statistically significant differences in favour of the newly requested combination (ELX/TEZ/IVA) versus placebo or the previously approved combination treatment (TEZ/IVA). With regard to the heterozygous minimal function (MF) mutations examined, differences to placebo are described under ELX/TEZ/IVA, and these are numerically approximately twice as large as those observed in the course of the TEZ/IVA development “residual function” mutations.

Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)			
Analysis	**Statistic**	**Placebo N=203**	**Trikafta N=200**
Primary efficacy analysis			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key secondary efficacy analyses			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through Week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Absolute change in Sweat Chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 1.13 (0.07)
Absolute change in Sweat Chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 18.1 (1.1)

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index.
‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sinopulmonary signs/symptoms.
†† Estimated event rate per year was calculated based on 48 weeks per year.

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Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103)			
Analysis*	**Statistic**	**Tezacaftor/ Ivacaftor# N=52**	**Trikafta N=55**
Primary efficacy analysis			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key secondary efficacy analyses			
Absolute change in Sweat Chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 16.0 (2.0)
$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor and ivacaftor run-in period. # Regimen of tezacaftor/ivacaftor and ivacaftor			

Source: information for healthcare professionals

6.4 Safety

A ‘Thorough QT/QTc’ study did not reveal any significant QT prolongation with positive moxifloxacin control for ELX mono at double the therapeutic dose in 31 subjects. There is extensive clinical safety experience for an ‘orphan’ indication from clinical trials (over 710 exposed patients in controlled studies, until mid-2019 approximately 330 patient years, including approximately 370 patients over multiple months). Averse events (AEs), ‘related AEs’, or severe AEs are not described as more common under treatment with ELX/TEZ/IVA versus placebo, but instead as rather rare. Compared to TEZ/IVA, the following signals are described for the new combination with ELX:

- More asymptomatic hepatobiliary laboratory parameter changes.
- More creatinine kinase (CK) elevations and ‘muscle-related AEs’. Additionally, in Study 102 two patients in the ELX/TEZ/IVA group with asymptomatic CK elevation in combination with physical exercise were classified with ‘rhabdomyolysis’.
- Skin rashes may also be more common, although serious dermatosis has not been described.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Currently, there are approximately 2000 different deficient variants of the CFTR gene known in addition to the common F508del mutation. The clinical severity of cystic fibrosis is correspondingly variable. However, it does not depend solely on the genotype, but rather also on additional factors such as environment or “modifier” genes.
In the clinical development submitted, patients with F508del / F508del and numerous heterozygous F/MF mutations were examined. For the F/MF mutations it can be assumed that, in terms of phenotype, they present predominantly or even completely as clinically severe disease, and that the effect of ELX/TEZ/IVA is predominantly, or even completely, determined by the effect solely on the F508del allele. The applicant demonstrates that, from a statistical perspective, a benefit outweighing the risks can be expected for patients with F/F and all F/MF mutations.
Heterozygous patients and F508del patients with mild secondary mutations were not examined. It can be assumed for at least a portion of such patients that, in terms of phenotype, they only have mild disease that may not require treatment. The benefit/risk ratio shown for F/F and F/MF mutations can

therefore not be transferred so easily to heterozygous patients with F508del and mild secondary mutations. The applicant could not convincingly demonstrate to what extent such patients, or at best subgroups, benefit from treatment. Therefore Swissmedic worded the indication as follows: "Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are either homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for the F508del mutation in the CFTR gene with a minimal function (MF) mutation (see "Clinical efficacy").".

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Trikafta 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 of adverse reactions.

Trikafta

Composition

Active substances

Morning dose:

Elexacaftor, tezacaftor, ivacaftor

Evening dose:

Ivacaftor

Excipients

Morning dose:

Tablet core:
Hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate
Tablet film coat:
Hypromellose, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow, iron oxide red
1 tablet contains 2.68 mg of sodium.

