



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

26 April 2021  
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Committee for Orphan Medicinal Products

## Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Kaftrio (ivacaftor / tezacaftor / elexacaftor)  
Treatment of cystic fibrosis  
EU/3/18/2116  
Sponsor: Vertex Pharmaceuticals (Ireland) Limited

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## 1. Product and administrative information

<b>Product</b>	
Active substances(s) at the time of orphan designation	Ivacaftor, 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, tezacaftor
Other name(s)	--
International Non-Proprietary Name	ivacaftor / tezacaftor / elexacaftor
Tradename	Kaftrio
Orphan condition	Treatment of cystic fibrosis
Sponsor's details:	Vertex Pharmaceuticals (Ireland) Limited 28-32 Pembroke Street Upper Dublin 2 D02 EK84 Co. Dublin Ireland
<b>Orphan medicinal product designation procedural history</b>	
Sponsor/applicant	Vertex Pharmaceuticals (Europe) Limited
COMP opinion date	8 November 2018
EC decision date	14 December 2018
EC registration number	EU/3/18/2116
<b>Post-designation procedural history</b>	
Transfer of sponsorship	Transfer from Vertex Pharmaceuticals (Europe) Limited to Vertex Pharmaceuticals (Ireland) Limited – EC decision of 12 February 2019
COMP opinion on review of orphan designation at the time of marketing authorisation	16 July 2020
<b>Type II variation procedural history</b>	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Peter Kiely
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	26 August 2020
Procedure start	12 September 2020
Procedure number	EMA/H/C/005269/II/0001
Invented name	Kaftrio
Proposed therapeutic indication	Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets 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 ( <i>CFTR</i> ) gene.  Further information on Kaftrio can be found in the European public assessment report (EPAR) on the Agency's website <a href="http://ema.europa.eu/en/medicines/human/EPAR/kaftrio">ema.europa.eu/en/medicines/human/EPAR/kaftrio</a>
CHMP opinion	25 March 2021

<b>COMP review of orphan medicinal product designation procedural history</b>	
COMP rapporteur(s)	Armando Magrelli / Elisabeth Johanne Rook
Sponsor's report submission	24 September 2020
COMP discussion and adoption of list of questions	3-5 November 2020 and 16-18 March 2021
COMP opinion (adoption via written procedure)	26 March 2021

## **2. Grounds for the COMP opinion**

### **2.1. Orphan medicinal product designation**

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing ivacaftor, 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, tezacaftor was considered justified based on preliminary clinical data showing improvement of lung function with the proposed product in patients homozygous for the F508del mutation and in patients heterozygous for F508del and a minimal function mutation;
- the condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- the condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made;
- in addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ivacaftor, 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, tezacaftor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that in the homozygous F508del patient population the proposed product has better effect on lung function than the combination of tezacaftor and ivacaftor, the CFTR modulators currently authorised for this patient population. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

### **2.2. Review of orphan medicinal product designation at the time of marketing authorisation**

The COMP opinion on the initial review of the orphan medicinal product designation in July 2020 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of cystic fibrosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;

- the condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Kaftrio may be of potential significant benefit to those affected by the orphan condition is confirmed. In patients homozygous for the *F508del* mutation of cystic fibrosis transmembrane conductance regulator (*CFTR*), Kaftrio showed better efficacy in the primary endpoint of lung function and in relevant secondary endpoints as compared to Symkevi, currently authorised for the condition. Kaftrio also showed clinical efficacy in patients heterozygous for *F508del* and minimal function mutations in the *CFTR*, for whom there is no specific *CFTR* modulator treatment authorized. The Committee considers that this constitutes a clinically relevant advantage for the patients affected by the condition.

### 3. Review of criteria for orphan designation at the time of type II variation

#### Article 3(1)(a) of Regulation (EC) No 141/2000

***Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made***

#### **Condition**

The present extension of indication "*Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets 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*" falls within the designated orphan condition 'treatment of cystic fibrosis'.

#### **Intention to diagnose, prevent or treat**

The medical plausibility has been confirmed for Kaftrio (ivacaftor/tezacaftor/elexacaftor) by the positive benefit/risk assessment of the CHMP. Please see EPAR.

