



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

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

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
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
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Europe) Limited
COMP opinion date	8 November 2018
EC decision date	18 December 2018
EC registration number	EU/3/18/2116
Post-designation procedural history	
Transfer of sponsorship	Transfer from Vertex Pharmaceuticals (Europe) Limited to Vertex Pharmaceuticals (Ireland) Limited – EC decision of 12 February 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Peter Kiely
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission date	14 October 2019
Procedure start date	31 October 2019
Procedure number	EMA/H/C/005269
Invented name	Kaftrio
Therapeutic indication	<p>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 <i>F508del</i> mutation in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) gene or heterozygous for <i>F508del</i> in the <i>CFTR</i> gene with a minimal function (MF) mutation.</p> <p>Further information on Kaftrio can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio</p>
CHMP opinion date	25 June 2020

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Eva Malikova
Sponsor's report submission date	7 November 2019
COMP discussion and adoption of list of questions	16-18 June 2020
COMP opinion date	16 July 2020

2. Grounds for the COMP opinion

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.

3. Review of criteria for orphan designation at the time of marketing authorisation

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 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 are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or

heterozygous for *F508del* in the *CFTR* gene with a minimal function (MF) mutation" falls within the designated orphan condition 'treatment of cystic fibrosis'.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

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. 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 <i>CFTR</i> gene: <i>G551D</i> , <i>G1244E</i> , <i>G1349D</i> , <i>G178R</i> , <i>G551S</i> , <i>S1251N</i> , <i>S1255P</i> , <i>S549N</i> or <i>S549R</i> (Gating patients) Kalydeco is indicated for the treatment of patients with CF aged 18 years and older who have an <i>R117H</i> mutation in the <i>CFTR</i> 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 (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 <i>F508del</i> mutation (F/F patients) or who are heterozygous for the <i>F508del</i> mutation and have 1 of the following mutations in the <i>CFTR</i> gene: <i>P67L</i> , <i>R117C</i> , <i>L206W</i> , <i>R352Q</i> , <i>A455E</i> , <i>D579G</i> , <i>711+3A→G</i> , <i>S945L</i> , <i>S977F</i> , <i>R1070W</i> , <i>D1152H</i> , <i>2789+5G→A</i> , <i>3272-26A→G</i> , and <i>3849+10kbC→T</i> (F/RF 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 authorized therapeutic indication.

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. The study assessed the added benefit of Kaftrio in comparison with Symkevi. 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 least square (LS) mean treatment difference of 10.0 percentage points (P<0.0001). In addition Kaftrio resulted in a statistically significant decrease in sweat chloride (SwCl) compared to Symkevi, with a LS 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).

Table 2. Study 103: Primary and Key Secondary Efficacy Analyses

Analysis	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Primary			
Absolute change from baseline in ppFEV ₁ at Week 4 (percentage points)	LS mean (SE)	0.4 (0.9)	10.4 (0.9)
	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean difference, 95% CI	--	10.0 (7.4, 12.6)
	<i>P</i> value versus TEZ/IVA	--	<0.0001
Key Secondary			
Absolute change from baseline in SwCl at Week 4 (mmol/L)	LS mean (SE)	1.7 (1.8)	-43.4 (1.7)
	95% CI of LS mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS mean difference, 95% CI	--	-45.1 (-50.1, -40.1)
	<i>P</i> value versus TEZ/IVA	--	<0.0001
Absolute change from baseline in CFQ-R RD score at Week 4 (points)	LS mean (SE)	-1.4 (2.0)	16.0 (2.0)
	95% CI of LS mean	(-5.4, 2.6)	(12.1, 19.9)
	LS mean difference, 95% CI	--	17.4 (11.8, 23.0)
	<i>P</i> value versus TEZ/IVA	--	<0.0001

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; *P*: probability; ppFEV₁: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

The difference between Kaftrio and Symkevi in the homozygous population is clinically relevant. It is acceptable that no comparison has been performed versus Orkambi, since the latter (also authorized for the homozygous patient population) has shown more modest effects on FEV₁ than Symkevi in earlier clinical studies.

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 an 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 LS mean difference in the absolute change of ppFEV1 through week 24 between Kaftrio (in combination with Kalydeco) and placebo was 14.3 percentage points (CI 95%: 12.7, 15.8; $p < 0.0001$) in favour of Kaftrio. The difference was already observable at week 4 (13.7 percentage points; 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% through Week 24. The hazard ratio for time-to-first pulmonary exacerbations through Week 24 was also in favour of Kaftrio (HR: 0.34; 95% CI 0.22, 0.52; $p < 0.0001$). A higher CRQ-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 kg/m² (95% CI: 0.85, 1.23; $p < 0.0001$) compared to placebo was seen in body mass index (BMI)

The significant benefit in MF/F508Del mutation, for which no specific CFTR modulator is authorized, is therefore also supported.

In conclusion, the significant benefit in homozygous F/F and in heterozygous F/MF mutations is supported by statistically significant and clinically relevant results of Kaftrio (in combination with Kalydeco) versus Symkevi (in combination with Kalydeco) in F/F and versus placebo in F/MF, for which no CFTR modulator is specifically authorized. The COMP granted a positive opinion based on the above.

4. COMP position adopted on 16 July 2020

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 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.

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.