Evening dose:

Tablet core:
Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate 167.2 mg, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate
Tablet film coat:
Carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, titanium dioxide
Printing ink:
Ammonium hydroxide, iron oxide black, propylene glycol, shellac
1 tablet contains 1.82 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Morning dose:

Film-coated tablet

Each film-coated tablet contains 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor as a fixed-dose combination tablet.
Orange, capsule-shaped tablet debossed with “T100” on one side and plain on the other (7.85 mm x 15.47 mm).

Evening dose:

Film-coated tablet

Each film-coated tablet contains 150 mg of ivacaftor.
Light blue, capsule-shaped tablet printed with “V 150” in black ink on one side and plain on the other (16.5 mm x 8.4 mm).

Indications/Uses

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are either homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene or heterozygous for the *F508del* mutation in the *CFTR* gene with a minimal function (MF) mutation («Clinical efficacy»).

Dosage/Administration

Trikafta should only be prescribed by physicians with experience in the treatment of CF. If the patient’s genotype is unknown, confirm the presence of two *F508del* mutations or the presence of one *F508del* mutation and a MF mutation using a genotyping assay.

Usual dosage

Adults and adolescents aged 12 years and older

The recommended dose is two tablets (each containing
elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) taken in the morning and one tablet (containing ivacaftor 150 mg) taken in the evening, approximately 12 hours apart.

Delayed Administration

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

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

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

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

Mode of administration

For oral use. Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, broken, or dissolved before swallowing.
Trikafta 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 «Pharmacokinetic»).
Food or drink containing grapefruit should be avoided during treatment with Trikafta (see «Interactions»).

Special dosage instructions

Patients with impaired hepatic function

Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.
Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C). Patients with severe hepatic impairment should not be treated with Trikafta.
No dose adjustment is recommended for patients with mild hepatic impairment (Child Pugh Class A) (see «Pharmacokinetic»).

Table 1: Recommendation for use in Patients with Hepatic Impairment

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

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

Patients with impaired renal function

No dose adjustment is recommended for patients with mild and moderate renal impairment. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see «Pharmacokinetic»).

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, and clarithromycin), the dose should be reduced as in Table 2 (see «Warnings and precautions» and «Interactions»).

Table 2: Dosing Schedule for Concomitant Use of Trikafta with Moderate and Strong CYP3A Inhibitors

Moderate CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4***
Morning Dose	Two elexacaftor/ tezacaftor/ivacaftor tablets	One ivacaftor tablet	Two elexacaftor/ tezacaftor/ivacaftor tablets	One ivacaftor tablet
Evening Dose^	No dose			

* Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets and one ivacaftor tablet on alternate days.
^ The evening dose of ivacaftor should not be taken.

Strong CYP3A Inhibitors				
	Day 1	**Day 2**	**Day 3**	**Day 4#**
Morning Dose	Two elexacaftor/ tezacaftor/ivacaftor tablets	No dose	No dose	Two elexacaftor/tezacaftor/ ivacaftor tablets
Evening Dose^	No dose			

\# Continue dosing with two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.
^ The evening dose of ivacaftor tablet should not be taken.

Children

The safety and efficacy of Trikafta in children aged less than 12 years have not been established (see «Undesirable effects» and «Properties/Effects»).

Elderly patients

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

Contraindications

Hypersensitivity to the active substances or to any of the excipients (see «Composition»).

Warnings and precautions

Effect on liver function tests

Elevated transaminases are common in patients with CF and have been observed in some patients treated with Trikafta. Assessments of transaminases (ALT and AST) are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted, and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, consider the benefits and risks of resuming treatment (see «Undesirable effects»).

Interactions with medicinal products

CYP3A inducers

Exposure to ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Trikafta efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see «Interactions»).

CYP3A inhibitors

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. Therefore, the dose of Trikafta should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see «Interactions» and Table 2 in «Dosage/Administration»).

Cataracts

Cases of non-congenital lens opacities without impact on vision have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation) a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Trikafta (see «Preclinical data»).