#### **Chronically debilitating and/or life-threatening nature**

There have been no changes in the seriousness of the condition since the time of orphan designation. The condition remains life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

#### **Number of people affected or at risk**

There have been no significant changes in the prevalence of the condition since the time of orphan designation. The sponsor calculated the current prevalence based mainly on registry data, concluding with a proposed estimate of 0.78 in 10,000 in the EU. This is in line with previous designations although more recently some studies suggest a slight increase in prevalence (also as result of better available treatments), which would be around 0.9 in 10,000 (not significantly different from the one proposed by the sponsor). Recently the COMP has often adopted less than 1 in 10,000 so to allow for slight fluctuations of prevalence based on different sources. This figure is also used for the present application.

## Article 3(1)(b) of Regulation (EC) No 141/2000

**Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.**

### Existing methods

The sponsor correctly identifies the currently authorized treatments for the condition, which can be broadly classified in: (1) CFTR modulators (i.e. correctors and potentiators) which target the underlying cause of the disease, i.e. target CFTR dysfunction; and (2) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy).

Centrally authorized products for the treatment of CF in the EU are presented in Table 1 below (from the sponsor's application)

**Table 1.** Centrally Authorized Medicinal Products for the Treatment of CF

Invented Name (INN)	Approval Date	Indication and Age Groups
Products Targeting CFTR Dysfunction		
Kalydeco (ivacaftor)	23 Jul 2012	Kalydeco is indicated for the treatment of patients with CF aged 12 months and older and weighing 7 kg or more who have 1 of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R (Gating patients) Kalydeco is indicated for the treatment of patients with CF aged 18 years and older who have an R117H mutation in the CFTR gene. (R117H patients)
Orkambi (lumacaftor/ivacaftor)	19 Nov 2015	Orkambi is indicated for the treatment of CF in patients aged 2 years and older who are homozygous for the <i>F508del</i> mutation in the CFTR gene (F/F patients).
Symkevi + Kalydeco (tezacaftor/ivacaftor)	31 Oct 2018	Symkevi is indicated in a combination regimen with Kalydeco 150 mg tablets for the treatment of patients with CF aged 12 years and older who are homozygous for the F508del mutation (F/F patients) or who are heterozygous for the F508del mutation and have 1 of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T (F/RF patients).

Kaftrio + Kalydeco (ELX/TEZ/IVA)	21 Aug 2020	Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation (F/F patients) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation (F/MF patients)
Products to Manage CF Symptoms		
Bronchitol (mannitol)	13 Apr 2012	Bronchitol is indicated for the treatment of CF in adults aged 18 years and above as an add-on therapy to best standard of care.
Cayston (aztreonam lysine)	21 Sep 2009	Cayston is indicated for the suppressive therapy of chronic pulmonary infections due to <i>P. aeruginosa</i> in patients with CF aged 6 years and older.
Colobreathe (colistimethate sodium)	13 Feb 2012	Colobreathe is indicated for the management of chronic pulmonary infections due to <i>P. aeruginosa</i> in patients with CF aged 6 years and older.
Quinsair (levofloxacin)	26 Mar 2015	Quinsair is indicated for the management of chronic pulmonary infections due to <i>P. aeruginosa</i> in adult patients with CF.
TOBI Podhaler (tobramycin)	20 Jul 2011	TOBI Podhaler indicated for the suppressive therapy of chronic pulmonary infection due to <i>P. aeruginosa</i> in adults and children aged 6 years and older with CF.
Vantobra (tobramycin)	18 Feb 2019	Vantobra is indicated for the management of chronic pulmonary infection due to <i>P. aeruginosa</i> in patients aged 6 years and older with CF.

### Significant benefit

The significant benefit is discussed for each of the patient populations covered by the proposed extended therapeutic indication.

NOTE: the significant benefit for F508Del homozygous (F/F) and for patients heterozygous for F508del and a minimal function (MF) mutation (patients F/MF) at point 1 and 2 below was already confirmed by the COMP in the discussion of the initial MA of Kaftrio or the type II variation (0085) of Kalydeco.

This extension to other mutations (points 3 and 4 below) was also discussed by the COMP at that time and in principle the Committee had favourable views already at that time.

#### 1. F508Del homozygous patient population (approximately 45% of the CF patient population)

Study 103 constitutes the main supportive evidence for the significant benefit in this patient group. This was a 4-week randomized, double-blind, active-controlled, parallel-group, multicenter study in subjects 12 years of age and older with a F508del mutation on both alleles (homozygous). The study assessed the added benefit of Kaftrio in comparison with Symkevi (TEZ-/IVA). In both cases the products were administered once a day, in combination regimen with Kalydeco, administered in the evening.

