HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
7 November 2012

KALYDECO 150 mg film-coated tablets
B/56 (CIP code: 34009 266 060 5 3)

Applicant: VERTEX

INN	ivacaftor
ATC Code (year)	R07AX02 (other respiratory system products)
Reason for review	**Inclusion**
Lists concerned	**National Health Insurance** (CSS L.162-17) **Hospital use** (CSP L.5123-2)
Indications concerned	**"KALYDECO is indicated for the treatment of cystic fibrosis in patients aged 6 years and older who have a *G551D* mutation in the *CFTR* gene (*G551D-CFTR* mutation)."**

AB	**Substantial actual benefit**
IAB	KALYDECO offers a **substantial** improvement in actual benefit **(IAB II)** in the treatment of cystic fibrosis in patients aged 6 years and older with the *G551D-CFTR* mutation.
Therapeutic use	**KALYDECO is a disease-modifying drug that should be prescribed from the outset in patients with cystic fibrosis aged 6 years and older who have the G551D-CFTR mutation.**
Recommendations	The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised)	Date of Marketing Authorisation: 23 July 2012 Further studies requested by the CHMP: - a long-term (observational) safety study: annual reports expected in December 2013, 2014, 2015, 2016 and the final report in 2017; - a pharmacokinetics study to evaluate other doses in patients aged 6 to 11 years: final report expected in late 2012; - a pharmacokinetics study to evaluate other doses in patients aged 6 to 11 years in study 110: final report expected in December 2014; - modelling and simulation studies to establish doses in patients treated with CYP3A inhibitors and patients with liver impairment: final reports expected in June 2013. Risk Management Plan (RMP) including monitoring of the following risks in particular: - Potential risks: effects on liver function tests, cataracts, cardiac arrhythmia; - Missing information: o effect on pregnancy and breastfeeding; o effect on pulmonary exacerbations and bacterial colonisation during long-term treatment; o effect in children aged 6 to 11 years; o effect in patients with an FEV_1 < 40%; o effect in patients with moderate to severe liver impairment; o safety in patients with cardiac disorders; o long-term safety; o clinical consequences of P-gp inhibition.
Prescription and dispensing conditions / special status	List I Orphan medicinal product (July 2008) Temporary usage authorisation in a patient group granted on 10 July 2012 for the indication “treatment of cystic fibrosis in patients aged 6 years and older who have the mutation *CFTR-551D* ”. Temporary usage authorisation for a named patient on 20/08/2012: 31 authorisations granted for the same indication. Medicine for initial six-monthly hospital prescription only. Unrestricted renewal.

ATC classification	2012	
	R	Respiratory system
	R07	Other respiratory system products
	R07A	Other respiratory system products
	R07AX	Other respiratory system products
	R07AX02	ivacaftor

02 BACKGROUND

Application for initial inclusion of the proprietary medicinal product KALYDECO (ivacaftor).
Ivacaftor is the first treatment that directly targets CFTR (*Cystic Fibrosis Transmembrane Conductance Regulator*) protein dysfunction in patients who have at least one *G551D* mutations.
Ivacaftor is a selective potentiator of the CFTR protein. *In vitro*, it improves chloride ion transport by increasing the opening of the CFTR channel. The mechanism of action through which ivacaftor prolongs the opening of certain mutated forms of CFTR has not been fully determined.

03 THERAPEUTIC INDICATIONS

"KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a *G551D* mutation in the *CFTR* gene (*G551D-CFTR* mutation)."

04 DOSAGE

"KALYDECO should only be prescribed by physicians with experience in the treatment of cystic fibrosis. If the patient's genotype is unknown, an accurate and validated genotyping method should be performed to confirm the presence of the *G551D* mutation in at least one allele of the *CFTR* gene before starting treatment.

Posology
Adults, adolescents and children aged 6 years and older: The recommended dose is 150 mg taken orally every 12 hours (300 mg total daily dose). KALYDECO should be taken with fat-containing food. Meals and snacks recommended in CF guidelines or in standard nutritional guidelines contain adequate amounts of fat. Examples of meals that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats. Food containing grapefruit or Seville oranges should be avoided during treatment with KALYDECO (see section 4.5 of the SmPC).

Elderly population: The efficacy and safety of KALYDECO in patients aged 65 years or older have not been evaluated.