Patients after organ transplantation

Elexacaftor/tezacaftor/ivacaftor 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.

Lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially ‘sodium-free’.

Interactions

Pharmacokinetic interactions

Medicinal products affecting the pharmacokinetics of Trikafta

CYP3A inducers

Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced Trikafta efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration of Trikafta with strong CYP3A inducers is not recommended (see «Warnings and precautions»).

Examples of strong CYP3A inducers include:

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

CYP3A inhibitors

Co-administration with itraconazole, a strong CYP3A inhibitor, increased elexacaftor AUC by 2.8 fold and tezacaftor AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of Trikafta should be reduced when co-administered with strong CYP3A inhibitors (see «Warnings and precautions» and Table 2 in «Dosage/Administration»).

Examples of strong CYP3A inhibitors include:

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

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9 to 2.3-fold. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dose of Trikafta should be reduced when co-administered with moderate CYP3A inhibitors (see «Warnings and precautions» and Table 2 in «Dosage/Administration»).

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

Co-administration of Trikafta with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor. Food or drink containing grapefruit should be avoided during treatment with Trikafta (see «Dosage/Administration»).

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 3.

Table 3: Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor

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

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

Medicinal products affected by Trikafta

CYP2C9 substrates

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

Potential for interaction with transporters

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

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Tezacaftor/ivacaftor increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration of Trikafta may increase exposures of medicinal products that are substrates of these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. In Study 445-102, mild increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX.

Hormonal contraceptives

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

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 4.

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

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

* Effect not clinically significant.

Pregnancy, lactation

Pregnancy

No adequate and well-controlled studies of Trikafta in pregnant women have been conducted. Animal studies with the individual active substances did not show any direct toxicity in terms of pregnancy, embryofetal development or postnatal development (see "Preclinical Data"). As a precautionary measure, use of the therapy should be avoided during pregnancy.

Lactation

It is not known whether elexacaftor, tezacaftor, ivacaftor or their metabolites are excreted into human breast milk. Available pharmacokinetic data in animals have shown excretion of elexacaftor, tezacaftor, and ivacaftor into the milk of lactating female rats. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with Trikafta taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data available on the effect of elexacaftor, tezacaftor, and ivacaftor on fertility in humans. In animal studies, elexacaftor and ivacaftor had an effect on the fertility of rats. In animal studies, tezacaftor showed no effect on mating behaviour and fertility parameters(see «Preclinical data»).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

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

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

Serious adverse drug reactions that occurred more frequently in Trikafta-treated patients compared to placebo were rash events in 3 (1.5%) Trikafta-treated patients vs.1 (0.5%) placebo. The most

common (≥10%) adverse drug reactions in patients treated with Trikafta were headache (17.3%), diarrhea (12.9%) and upper respiratory tract infection (11.9%).
The safety profile of Trikafta was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted FEV_1 ($ppFEV_1$), and geographic regions.

Tabulated list of adverse reactions

Table 5 reflects adverse reactions observed with elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor. Adverse drug reactions for Trikafta are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 5: Adverse reactions during use of elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor and ivacaftor alone		
MedDRA System Organ Class	**Adverse Reactions**	**Frequency**
Infections and infestations	Upper respiratory tract infection*, Nasopharyngitis	very common
	Rhinitis*, Influenza*	common
Metabolism and nutrition disorders	Hypoglycaemia*	common
Nervous system disorders	Headache*, Dizziness*	very common
Ear and labyrinth disorders	Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder	common
	Ear congestion	uncommon
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain, Nasal congestion*	very common
	Rhinorrhoea*, Sinus congestion, Pharyngeal erythema, Abnormal breathing*	common
	Wheezing*	uncommon
Gastrointestinal disorders	Diarrhoea*, Abdominal pain*	very common
	Nausea, Abdominal pain upper*, Flatulence*	common
Hepatobiliary disorders	Transaminase elevations	very common
	Alanine aminotransferase increased*, Aspartate aminotransferase increased*	common
Skin and subcutaneous tissue disorders	Rash*	very common
	Acne*, Pruritus*	common
Reproductive system and breast disorders	Breast mass	common
	Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain	uncommon
Investigations	Bacteria in sputum	very common
	Blood creatine phosphokinase increased*	common
	Blood pressure increased*	uncommon
*Adverse reactions observed during clinical studies with elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor.		