Kaftrio resulted in a statistically significant improvement in the primary endpoint of absolute change in ppFEV1 at Week 4 compared to Symkevi, with a treatment difference of 10.0 percentage points (P<0.0001). In addition, Kaftrio resulted in a statistically significant decrease in SwCl compared to Symkevi, with mean treatment difference of -45.1 mmol/L (P <0.0001 [95% CI: -50.1, -40.1]) for absolute change at Week 4, and in a significant increase in CFQ-R RD compared to Symkevi, with a LS mean treatment difference of 17.4 points (P<0.0001 [95% CI: 11.8, 23.0]) for absolute change at Week 4. Table 2 below shows the results (from the CHMP assessment report).

2. Patients heterozygous for F508del and a MF (minimal function) mutation (approximately 25% of the total CF population).

The significant benefit for this patient population is supported by study 102, which was a 24-week randomized, double blind, placebo controlled, parallel group, multicenter study in subjects 12 years of age and older, who had an F508del mutation on one allele and a MF mutation on the other allele resulting in either no CFTR protein, or a protein that does not respond to IVA and TEZ/IVA in vitro.

The difference in the absolute change of ppFEV1 through week 24 between Kaftrio (in combination with Kalydeco) and placebo was 14.3% (CI 95%: 12.7 – 15.8; p<0.0001) in favour of Kaftrio. The difference was already observable at week 4 (13.7%; CI 95% 12.0 - 15.3; p<0.0001). For pulmonary exacerbations, the rate ratio was 0.37 (95% CI: 0.25 – 0.55, p<0.0001) in favor of Kaftrio plus Kalydeco, with an overall reduction of 63%. The hazard ratio for time-to-first pulmonary exacerbations was also in favour of Kaftrio (HR: 0.34; 95% CI 0.22, 0.52; nominal p<0.0001). A higher CFQ-R RD score was observed in the treated arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). In addition, an absolute change of 1.04 (95% CI: 0.85, 1.23; p<0.0001) compared to placebo was seen in body mass index (BMI)

The significant benefit in subjects with MF/F508Del mutation, for which no specific CFTR modulator is authorized, was therefore supported, and confirmed by the COMP in July 2020.

Points 3 and 4 below present a combined discussion on the remaining mutations that have been studied by the sponsor, which are now all included in the therapeutic indication ("*treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene*")

3. Patients who are heterozygous for F508Del and a residual function mutation (F/RF) (approximately 5% of the total CF population)

Authorized treatments: Symkevi is indicated in a combination regimen with Kalydeco 150 mg tablets for the treatment of patients with CF aged 12 years and older who are heterozygous for the F508del mutation and have 1 of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T (Section 4.1).

- 4) Patients who are heterozygous for F508Del with a gating mutation (F/G)

Authorized treatments: Kalydeco (IVA) is indicated for the treatment of CF patients who have 1 of the following gating mutations, irrespective of the mutation on the other allele (i.e. not specifically F508del): G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N or S549R (Section 4.1).

Real world data from the US CFFPR for F/RF and F/G patients treated with VX-445/TEZ/IVA was provided by the sponsor, from post-marketing use in the US. From 21 October 2019 through 31 December 2019, a total of 521 F/G or F/RF patients had a record of VX-445/TEZ/IVA treatment



initiation in CFFPR. Of these patients, 297 patients (57%) had lung function measurements available both at baseline and follow-up and were included in these analyses.

Gating mutations eligible for inclusion in the analyses were G1069R, G1244E, G1349D, G178R, G551D, G551S, R1070Q, R117H, S1251N, S1255P, S549N, or S549R. RF mutations eligible for inclusion in the analyses were 2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+3A->G, A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, or S977F.

The vast majority of the F/G and F/RF patients included in this analysis were receiving CFTR modulator therapy prior to initiating VX-445/TEZ/IVA treatment (97.8% of F/G patients and 89.4% F/RF patients were exposed to at least one other CFTR modulator in 2019). The mean baseline ppFEV1 values were 69.0 for the F/G patients and 66.6 for the F/RF patients. An improvement in ppFEV1 from baseline was observed for both genotype groups: mean of 4.3 percentage points (95% CI: 2.7, 5.9) for the F/G patients, and 2.7 percentage points (95% CI: 1.7, 3.7) for the F/RF patients (Table 2).