Renal impairment: No dose adjustment is necessary for patients with mild to moderate renal impairment. Caution is recommended while using ivacaftor in patients with severe renal impairment (creatinine clearance less than or equal to 30 ml/min) or end-stage renal disease. (See sections 4.4 and 5.2 of the SPC.)

Hepatic impairment: No dose adjustment is necessary for patients with mild hepatic impairment (Child-Pugh Class A). A reduced dose of 150 mg once daily is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There is no experience of use of KALYDECO in patients with severe hepatic impairment. The use of KALYDECO in these patients is therefore not recommended unless the benefits outweigh the risks. In such case, the starting dose should be 150 mg every other day. Dosing intervals should be modified according to clinical response and tolerability (see sections 4.4 and 5.2 of the SPC).

Concomitant use of CYP3A inhibitors: When co-administered with potent inhibitors of CYP3A (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin), KALYDECO should be administered at a dose of 150 mg twice a week (see sections 4.4 and 4.5 of the SmPC).
When co-administered with moderate inhibitors of CYP3A (e.g. fluconazole, erythromycin), KALYDECO should be administered at a single daily dose of 150 mg (see sections 4.4 and 4.5 of the SmPC).

Paediatric population: The safety and efficacy of KALYDECO in children aged less than 6 years have not been established. No data are available.

Method of administration: For oral use. Patients should be instructed to swallow the tablets whole (e.g. : patients should not chew, break or dissolve the tablet)."

05 THERAPEUTIC NEED

Cystic fibrosis is a serious genetic disorder characterised by defective CFTR protein. The lack of functional CFTR protein in the epithelial cell membranes causes abnormally salty sweat and abnormally viscous mucous secretions (responsible for stasis, obstruction and secondary infection in the lungs).
Bacterial colonisation of the lungs occurs very early in the natural course of the disease and progresses over time. This causes impaired pulmonary function.
The disease is chronic, usually progressive, and generally becomes apparent in early childhood, sometimes from birth. The most common form involves a combination of respiratory problems, gastrointestinal disorders (steatorrhoea and/or constipation) and exocrine pancreatic insufficiency (failure to absorb fats, delayed growth). Mortality and morbidity are primarily caused by the bronchopulmonary effects.

Patients with cystic fibrosis require intervention from a multidisciplinary team (treating doctor, specialist centres, team of health professionals including a physiotherapist and a nurse), working in a specialist cystic fibrosis centre (CRCM).

To date, treatment is only symptomatic and is required for life. A lung transplant or even a liver transplant may be offered as a last resort in advanced forms.

Symptomatic management involves four types of complementary interventions that target symptoms:

- respiratory management: physiotherapy, inhaled dornase alfa, inhaled mannitol, antibiotic therapy;
- nutritional and digestive management;
- an optimum immunisation programme, adhering to the vaccination schedule;
- therapeutic education of patients.

To date, there is no treatment that acts directly on the pathophysiological mechanism of the disease.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Currently, only symptomatic treatments are available for cystic fibrosis patients:

- Management of respiratory symptoms: inhaled dornase alfa (PULMOZYME), inhaled mannitol (BRONCHITOL[1]), inhaled corticosteroids and bronchodilators, antibiotic therapy for exacerbations or chronic infection;
- Nutritional care: fat-soluble vitamins (A, D, E, K), trace elements (iron, zinc, selenium), supplementation with sodium chloride, and treatment of exocrine pancreatic insufficiency with pancreatic enzymes.

06.2 Other health technologies

Daily chest physiotherapy is also a key element of respiratory management.

A lung transplant or even a liver transplant may be offered as a last resort in advanced forms.

Conclusion

To date, there are no medicinal products or other health technologies that act directly on the pathophysiological mechanism of cystic fibrosis.

07 INTERNATIONAL INFORMATION ABOUT THE MEDICINE

Country	REIMBURSEMENT	
	YES/NO If no, why	Population(s) MA or restricted population
Germany	YES 15/08/2012	
USA	YES 31/01/2012	Treatment of cystic fibrosis (CF) in patients aged 6 years and older who have a *G551D* mutation Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene

[1] Currently under evaluation by the Transparency Committee.

08 ANALYSIS OF AVAILABLE DATA

In support of the application for inclusion of KALYDECO (ivacaftor) in the treatment of cystic fibrosis in patients aged 6 years and older who have a *G551D* mutation in the *CFTR* gene, the pharmaceutical company has submitted:

- two phase III clinical studies (pivotal studies) with the objective of comparing the efficacy of ivacaftor with placebo in terms of change in FEV_1 (forced expiratory volume in 1 second) after 24 weeks, in:
  - 161 patients aged 12 years and over (STRIVE study);
  - 52 patients aged 6 to 11 years (ENVISION study);
- one open-label extension study in patients included in the two above-mentioned studies (PERSIST);
- one study conducted in patients homozygous for the *F508del-CFTR* mutation (DISCOVER), which does not correspond to the indication recognised by the Marketing Authorisation.