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

- A 4-week, randomized, double-blind, active-controlled study in 107 patients (Study 445-103).
- A 96-week, open-label safety and efficacy study (Study 445-105) for patients rolled over from Studies 445-102 and 445-103, with interim analysis performed on 509 patients including 58 patients with ≥48 weeks of cumulative treatment with Trikafta.

Description of selected undesirable effects

Transaminase elevations

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

Rash Events

In Study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in Trikafta- and 6.5% in placebo-treated patients. The rash events were generally mild to moderate in severity. The incidence of rash events by patient sex was 5.8% in males and 16.3% in females in Trikafta-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients.
A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, consider interrupting Trikafta and hormonal contraceptives. Following the resolution of rash, consider resuming Trikafta without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.

Increased Creatine Phosphokinase

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

Increased Blood Pressure

In Study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for Trikafta-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).
The proportion of patients who had systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on at least two occasions was 5.0% and 3.0% in Trikafta-treated patients respectively, compared with 3.5% and 3.5% in placebo-treated patients, respectively.

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

Treatment

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

Properties/Effects

ATC code

R07AX32

Mechanism of action

Elexacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. Clinical outcomes were consistent with *in vitro* results and indicate that a single *F508del* mutation is sufficient to result in a significant clinical response (see «Clinical efficacy»).

Pharmacodynamics

Pharmacodynamic effects

Effects on sweat chloride

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

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

Cardiovascular Effects

Effect on QT interval

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

Heart Rate

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

Clinical efficacy

The efficacy of Trikafta in patients with CF was demonstrated in two Phase 3, double-blind, controlled studies (Studies 445-102 and 445-103). Studies 445-102 and 445-103 each enrolled CF patients with at least one *F508del* mutation. Significant clinical benefit was demonstrated in both studies. Trikafta was developed as a combination therapy containing elexacaftor, tezacaftor, and ivacaftor. The benefit of elexacaftor alone and tezacaftor alone in comparison with the combination therapy has not been investigated in clinical studies, and these active substances are not individually available as medicinal products .

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

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

Patients in Studies 445-102 and 445-103 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies. Patients had a confirmed diagnosis of CF and at least one *F508del* mutation. Patients who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 x

ULN, or total bilirubin ≥2 x ULN), were excluded. Patients in Studies 445-102 and 445-103 were eligible to roll over into a 96-week open-label extension study.