**Table 2.** CFFPR Data for F/G and F/RF Patients Who Initiated Treatment With VX-445/TEZ/IVA Between 21 October 2019 and 31 December 2019

Subgroup	Patients n	Pre- VX-445/TEZ/IVA ppFEV <sub>1</sub>	Post- VX-445/TEZ/IVA ppFEV <sub>1</sub> <sup>a</sup>	Change in ppFEV <sub>1</sub>	95% CI for Change in ppFEV <sub>1</sub> <sup>b</sup>
		Mean (SD)	Mean (SD)	Mean (SD)	
F/G	136	69.0 (26.1)	73.3 (25.2)	+4.3 (9.6)	(2.7, 5.9)
F/RF	161	66.6 (25.1)	69.3 (24.8)	+2.7 (6.6)	(1.7, 3.7)

Source: data on file from CFFPR

<sup>a</sup> Post-treatment ppFEV<sub>1</sub> data examined through 15 March 2020

<sup>b</sup> 95% CI was calculated by Vertex based on one sample t test.

In addition to these data, which were already presented in the initial MA, the sponsor added the results from Study 104, an 8-week, randomized, double-blind, active-controlled, parallel-group, multicenter study in patients with an F/Gating or F/RF genotype. Study 104 was designed to compare ELX/TEZ/IVA efficacy to the currently approved CFTR modulator therapy (IVA for F/Gating subjects and TEZ/IVA for F/RF subjects).

In study 104 treatment with VX-445/TEZ/IVA resulted in statistically significant improvements of the primary endpoint of FEV1 as well as improvements in clinically relevant secondary endpoints such as sweat chloride and functional score of the respiratory domain, CFQ-R RD.

In patients with F/residual function (RF) mutations, Kaftrio in combination with Kalydeco resulted in improvement versus standard-of-care Symkevi in the primary endpoint ppFEV1 (LS mean treatment difference: 2.0 percentage points; nominal P= 0.0093], sweat chloride (LS mean treatment difference -24.8 mmol/L; nominal P <0.0001]), and CFQ-R RD (8.5 points; nominal P value = 0.0003). The secondary endpoints supported the clinical relevance of the relatively small change in ppFEV1 that was achieved.

In patients with F/Gating mutations, Kaftrio in combination with Kalydeco resulted in improvements versus Kalydeco for percentage predicted FEV1 (ppFEV1: LS mean treatment difference: 5.8 percentage points; nominal P <0.0001], sweat chloride (LS mean treatment difference: -20.0 mmol/L; nominal P <0.0001) and CFQ-R RD (LS mean treatment difference: 8.9 points; nominal P = 0.0008]).

The study included a 4-week Run-in Period where subjects received the approved CFTR modulator therapy; therefore, the improvement in the Kaftrio group was on top of the improvements that had been achieved with treatment with Kalydeco alone, or Symkevi.

In conclusion, the significant benefit in heterozygous F/RF and F/G mutations is supported by real life data from the study performed in the US, as well as by the results of study 104, showing clinically meaningful efficacy in patients who had been previously treated with Kalydeco alone, or Symkevi (depending on the mutations for which they were authorised).

#### **4. COMP list of issues**

Not applicable

## 5. COMP position adopted on 26 March 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of cystic fibrosis (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Kaftrio will be of significant benefit to those affected by the orphan condition is confirmed. In patients with at least one residual function F508del mutation of the cystic fibrosis transmembrane conductance regulator gene, Kaftrio in combination with Kalydeco showed better efficacy in the primary endpoint of lung function and in relevant secondary endpoints as compared to Symkevi, currently authorised for the condition. In patients with gating mutations, Kaftrio in combination with Kalydeco also showed better efficacy in lung function versus Kalydeco alone. In addition, Kaftrio in combination with Kalydeco can now be used in all patients who have at least one F508del allele. The Committee considers that this constitutes a clinically relevant advantage for the patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Kaftrio, ivacaftor, 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, tezacaftor, (ivacaftor / tezacaftor / elexacaftor) for treatment of cystic fibrosis (EU/3/18/2116) is not removed from the Community Register of Orphan Medicinal Products.