08.1 Efficacy

8.1.1 STRIVE[2] (VX08-770-102) and ENVISION (VX08-770-103) studies

These two studies have the same methodology, and only differ in terms of the age of patients included (patients aged 12 years and over in the STRIVE study, and patients aged 6 to 11 years in the ENVISION study).

Method: randomised, double-blind, phase III comparative studies of ivacaftor (KALYDECO) 150 mg twice daily versus placebo in combination with standard treatments,[3] conducted in patients with cystic fibrosis who have a *G551D-CFTR* mutation, treated for 24 weeks followed by a 48-week extension phase.

Inclusion criteria: patients with a diagnosis of cystic fibrosis confirmed by a sweat chloride concentration ≥ 60 mmol/l or two genetic mutations characteristic of cystic fibrosis **and** chronic lung disease or gastrointestinal or nutritional disorders, and:

- a *G551D* mutation on at least one *CFTR* allele;
- an FEV_1 of 40% to 90% on randomisation (STRIVE study) or 40% to 105% (ENVISION study);
- aged 12 years and over (STRIVE study) or 6 to 11 years old (ENVISION study);
- body weight ≥ 15 kg (ENVISION study).

Treatments:
STRIVE study:
Standard treatment + KALYDECO 150 mg twice daily, n = 83.
Standard treatment + placebo, n = 78.

ENVISION study:
Standard treatment + KALYDECO 150 mg twice daily, n = 26.
Standard treatment + placebo, n = 26.

Primary efficacy endpoint: absolute change in percentage of predicted FEV_1 after 24 weeks of treatment, in comparison with value on inclusion.

[2] Ramsey BW et al. A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation. N Engl J Med 2011; 365: 1663-72.
[3] Including high-dose ibuprofen, dornase alfa (PULMOZYME), TOBI, or other inhaled antibiotics.

Secondary endpoints included:

- absence of pulmonary exacerbations (STRIVE study only);
- change in respiratory symptoms, evaluated through the validated[4] CFQ-R[5] questionnaire;
- change in sweat chloride concentration;
- change in patient weight.

Tertiary endpoints included:

- number of clinical events (exacerbations, number of antibiotic treatments);
- durations of treatment with antibiotics.

RESULTS: see Tables 1 and 2

The patients included in these two studies typically had an FEV_1 > 70% with a mean age of about 25 years and an age-adjusted weight of -0.5 ± 0.95 points in the STRIVE study and -0.08 ± 0.89 points in the ENVISION study.

In the STRIVE study, mean FEV_1 was 63.6% and 41.6% of patients had an FEV_1 > 70%.

In the ENVISION study, mean FEV_1 was 84.2% and 76.9% of patients had an FEV_1 > 70%.

In the STRIVE study:

On inclusion, the characteristics of patients were comparable:

- Mean FEV_1 was 63.6% (16.43) with 58.4% of patients having an FEV_1 < 70%.
- Mean patient weight was 61.47 ± 14.056 kg.
- Mean sweat chloride concentration was 100.24 ± 10.275 mmol/l.
- The number of hospitalisations for pulmonary exacerbations in the year prior to inclusion was 0.5 ± 1.11; the frequency of exacerbations observed in patients included was not recorded and was not an inclusion criterion for the study.

Table 1: Results for the primary and secondary endpoints after 24 weeks of treatment

	KALYDECO	Placebo	Difference [95% CI] – p
STRIVE study (patients > 12 years)	**n = 83**	**n = 78**	
Primary endpoint at W24			
- Mean baseline value	63.5	63.7	
- Mean value at W24	73.8	63.3	**Difference +10.6***
- Absolute change in % of predicted FEV_1 at W24	+10.4	-0.2	**[8.6; 12.6]** **p < 0.0001**
Secondary endpoints			
- Absence of pulmonary exacerbations (% of patients)	78%	51%	HR = 0.39 [0.23; 0.71] p = 0.0016
- Change in respiratory symptoms (CFQ-R points)	+5.97 points	-2.10 points	Difference 8.08 points [4.73; 11.42] p < 0.0001
- Change in sweat chloride concentration	-48.70 mmol/l	-0.77 mmol/l	Difference -47.93 mmol/l [-51.34; -44.52] p < 0.0001
- Change in patient weight	+2.95 kg	+0.21 kg	Difference +2.75 [1.76; 3.74] p < 0.0001

* corresponds to a change of 0.367 litres

[4] Quittner et al. Development and Validation of the Cystic Fibrosis Questionnaire in the United States: A Health-Related Quality-of-Life Measure for Cystic Fibrosis. *Chest* 2005; 128: 2347-2354.