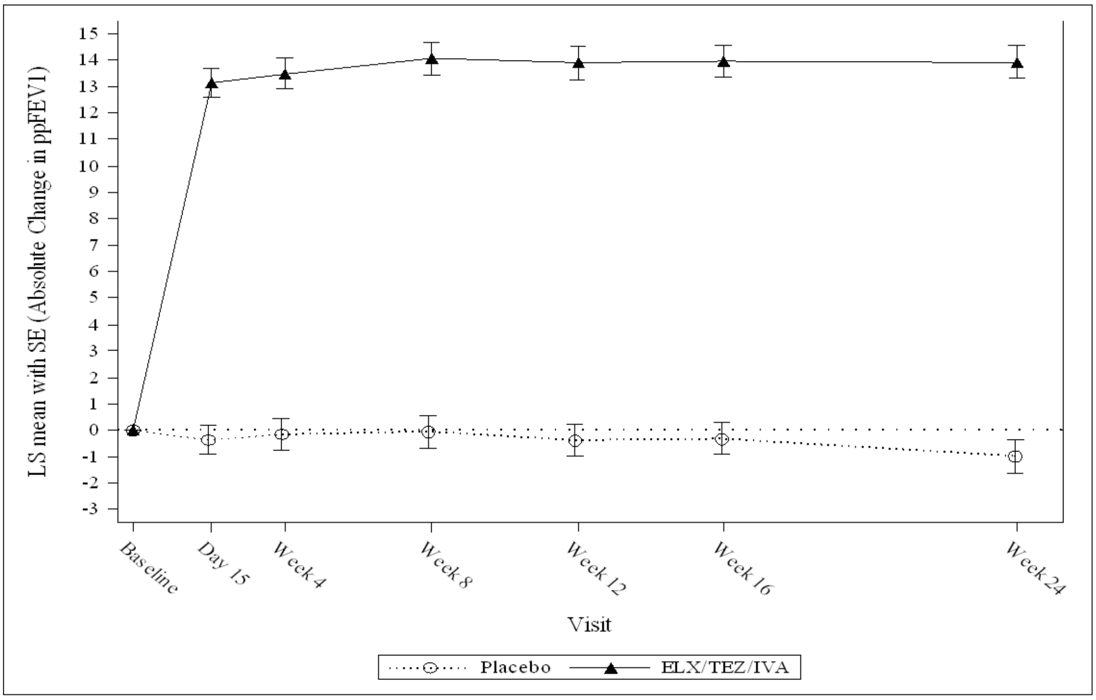
Study 445-102

In Study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24. Treatment with Trikafta compared to placebo resulted in statistically significant improvement in $ppFEV_1$ of 14.3 percentage points (95% CI: 12.7, 15.8; *P*<0.0001) (Table 6). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained through the 24-week treatment period (Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region. A total of 18 patients receiving Trikafta had $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population. See Table 6 for a summary of primary and key secondary outcomes.

Table 6: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)			
Analysis	**Statistic**	**Placebo N=203**	**Trikafta N=200**
Primary efficacy analysis			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key secondary efficacy analyses			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through Week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Absolute change in Sweat Chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 1.13 (0.07)
Absolute change in Sweat Chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 18.1 (1.1)

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index.
‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.
†† Estimated event rate per year was calculated based on 48 weeks per year.

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



SE: Standard Error

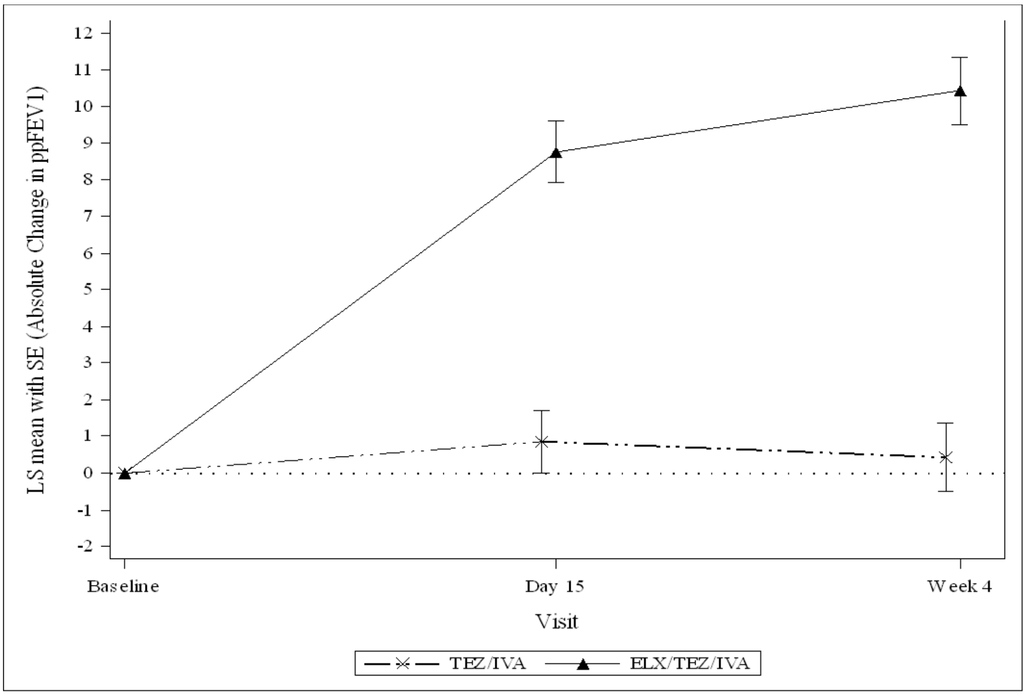
ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor

