20 March 2025
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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

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	
Designated active substance(s)	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 Unit 49 Block 5 Northwood Court Northwood Crescent Northwood Dublin 9 D09 T665 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Vertex Pharmaceuticals (Europe) Limited
COMP opinion	8 November 2018
EC decision	14 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
COMP opinion on review of orphan designation at the time of marketing authorisation	16 July 2020
COMP opinion on review of orphan designation at the time of type II variation	26 March 2021
Type II variation procedural history	
Rapporteur / Co-rapporteur	Peter Mol / Finbarr Leacy
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	8 November 2023
Procedure start	25 November 2023
Procedure number	EMEA/H/C/002494/WS2551/0121
Invented name	Kaftrio

Proposed therapeutic indication	Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Further information on Kaftrio can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/kaftrio
CHMP opinion	27 February 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cecile Dop / Enrico Costa
Sponsor's report submission	8 December 2023
COMP discussion	18-20 March 2025
COMP opinion	20 March 2025

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 designation in 2018 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 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.

2.3. Review of orphan medicinal product designation at the time of type II variation

The COMP opinion on the review of the orphan medicinal product designation for type II variation in 2021 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 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.

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

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. This gene is responsible for expression of a protein called the CF transmembrane conductance regulator. This protein regulates chloride transport. Over 2000 mutations in CFTR are found, but not all of them causes CF. The main pathogenetic mechanism in cystic fibrosis is a defect in the cellular Na+/Cl- transport pump, with defect in Na+ and Cl- regulation across the cellular membranes at the one known as CFTR site. The most common mutation is the deletion of phenylalanine at the 508 locus, referred to as delta (Δ) F508. CF patients have exocrine gland dysfunction involving multiple organ systems, with production of thick mucus in the bronchial tree, leading to bronchiectasis, chronic respiratory infections, and they present with pancreatic enzyme insufficiency and associated complications. The life-expectancy of CF has increased in the past years; however, most of the patients still die before the age of forty at the present date, mainly due to the pulmonary component of the disease.

The approved therapeutic indication "Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1) and Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1)" falls within the scope of 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, 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 estimates the prevalence of cystic fibrosis (CF) in Europe using data from the European Cystic Fibrosis Society Patient Registry (ECFSPR), which collects demographic and clinical information from consenting individuals with CF across European countries. As the exact prevalence of CF is not well-defined, the sponsor utilizes the 2021 ECFSPR report to derive an estimate.

To calculate prevalence, the sponsor first identifies country-specific CF case counts from the registry and applies adjustments based on the estimated coverage percentage of each country's registry data. This adjustment aims to approximate the total number of CF cases within each country. The sum of these estimated cases results in a total CF population estimate of 38,776 individuals across the EU and EEA (Table 1).

The prevalence estimate is derived by dividing the total estimated CF cases by the total population of the included countries, which is based on United Nations Population Division's 2022 World Population Prospects. This calculation results in an overall estimated prevalence of 0.86 cases per 10,000 persons, with country-specific prevalence ranging from 0.19 per 10,000 (Finland) to 2.99 per 10,000 (Ireland). These estimates remain below the 5 per 10,000 orphan designation threshold.

The sponsor's analysis provides an estimate of CF prevalence based on available registry data, adjusted case estimates, and population-based calculations. The findings indicate that CF remains within the prevalence threshold for orphan designation in the EU and EEA. Recently the COMP has often adopted approximately 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