[5] The CFQ-R is a questionnaire specifically designed to evaluate quality of life in adolescents and adults with cystic fibrosis. This questionnaire covers three areas (quality of life, symptoms and general health) and is made up of 44 items (see Appendix 1). The scores obtained are calculated from patients' answers. A change of ≥ 4 points from baseline is considered to be clinically relevant in patients with stable cystic fibrosis (Quittner 2009), and ≥ 8.5 points in patients with exacerbations.

In the STRIVE study, after 24 weeks of treatment, a significant improvement in the percentage of predicted FEV_1 (primary endpoint) was observed with KALYDECO in comparison with placebo: + 10.4 versus -0.2, difference +10.6, 95% CI [8.6; 12.6], p < 0.0001.
Significant improvements were also observed in the secondary endpoints, in particular:

- Absence of exacerbations: HR 0.39 [0.23; 0.71]. The number of hospitalisations for pulmonary exacerbations in the year prior to inclusion was low (0.5 ± 1.11) and comparable in both groups; furthermore, the frequency of exacerbations observed before inclusion is not known; therefore, this result is difficult to interpret.
- Respiratory symptoms reported by the patient (CFQ-R): a gain of 8.08 points [4.73; 11.42], on a 100-point scale.
- Sweat chloride concentration: a decrease of 47.93 mmol/l [-51.34; -44.52], from a mean baseline concentration of 100.24 ± 10.275 mmol/l.
- Change in patient weight: a gain of 2.75 kg [1.76; 3.74] from a mean weight on inclusion of 61.47 ± 14.056 kg.

After 48 weeks of treatment, these effects were maintained.

Tertiary analyses had also been planned to study the impact of KALYDECO treatment on antibiotic use; although the durations of treatment were reduced after 48 weeks (6.68 days with KALYDECO versus 11.03 days with placebo, p = 0.018), the number of pulmonary exacerbations requiring antibiotic treatment was not significantly reduced (28 versus 47, RR 0.558 [0.292; 1.067], NS).

In the ENVISION study:

On inclusion, the characteristics of patients were mostly comparable:

- Mean patient weight was 30.93 ± 8.628 kg.
- Sweat chloride concentration was 104.55 ± 11.919 mmol/l.
- The number of hospitalisations for pulmonary exacerbations in the year prior to inclusion was 0.2 ± 0.64; the frequency of exacerbations observed in patients included was not recorded and was not an inclusion criterion for the study.

Nonetheless, it should be noted that there was a difference in the distribution of patients as regards to baseline FEV_1:

- Mean FEV_1 on inclusion was 84.2% (18.1).
- 23.1% of patients had an FEV_1 < 70%: 30.8% (8 patients) in the placebo group and 15.4% (4 patients) in the KALYDECO group.
- 34.6% of patients had an FEV_1 between 70% and 90%: 23.1% (6 patients) in the placebo group and 46.2% (12 patients) in the KALYDECO group.

Table 2: Results for the primary and secondary endpoints after 24 weeks of treatment

	KALYDECO	Placebo	Difference [95% CI] p
ENVISION study (patients aged 6 to 11 years)	**n = 26**	**n = 26**	
Primary endpoint at W24			
- Mean baseline value	84.73	83.00	
- Mean value at W24	97.47	82.52	**Difference +12.45**
- Absolute change in % of predicted FEV_1 at W24	+12.58	0.13	**[6.56; 18.34]** **p < 0.0001**
Secondary endpoints			
- Change in respiratory symptoms (CFQ-R points)	+6.31 points	-0.25 points	Difference 6.06 points [-1.41; 13.53] NS
- Change in sweat chloride concentration	-55.53 mmol/l	-1.21 mmol/l	Difference -54.32 mmol/l [-61.83; -46.82] p < 0.0001
- Change in patient weight	+3.69 kg	+1.79 kg	Difference +1.90 [0.86; 2.94] p = 0.0004

In the ENVISION study, after 24 weeks of treatment, a significant improvement in the percentage of predicted FEV_1 (primary endpoint) was observed with KALYDECO in comparison with placebo: +12.58 versus 0.13, difference +12.45 [6.56; 18.34], $p < 0.0001$.