Study 445-103

In Study 445-103 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with Trikafta compared to the regimen of tezacaftor/ivacaftor and ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; *P*<0.0001) (Table 7). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region. See Table 7 for a summary of primary and key secondary outcomes.

Table 7: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103)			
Analysis*	**Statistic**	**Tezacaftor/ Ivacaftor# N=52**	**Trikafta N=55**
Primary efficacy analysis			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key secondary efficacy analyses			
Absolute change in Sweat Chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 16.0 (2.0)
$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor and ivacaftor run-in period. # Regimen of tezacaftor/ivacaftor and ivacaftor			

Figure 2: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Study 445-103



SE: Standard Error

TEZ/IVA: tezacaftor/ivacaftor

ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor

Study 445-105

An ongoing, 96-week open-label extension study to evaluate the safety and efficacy of long-term treatment with Trikafta is being conducted in patients who rolled over from Studies 445-102 and 445-103. For patients homozygous for the *F508del* mutation who rolled over from Study 445-103 (n=107), an interim efficacy analysis was conducted when they completed Week 24 visit of Study 445-105. Patients who received Trikafta in Study 445-103, and continued treatment in Study 445-105, continued to show values similar to those observed during the controlled study phase for ppFEV1, CFQ-R respiratory domain score, and sweat chloride, through 28 weeks of cumulative treatment (i.e., through week 24 in study 445-105). The outcomes of the annual pulmonary exacerbation event rate through 28 weeks of cumulative treatment (i.e. through week 24 in study 445-105), and BMI and BMI-z score at 28 weeks of cumulative treatment (week 24 in study 445-105), were similar to those seen in patients with the genotypes studied in study 445-102.

Pharmacokinetics

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. The pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor in patients with CF aged 12 years and older are shown in Table 8.

Table 8: Mean (SD) Pharmacokinetic Parameters of Elexacaftor, Tezacaftor and Ivacaftor at Steady State in Patients with CF Aged 12 Years and Older

	Drug	**C_{max} (µg/mL)**	**AUC_{0-24h} or AUC_{0-12h} (µg·h/mL)***
Elexacaftor 200 mg and tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Elexacaftor	9.15 (2.09)	162 (47.5)
	Tezacaftor	7.67 (1.68)	89.3 (23.2)
	Ivacaftor	1.24 (0.34)	11.7 (4.01)

*AUC_{0-24h} for elexacaftor and tezacaftor and AUC_{0-12h} for ivacaftor

Table 9: Pharmacokinetic Parameters of Trikafta Components

	Elexacaftor	**Tezacaftor**	**Ivacaftor**
General Information			
AUC (SD), µg·h/mL[a]	162 (47.5)[b]	89.3 (23.2)[b]	11.7 (4.01)[c]
C_{max}, (SD), µg/mL[a]	9.2 (2.1)	7.7 (1.7)	1.2 (0.3)
Time to Steady State, days	Within 7 days	Within 8 days	Within 3-5 days
Accumulation Ratio	2.2	2.07	2.4
Absorption			
Absolute Bioavailability	80%	Not determined	Not determined
Median T_{max} (range), hours	6 (4 to 12)	3 (2 to 4)	4 (3 to 6)
Effect of Food	AUC increases 1.9- to 2.5-fold	No clinically significant effect	Exposure increases 2.5- to 4-fold