Estimated Prevalence of CF in the EU/EEA

	ECFSR (2021 Report)[a]			**Estimated Prevalence**	
	CF Cases (n)	**Estimated Coverage (%)**	**Estimated CF Cases (n)**	**Total Population[b]**	**CF Cases Per 10,000 Persons**
Austria	877	>90	974	8,922,082	1.09
Belgium	1387	>90	1,541	11,611,420	1.33
Bulgaria	208	87	239	6,885,868	0.35
Croatia	148	>95	156	4,060,136	0.38
Cyprus	34	>80	43	1,244,188	0.34
Czech Republic	681	99	688	10,510,751	0.65
Denmark	561	99	567	5,854,241	0.97
Finland	97	90	108	5,535,992	0.19
France	7,136	>90	7,929	64,531,444	1.23
Germany	6,789	80	8,486	83,408,555	1.02
Greece	618	80	773	10,445,365	0.74
Hungary	508	98	518	9,709,786	0.53
Iceland	14	>90	16	370,335	0.42
Ireland	1,325	89	1,489	4,986,526	2.99
Italy	5,994	98	6,116	59,240,330	1.03

Latvia	47	>90	52	1,873,919	0.28
Lithuania	41	70	59	2,786,651	0.21
Luxembourg[c]	28	60	47	639,321	0.73
Netherlands	1,596	95	1,680	17,501,696	0.96
Norway	344	85	405	5,403,021	0.75
Poland	1,430	84	1,702	38,307,726	0.44
Portugal	366	>95	385	10,290,103	0.37
Romania	268	54	496	19,328,560	0.26
Slovakia	295	>90	328	5,447,622	0.60
Slovenia	118	>95	124	2,119,410	0.59
Spain	2,532	83	3,051	47,486,935	0.64
Sweden	765	>95	805	10,467,097	0.77
Total	**34,207**	**--**	**38,776**	**448,969,075**	**0.86**

EEA: European Economic Area; EU: European Union
[a] ECFSR (2021 Report) data not available for the following countries: Estonia, Malta, Liechtenstein, and Northern Ireland
[b] Total population based on United Nations, Population Division, World Population Prospects 2022
[c] In Luxembourg, an adult centre did not provide data for 2021.

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 describes the current treatment landscape for cystic fibrosis (CF), noting that while there is no cure, available therapies fall into two main categories: (1) treatments that manage symptoms, complications, and comorbidities (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy), and (2) CF transmembrane conductance regulator (CFTR) modulators, which target the underlying cause of the disease. The introduction of CFTR modulators represents a significant advancement in CF treatment, as they have been shown to modify disease progression in patients with specific CFTR mutations, including severe (e.g., F508del, MF mutations, or gating mutations) and RF mutations.

The sponsor provides an overview of centrally authorized medicinal products for CF treatment in the European Union (EU) (Table 2).

In addition to centrally authorized treatments, several nationally authorized therapies are available, including generic antibiotics (e.g., ciprofloxacin, meropenem trihydrate), mucolytics (e.g., dornase alfa), and anti-inflammatory agents. Other supportive treatments, such as hypertonic saline (classified as a medical device) and chest physiotherapy, are also commonly used.

Centrally Authorized Medicinal Products for the Treatment of CF

Invented Name **(INN)**	**Initial MAA Approval Date**	**Current Indication and Age Groups**
Products Targeting CFTR Dysfunction		
Kalydeco (ivacaftor)	23 Jul 2012	Kalydeco is indicated for the treatment of patients with CF aged 1 month and older and weighing 3 kg or more who have an *R117H CFTR* mutation (*R117H* patients) or 1 of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E, G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P, S549N* or *S549R* (Gating patients)
Orkambi (lumacaftor/ ivacaftor)	19 Nov 2015	Orkambi is indicated for the treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation (F/F patients).
Symkevi + Kalydeco (tezacaftor/ivacaftor)	31 Oct 2018	Symkevi is indicated in a combination regimen with Kalydeco for the treatment of patients with CF aged 6 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 (ELX/TEZ/IVA)	21 Aug 2020	Kaftrio is indicated in a combination regimen with ivacaftor for the treatment of CF in patients aged 2 years and older who have at least one *F508del* mutation in the *CFTR* gene (F-any 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 *Pseudomonas aeruginosa* 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 *P aeruginosa* 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 *P aeruginosa* in adult patients with CF.
TOBI Podhaler (tobramycin)	20 Jul 2011	TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to *P aeruginosa* in adults and children aged 6 years and older with CF.