Significant improvements were also observed in some secondary endpoints, in particular:
- Sweat chloride concentration: -54.32 mmol/l [-61.83; -46.82] from a mean baseline concentration of 104.55 ± 11.919 mmol/l.
- Change in patient weight: gain of 1.90 kg [0.86; 2.94] from a mean weight on inclusion of 30.93 ± 8.628 kg.

On the other hand, no significant difference was observed in respiratory symptoms reported by the patient (CFQ-R): gain of 6.06 points [-1.41; 13.53], NS (on a 100-point scale).
Pulmonary exacerbations were not an endpoint in the ENVISION study.
After 48 weeks of treatment, these effects were maintained.

8.1.2 PERSIST study

This open-label extension study included patients from the STRIVE and ENVISION studies. It is still ongoing and only an intermediate analysis report is available, at week 48 for STRIVE-PERSIST and at week 24 for ENVISION-PERSIST. In these studies, all patients were treated with KALYDECO and only a descriptive analysis was planned.

The STRIVE-PERSIST study included 144 patients from the STRIVE study, of whom 143 patients have been followed up for 48 further weeks (total of 96 weeks). After the 48 weeks of additional, open-label follow-up, the efficacy of KALYDECO on absolute FEV_1 value was maintained:
- in patients who had initially received a placebo: + 9.4%;
- in patients who had initially received ivacaftor: + 9.5%.

The ENVISION-PERSIST study included 48 patients from the ENVISION study who have been followed up for 24 further weeks (total of 48 weeks). After the 24 weeks of additional, open-label follow-up, the efficacy of KALYDECO on absolute FEV_1 value was maintained:
- in patients who had initially received a placebo: + 8.1%;
- in patients who had initially received ivacaftor: + 10.1%.

8.1.3 DISCOVER study

This phase IIb study compared ivacaftor (KALYDECO) to placebo. It was a randomised (4:1), double-blind study conducted in 140 patients with cystic fibrosis, aged 12 years and over, who were homozygous for the *F508del-CFTR* mutation and had an $FEV_1 \geq 40\%$.

The primary efficacy endpoint was absolute change in FEV_1 from baseline to 16 weeks of treatment.
The secondary endpoints were absolute change in patients' sweat chloride levels, weight, and quality of life as evaluated by the CFQ-R questionnaire, from baseline to week 16.

After 16 weeks of treatment, no significant difference was observed between KALYDECO and placebo for any of the specified endpoints, with the exception of sweat chloride concentration (secondary endpoint).
Therefore, the efficacy of KALYDECO in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation was not demonstrated.

08.2 Adverse effects

In the STRIVE study, after 48 weeks, adverse events had been observed in 74/161 patients (46%): 40 patients from the KALYDECO group (48.2%) and 34 patients from the placebo group (43.6%). The most common adverse events (> 4%) were:

- cough: 1 versus 5 patients;
- headache: 4 patients in each group;
- upper respiratory tract infection: 4 versus 1 patient;
- diarrhoea: 4 versus 5 patients;
- increased ALTs: 5 versus 4 patients;
- increased ASTs: 5 versus 1 patient.

In the ENVISION study, adverse events were observed in 16/52 patients (30.7%): 10 patients from the KALYDECO group (38.5%) and 6 patients from the placebo group (23.1%). The most common adverse events (> 5%) were:

- cough: 1 versus 2 patients;
- abdominal pain: 2 versus 0 patients;
- increased eosinophils: 2 versus 0 patients;
- Cutaneous rash: 1 versus 2 patients;
- fever: 0 versus 2 patients.

In the PERSIST open-label extension study, adverse effects were identical to those observed in the double-blind phases and their incidence remained constant. The most common adverse effects were cough (in about 30% of patients) and upper respiratory tract infection (in about 20% of patients).

According to the SPC, the adverse events most commonly observed with KALYDECO (ivacaftor) have been:

- in children aged 6 to 11 years: nasopharyngitis, upper respiratory tract infection, headache, nasal congestion, oropharyngeal pain, abdominal pain, diarrhoea (only in children);
- in patients aged 12 years and over, additionally: rhinitis, dizziness.