Table 9: Pharmacokinetic Parameters of Trikafta Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
	(moderate-fat meal)		
Distribution			
Mean (SD) Apparent Volume of Distribution, L[d]	53.7 (17.7)	82.0 (22.3)	293 (89.8)
Protein Binding[e]	> 99%	approximately 99%	approximately 99%
Elimination			
Mean (SD) Effective Half-Life, hours[f]	27.4 (9.31)	25.1 (4.93)	15.0 (3.92)
Mean (SD) Apparent Clearance, L/hours	1.18 (0.29)	0.79 (0.10)	10.2 (3.13)
Metabolism			
Primary Pathway	CYP3A4/5	CYP3A4/5	CYP3A4/5
Active Metabolites	M23-ELX	M1-TEZ	M1-IVA
Metabolite Potency Relative to Parent	Similar	Similar	approximately 1/6th of parent
Excretion[g]			
Primary Pathway	• Feces: 87.3% (primarily as metabolites) • Urine: 0.23%	• Feces: 72% (unchanged or as M2-TEZ) • Urine: 14% (0.79% unchanged)	• Feces: 87.8% • Urine: 6.6%

[a] Based on elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours at steady state in patients with CF aged 12 year and older.
[b] $AUC_{0\text{-}24h}$.
[c] $AUC_{0\text{-}12h}$.
[d] Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.
[e] Elexacaftor and tezacaftor bind primarily to albumin. Ivacaftor primarily bind to albumin, alpha 1-acid glycoprotein and human gamma-globulin.
[f] Mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.
[g] Following radiolabeled doses.

Absorption

See Table 9, Pharmacokinetic Parameters of Trikafta Components

Distribution

See Table 9, Pharmacokinetic Parameters of Trikafta Components

Metabolism

See Table 9, Pharmacokinetic Parameters of Trikafta Components

Elimination

See Table 9, Pharmacokinetic Parameters of Trikafta Components

Kinetics in specific patient groups

Hepatic impairment

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 25% higher AUC and a 12% higher C_{max} for elexacaftor, 20% higher AUC but similar C_{max} for tezacaftor, and a 1.5-fold higher AUC and a 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics.

Tezacaftor and ivacaftor

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

Ivacaftor

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

Renal impairment

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or in patients with end stage renal disease.
In human pharmacokinetic studies of elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor in urine (only 0.23%, 13.7% [0.79% as unchanged drug], and 6.6% of total radioactivity, respectively).
Based on population pharmacokinetic (PK) analysis, exposure of elexacaftor was similar in patients with mild renal impairment (N=75, eGFR 60 to less than 90 mL/min/1.73 m^2) relative to patients with normal renal function (N=341, eGFR 90 mL/min/1.73 m^2 or greater).
In population PK analysis conducted in 817 patients administered tezacaftor alone or in combination with ivacaftor in Phase 2 or Phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min/1.73 m^2) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min/1.73 m^2) did not affect the clearance of tezacaftor significantly.

Gender

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

Pediatric patients 12 to less than 18 years of age

Elexacaftor, tezacaftor and ivacaftor exposures observed in Phase 3 studies as determined using population PK analysis are presented by age group in Table 10. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 12 to less than 18 years of age are similar to that of adult patients.

Table 10. Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures by Age Group

Age group	Dose	Elexacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL)	Tezacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL)	Ivacaftor $AUC_{0\text{-}12h,ss}$ (µg·h/mL)
Adolescent patients (12 to <18 years)	elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h	147 (36.8)	88.8 (21.8)	10.6 (3.35)
Adult patients (≥18 years)		168 (49.9)	89.5 (23.7)	12.1 (4.17)

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

Preclinical data

Elexacaftor/tezacaftor/ivacaftor

Repeated dose toxicity studies in rats and dogs in which elexacaftor, tezacaftor and ivacaftor were administered in combination to assess the potential for additive and/or synergistic toxicity did not result in unexpected toxicities or interactions. No safety pharmacology, genotoxicity, carcinogenicity or reproductive toxicity studies were performed with Trikafta. However, studies with the individual substances are available.

