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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Kalydeco (ivacaftor)
Treatment of cystic fibrosis
EU/3/08/556
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	N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide
Other name	NA
International Non-Proprietary Name	Ivacaftor
Tradename	Kalydeco
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	Voisin Consulting S.A.R.L.
COMP opinion	14 May 2008
EC decision	8 July 2008
EC registration number	EU/3/08/556
Post-designation procedural history	
Transfer of sponsorship	Transfer from Voisin Consulting S.A.R.L to Vertex Pharmaceuticals (U.K.) – EC decision of 30 August 2011
COMP opinion on review of orphan designation at the time of marketing authorisation	13 June 2012
Transfer of sponsorship	Transfer from Vertex Pharmaceuticals (U.K.) to Vertex Pharmaceuticals (Europe) Limited – EC decision of 12 August 2015
COMP opinion on review of orphan designation at the time of type II variation	13 September 2018
Transfer of sponsorship	Transfer from Vertex Pharmaceuticals (Europe) Limited to Vertex Pharmaceuticals (Ireland) Limited – EC decision of 21 November 2018
Type II variation procedural history	
Rapporteur / Co-rapporteur	Maria Concepcion Prieto Yerro / Melinda Sobor
Applicant	Vertex Pharmaceuticals (Ireland) Limited
Application submission	7 April 2020
Procedure start	25 April 2020
Procedure number	EMA/H/C/002494/II/0085
Invented name	Kalydeco

Proposed therapeutic indication	Extension of indication to include the combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation in the *CFTR* gene or heterozygous for F508del in the *CFTR* gene with a minimal function (MF) mutation. Further information on Kalydeco can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/kalydeco
CHMP opinion	23 July 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Armando Magrelli / Gloria Maria Palomo Carrasco
Sponsor's report submission	28 May 2020
COMP discussion	14-16 July 2020
COMP opinion (adoption via written procedure)	29 July 2020

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 2008 designation was based on the following grounds:

- cystic fibrosis (hereinafter referred to as "the condition") was estimated to be affecting approximately 1.2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life threatening due to respiratory failure and reduced overall survival;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide may be of significant benefit to those affected by the condition.

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

- the proposed therapeutic indication "treatment of cystic fibrosis in patients age 6 years and older who have a G551D mutation in the CFTR gene" falls entirely within the scope of the orphan indication 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 at the time of the review of the designation criteria. The prevalence is at

present estimated at 0.7 in 10,000 persons in the EU, based on evidence coming from relevant literature and European registries;

- the seriousness of the condition was estimated not to have changed at the time of the review of the designation criteria. The condition is life-threatening and chronically debilitating, in particular due to the recurrent and resistant respiratory infections with development of bronchiectasis. Death can occur from terminal respiratory failure or from haemoptysis due to erosion of large pulmonary vessels
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that ivacaftor may be of potential significant benefit to those affected by the orphan condition still holds. The significant benefit is based on the innovative mechanism of action of ivacaftor which, unlike the current products authorized in the EU, directly targets the underlying pathomechanism of the disease. Such mechanism of action has been shown to translate into clinical efficacy, as shown by a significant improvement in lung function, and a decrease in the number of pulmonary exacerbations. This constitutes a therapeutic advantage for the cystic fibrosis sub-population affected by the G551D gating mutation, when ivacaftor is either used alone or in combination with currently authorized products for the treatment of cystic fibrosis, e.g. depending on the stage of the disease and the presence of pulmonary infections.

2.3. Review of orphan medicinal product designation at the time of type II variation (EMEA/H/C/002494/II/0063/G)

The COMP opinion on the initial review of the orphan medicinal product designation in 2018 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication 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 in 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 of treatment of the condition have been authorised in the European Union, the assumption that Kalydeco will be of significant benefit to those affected by the orphan condition is confirmed. This is based on clinical data showing the better tolerability of Symkevi in combination with Kalydeco in patients with homozygous F508del mutation who had to discontinue treatment with Orkambi, with comparable efficacy. The significant benefit of Symkevi in combination with Kalydeco in patients heterozygous for F508del and one of the residual function mutations included in the authorized therapeutic indication, for whom no specific CFTR modulator treatment is authorized, was considered justified based on clinical data showing improved efficacy versus placebo.

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 to include the combination regimen with ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who are homozygous for the *F508del* mutation in the *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. 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 *F508del* 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 *F508del* mutation (F/F patients) or who are heterozygous for the *F508del* mutation and have 1of 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).
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 *P. 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 indicated for the suppressive therapy of chronic pulmonary infection due to *P aeruginosa* 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 *P aeruginosa* in patients aged 6 years and older with CF.

Significant benefit

The currently proposed indications of Kalydeco in combination with Kaftrio comprise subpopulations in which approved modulator therapies are available (F508del homozygous patients (F/F), patient heterozygous for F508del and a specific residual function mutation (F/RF) or a specific gating mutation (F/G). For the populations heterozygous for F508del and a minimal function mutation (F/MF) no treatment is available.

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 plus Kalydeco in comparison with Symkevi. In both cases the products were administered once a day, in combination regiment with Kalydeco, administered in the evening.

Kaftrio plus Kalydeco 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 plus Kalydeco 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)**
	P 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)
	P 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)
	P 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; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

The difference between the regimens containing Kalydeco plus Kaftrio or 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 (Kalydeco) and TEZ/IVA (Symkevi) in vitro.

The least squares (LS) mean treatment 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 the active treatment. 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 plus Kalydeco (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001). A higher CRQ-R RD score was observed through Week 24 in the treated arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). In addition, a LS mean absolute change of 1.04 kg/m^2 (95% CI: 0.85, 1.23; p<0.0001) compared to placebo at Week 24 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 29 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 in 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 Kalydeco may be of 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*), Kalydeco in combination regimen with Kaftrio showed better efficacy in the primary endpoint of lung function and in relevant secondary endpoints as compared to Symkevi, currently authorized for the condition. The combination regimen 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 Kalydeco, N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide, ivacaftor, for treatment of cystic fibrosis (EU/3/08/556) is not removed from the Community Register of Orphan Medicinal Products.