Hepatic effects:

In the clinical studies discussed above, notable increases in liver enzymes were observed, which resolved when treatment was stopped. Therefore, special warnings and precautions for use have been included in the SPC, which state, *"Moderate transaminase [alanine transaminase (ALT) or aspartate transaminase (AST)] elevations are common in subjects with CF. Overall, the incidence and clinical features of transaminase elevations in clinical trials was similar between subjects in the ivacaftor and placebo treatment groups (see section 4.8 of SPC). In the subset of patients with a medical history of elevated transaminases, increased ALT or AST have been reported more frequently in patients receiving ivacaftor compared to placebo. Therefore, liver function tests are recommended prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop unexplained increased transaminase levels during treatment should be closely monitored until the abnormalities resolve and consideration should be given to the continuation of treatment after assessment of the individual benefits and risks."*

In addition, as effects on liver function have been identified as a potential risk, they will be monitored as part of the RMP.

In view of this situation, the Transparency Committee wishes to be promptly informed by the pharmaceutical company of any new data available; if necessary, the medicinal product may be re-evaluated on the basis of these data.

08.3 Summary & discussion

The application for the inclusion of KALYDECO (ivacaftor) in the treatment of cystic fibrosis in patients aged 6 years and older who have a *G551D* mutation in the *CFTR* gene is supported by two randomised, double-blind studies comparing ivacaftor to placebo, one conducted in 161 patients aged ≥ 12 years (STRIVE study) and the other in 52 patients aged 6 to 11 years (ENVISION study). The primary efficacy endpoint was absolute change in FEV_1 between inclusion and 24 weeks. An open-label extension study (PERSIST) during which all patients were treated with KALYDECO was also initiated at the end of these two studies.
The application also included one study conducted in 140 patients aged over 12 years and homozygous for the *F508del-CFTR* mutation (DISCOVER), which does not correspond to the indication validated by the Marketing Authorisation.

Main efficacy results
The patients included in these two studies typically had a FEV_1 > 70% with a mean age of about 25 years and an age-adjusted weight of -0.5 ± 0.95 points in the STRIVE study and -0.08 ± 0.89 points in the ENVISION study. No patient with a FEV_1 < 40% was included in either study.
In the STRIVE study, mean FEV_1 was 63.6% and 41.6% of patients had a FEV_1 > 70%.
In the ENVISION study, mean FEV_1 was 84.2% and 76.9% of patients had a FEV_1 > 70%.

In patients aged 12 years and over, after 24 weeks of treatment with KALYDECO in comparison with placebo:
- FEV_1 (primary endpoint) was improved: +10.4 versus -0.2, difference +10.6, 95% CI [8.6; 12.6], p < 0.0001;
- the percentage of patients without exacerbations (secondary endpoint) was higher: HR 0.39 [0.23; 0.71]. However, this result is difficult to interpret because the number of hospitalisations for pulmonary exacerbations in the year prior to inclusion was low (0.5 ± 1.11) and the frequency of exacerbations before inclusion is not known;
- respiratory symptoms (secondary endpoint) reported by the patient (CFQ-R) were improved with an increase of 8.08 points [4.73; 11.42] on a 100-point scale;
- sweat chloride concentration (secondary endpoint) was reduced by 47.93 mmol/l [-51.34; -44.52], from a mean baseline concentration of 100.24 ± 10.275 mmol/l;
- weight gain (secondary endpoint) was greater with an increase of +2.75 kg [1.76; 3.74] from a mean weight on inclusion of 61.47 ± 14.056 kg.

In patients aged 6 to 11 years, after 24 weeks of treatment with KALYDECO in comparison with placebo:
- FEV_1 (primary endpoint) was improved: +12.58 versus 0.13, difference +12.45 [6.56; 18.34], p < 0.0001; however, the FEV_1 of patients on inclusion was not consistent between the groups;
- sweat chloride concentration (secondary endpoint) was reduced by -54.32 mmol/l [-61.83; -46.82], from a mean baseline concentration of 104.55 ± 11.919 mmol/l;
- weight gain (secondary endpoint) was greater with an increase of +1.90 kg [0.86; 2.94] from a mean weight on inclusion of 30.93 ± 8.628 kg;
- the difference in respiratory symptoms (secondary endpoint) reported by the patient (CFQ-R) was not statistically significant, despite an increase of 6.06 points [-1.41; 13.53] on a 100-point scale;
- upper respiratory tract infections, which did not constitute an endpoint, were more common at 23.1% versus 7.7%.