Elexacaftor

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

Repeat dose toxicity

In the 6-month rat toxicity study, the primary target organs were the glandular stomach (erosion), testes and epididymis (degeneration/atropy of the seminiferous tubules, oligospermia/aspermia), and bone marrow (decreased hematopoietic cellularity). These effects were primarily observed at non-tolerated doses of ≥40 mg/kg/day in male animals and 30 mg/kg/day in female animals. Plasma exposure (AUC) in animals at NOAEL (15 mg/kg/day) was approximately 3-fold (males) and 11-fold (females) the maximum recommended dose for humans [MRHD]. In the 9-month dog toxicity study, minimal or mild non-adverse bilateral degeneration/atrophy of the seminiferous tubules of the testes was present in males administered elexacaftor at 14 mg/kg/day dose (14 times the MRHD based on summed AUCs of elexacaftor and its metabolites) that did not resolve during the limited recovery period, however without further sequelae. The human relevance of these findings is unknown.

Reproduction toxicity

Elexacaftor was associated with lower male and female fertility, male copulation, and female conception indices in males at 75 mg/kg/day (6 times the MRHD based on summed AUCs of elexacaftor and its metabolite) and in females at 35 mg/kg/day (7 times the MRHD based on summed AUCs of elexacaftor and its metabolite).
Elexacaftor was not teratogenic in rats at 40 mg/kg/day and at 125 mg/kg/day in rabbits (approximately 9 and 4 times, respectively, the MRHD based on summed AUCs of elexacaftor and its metabolites [for rat] and AUC of elexacaftor [for rabbit]). In rat fetuses a lower mean body weight was observed after treatment of the mother animals with ≥ 25 mg/kg/day (approximately 4 times the MRHD based on AUC). No adverse effects were noted in the rat pre- and post-natal development study with doses of up to 10 mg/kg/day (around 1-fold the MRHD based on the summed AUCs of elexacaftor and its metabolites). Placental transfer of elexacaftor was observed in pregnant rats.

Juvenile toxicity

No adverse effects were noted in juvenile rats dosed from postnatal Day 7 through Day 70 with doses that led to plasma exposure of approx. 3-fold (males) and 5-fold (females) the AUC in paediatric patients (aged 12 years and older).

Carcinogenicity

Elexacaftor was shown to be non-carcinogenic in a 6 month study in Tg.rasH2 mice.

<u>Tezacaftor</u>

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

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 tezacaftor was observed in pregnant rats.

<u>Ivacaftor</u>

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

Reproductive toxicity

Ivacaftor affected the fertility and reproductive performance indices of male and female rats at doses of 200 mg/kg/day (approximately 7 and 5 times the MRHD, respectively, based on the summed 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 estrous 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 were attributed to severe toxicity in rats under a dose of 200 mg/kg/day. No effects on male or female fertility and reproductive performance indices were observed after doses of ≤ 100 mg/kg/day (approximately 5-fold and 3-fold, respectively, the MRHD based on the summed 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 6 and 16 times the MRHD, respectively, based on the sum of AUCs of ivacaftor and its metabolites). Effects on fetal 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 pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day, ivacaftor 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 ivacaftor was observed in pregnant rats and rabbits.

Juvenile toxicity

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.2 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in fetuses derived from rat dams treated with ivacaftor on gestation Days 7 to 17, in rat pups exposed to ivacaftor 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 ivacaftor. The potential relevance of these findings in humans is unknown.

Other information

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the container.

Special precautions for storage

Do not store above 30°C.
Keep out of the sight and reach of children.

Authorisation number

67773 (Swissmedic)

Packs

Trikafta film-coated tablets
Pack size of 84 tablets (4 weekly wallets, each with 14 elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg film-coated tablets and with 7 ivacaftor 150 mg film-coated tablets). [A]

Marketing authorisation holder

Vertex Pharmaceuticals (CH) GmbH
6300 Zug

Date of revision of the text

October 2020