Kaftrio (Product No. EMEA/H/C/005269) was granted marketing authorization (MA) in the European Union (EU) on August 21, 2020, for use in combination with ivacaftor 150 mg tablets. It is indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1).

The proposed extension aims to broaden Kaftrio's indication to include younger patients and a wider range of genetic mutations. The revised indications are as follows:

- Kaftrio tablets are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, or
- Kaftrio granules are indicated in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in paediatric patients aged 2 to less than 6 years who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1).

For further details on posology and clinical data, refer to the Summary of Product Characteristics (SmPC).

Comparison with existing cystic fibrosis therapies

Given its mechanism of action as a CFTR modulator, the relevant comparison is considered against other CFTR modulators that have already been authorized, rather than treatments that address only the symptoms or complications of cystic fibrosis (CF). While conventional CF therapies, such as mucolytics, antibiotics, bronchodilators, and pancreatic enzyme supplements, play a critical role in managing the symptoms and complications of cystic fibrosis, they do not correct for the underlying CFTR protein dysfunction that causes the disease. As a result, their therapeutic goals and mechanisms of action are fundamentally different from those of CFTR modulators like Kaftrio, which directly target the defective protein. Although these therapies may continue to be used alongside CFTR modulators in clinical practice, they do not represent an appropriate comparator for evaluating the efficacy of a disease-modifying treatment. Therefore, comparisons should focus on other CFTR modulators that share a similar mechanism of action.

The extension of Kaftrio's indication is particularly significant for the non-F508del (non-F) CF population, which represents approximately 20% of people with CF (pwCF). This genetically diverse group includes over 1,800 CFTR variants, many of which have not been clinically evaluated due to their rarity. Consequently, access to CFTR modulator therapy has been limited for this patient population.

Among non-F CF patients, a subset of approximately 5% of pwCF are homozygous for Class I mutations, which are known to be non-responsive to CFTR modulator therapy. This limitation has been explicitly addressed in the SmPC, with a warning in section 4.4 stating that Kaftrio is not effective in these patients. However, for other non-Class I homozygous mutations, the extension of Kaftrio's indication is supported by the data submitted.

Based on this comprehensive body of evidence and input from clinical experts, the Committee for Medicinal Products for Human Use (CHMP) concluded that Kaftrio's benefit-risk (B/R) profile supports extending its indication to all non-Class I CF mutations, while maintaining restrictions for pwCF homozygous for Class I mutations.

In the EU and other regions, there are currently no CFTR modulator therapies available for the majority of pwCF with an ELX/TEZ/IVA-responsive, non-F508del CFTR mutation. The expansion of Kaftrio's

indication therefore addresses an unmet medical need, offering a treatment option for CF patients who previously had no approved CFTR modulator.

In conclusion, the Committee for Orphan Medicinal Products (COMP) has recognized that Kaftrio is intended (as per the respective SmPC) for patient groups for whom existing medicinal products are not authorized, or where current treatments — such as those primarily addressing symptoms or complications of cystic fibrosis — may be considered insufficient in managing the underlying cause of the disease. While these conventional therapies remain important for overall disease management, they do not address CFTR dysfunction. As a result, previously available CF therapies cannot be regarded as being satisfactory methods for these patients relevant for a discussion on the significant benefit.

In conclusion, the Committee for Orphan Medicinal Products (COMP) has recognized that Kaftrio is intended (as per the respective SmPC) for patient groups for whom existing medicinal products are not authorized, or where current treatments are inadequate. As a result, previously available CF therapies cannot be regarded as being satisfactory methods for these patients relevant for a discussion on the significant benefit.

Significant benefit

Not applicable.

4. COMP position adopted on 20 March 2025

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 approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Kaftrio.

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/tezacaftor/elexacaftor for treatment of cystic fibrosis (EU/3/18/2116) is not removed from the Community Register of Orphan Medicinal Products.