The PERSIST extension study, which included patients from the STRIVE and ENVISION studies, is still ongoing and only an intermediate analysis report is available, at week 48 for STRIVE-PERSIST and at week 24 for ENVISION-PERSIST. At the end of these open-label extension phases, KALYDECO efficacy was maintained for the endpoints studied, in particular the percentage of predicted FEV_1.

In the DISCOVER study, in patients homozygous for the *F508del-CFTR* mutation and with an FEV_1 ≥ 40% (off-label use), no difference was observed between KALYDECO and placebo after 16 weeks of treatment, across all endpoints (FEV_1, weight, quality of life).

Main safety results

The adverse events observed more frequently with KALYDECO than with placebo were:

- in the STRIVE study: upper respiratory tract infection, increased ALTs and ASTs;
- in the ENVISION study: abdominal pain, increased eosinophils.

In clinical studies, notable increases in liver enzymes were observed, which resolved when treatment was stopped. Furthermore, as this has been identified as a potential risk, it will be monitored as part of the RMP, and close monitoring of liver transaminases is necessary.

Main points of discussion and missing data

It is not known what implications the results of the two pivotal studies (STRIVE and ENVISION) and their open-label extension phase will have for the course of the disease in patients. Finally, due to the lack of morbidity-mortality and long-term safety data, the benefit of the medicine in the overall management of the disease and its evolution, particularly in terms of bacterial colonisation in the lungs and resistance to antibiotics, cannot be evaluated.

08.4 Planned studies

A complete list of planned studies, including the CHMP requests and studies planned by the pharmaceutical company, is given in Appendix 2.

09 THERAPEUTIC USE[6,7,8]

Patients with cystic fibrosis require intervention from a multidisciplinary team (treating doctor, specialist centres, team of health professionals including a physiotherapist and a nurse). Treatment is symptomatic and is required for life. It involves complementary interventions, in particular respiratory management, nutritional management and therapeutic education.

Respiratory management involves:
- daily respiratory physiotherapy;
- aerosol therapy, with:
  - inhaled dornase alfa (PULMOZYME), which moderately improves respiratory function and the number of exacerbations requiring intravenous antibiotic therapy. This should be followed by a 30-minute respiratory physiotherapy session. Inhaled mannitol (BRONCHITOL[9]) may also be used;
  - The data available cannot support any recommendation for the systematic prescription of inhaled corticosteroids and bronchodilators. A beta-2 mimetic can be offered in the event of exacerbations, or as long-term treatment during a stable period (with regular re-evaluation of the clinical benefit), or in a nebuliser using short-acting beta-2 mimetics before starting a physiotherapy session to improve bronchial drainage;
- antibiotic therapy is needed in the event of an exacerbation or chronic infection, as successive courses or as long-term treatment.

  The other treatments for respiratory disorders in cystic fibrosis are oral corticosteroids, taken as a short course after a 14-day course of antibiotics prescribed for an exacerbation, in cases where there is no clinical and/or functional improvement (expert opinion), or in the event of allergic pulmonary aspergillosis.

  A lung transplant or even a liver transplant may be offered as a last resort in advanced forms.

Nutritional management consists of a high-calorie, lipid-normal diet, the use of lipid-soluble vitamins (A, D, E, K) and trace elements (iron, zinc, selenium), supplementation with sodium chloride, and treatment of exocrine pancreatic insufficiency with pancreatic enzymes.

Therapeutic use of KALYDECO:

KALYDECO's efficacy has been demonstrated in patients with cystic fibrosis aged 6 years and older who have a G551D mutation in the CFTR gene, in particular in terms of clear improvement in FEV_1 in the short to medium term. Furthermore, the medicine improves patients' nutritional status (weight gain) as well as sweat sodium concentration, a biological marker for the disease. It is not known what implications these results have for the course of the disease in patients, but it seems that established pulmonary lesions cannot heal. Finally, due to the lack of data on morbidity, mortality, the course of bacterial colonisation in the lungs, and long-term safety, the benefit of the medicine in the overall management of the disease and its evolution cannot be evaluated.

Taking all of these aspects into account, KALYDECO is a disease-modifying drug that should be prescribed from the outset in patients with cystic fibrosis aged 6 years and older and with the G551D-CFTR mutation. The optimal duration of treatment is not known.

[6] Consensus conference. Prise en charge du patient atteint de mucoviscidose. Pneumologie et infectiologie, November 2002.
[7] Bellon G. Mucoviscidose. Encyclopédie Orphanet. April 2006. http://www.orphanet.fr
[8] Long-term conditions guide. Cystic Fibrosis: National Diagnosis and Care Protocol for a Rare Disease. HAS, November 2006
[9] Currently under evaluation by the Transparency Committee.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

Taking into account all of this information, and after discussion and a vote, the Committee concludes:

010.1 Actual benefit

- Cystic fibrosis is a serious disease which is life-threatening for patients.
- The proprietary medicinal product KALYDECO (ivacaftor) is intended as curative therapy.
- The efficacy/adverse effects ratio for this medicinal product is high.
- To date, there is no treatment that acts directly on the pathophysiological mechanism of the disease.
- This proprietary medicinal product is a first-line or second-line therapy.

- Public health benefit:

  In terms of public health, while cystic fibrosis is a serious disease which is at present incurable, the burden of this disease is moderate because of its low prevalence. In the indication concerned, the burden is low because only a limited number of patients have the G551D-CFTR mutation.

  Improvement in the quality of management of this disease is a public health need that is an established priority (2nd Rare Diseases Plan 2011-2014).

  Given the results observed for FEV_1 and respiratory function symptoms, KALYDECO is expected to have a moderate impact on the symptoms presented by patients treated. In the absence of conclusive morbidity data and quality of life data (only the results from the "respiratory symptoms" subscale of the CFQ-R questionnaire were presented), the impact of KALYDECO on morbidity and quality of life cannot be quantified. Furthermore, it is not certain to what extent these clinical trial results are applicable to current practice, especially as patients with a $FEV_1 < 40\%$ (severe patients) were not included and there are no long-term data.

  Therefore, KALYDECO partially meets the public health need identified.

  Consequently, in view of the data available and taking into account the low number of patients concerned, it is expected that the proprietary medicinal product KALYDECO will have a limited public health benefit in patients with cystic fibrosis who have the G5551D-CFTR mutation.

Consequently, the Committee considers that the actual benefit of KALYDECO is substantial.

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "treatment of cystic fibrosis in patients aged 6 years and older who have a G551D mutation in the CFTR gene (*G551D-CFTR* mutation)" and at the dosages in the Marketing Authorisation.

- Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

KALYDECO offers an important improvement in actual benefit **(IAB II)** in the treatment of cystic fibrosis in patients aged six years and older with the *G551D-CFTR* mutation.

010.3 Target population

The target population of KALYDECO is patients with cystic fibrosis, aged 6 years and older, who have the *G551D-CFTR* mutation and have not received a transplant.

It can be estimated from the following factors:

- According to the French cystic fibrosis register 2010, 96 patients had a G551D mutation, of whom 74 were aged 6 years and over and 9 had received a transplant, i.e. 65 patients.
- Since this register only covers 88% of the French population, by extrapolation, the number of patients can be estimated to be 74.

The target population of KALYDECO is therefore a maximum of 80 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

This is not appropriate for the prescription conditions. Note that for treatments lasting one month, the Committee recommends standardisation of the size of packs to 30 days' treatment, in accordance with its discussions of 20 July 2005.

◗ Request for data

The Transparency Committee wishes to be informed by the pharmaceutical company of new available data annually, particularly as concerns hepatic disorders.

◗ Exception drug status

The Committee would like this product to have exception drug status.

Appendix 1: CFQ-R

Table 1—*CFQ-Teen/Adult Scales*

QOL Dimensions Items	Items, No	Sample items
Physical functioning	8	Physical 2: Walking as fast as others
Role	2	Role 37: How often were you absent from school/work during the last 2 weeks because of your illness or treatments?
Vitality	4	Role 9: You felt tired
Emotional functioning	5	Emotion 12: You felt worried
Social	5	Social 29: I get together with my friends a lot
Body image	3	Body 23: I think I am too thin
Eating disturbances	3	Eating 21: I have to force myself to eat
Treatment burden	2	Treatment 16: Compared to 3 months ago, how much time do you currently spend on your treatment?
Health perceptions	3	Health 33: I feel healthy
Weight	1	Weight 39: Have you had trouble gaining weight?
Respiratory symptoms	6	Respiratory 45: Have you had trouble breathing?
Digestive symptoms	2	Digestive 48: Have you had abdominal pain?
Total	**44**	

Appendix 2: Summary of the programm of studies

Actions	Milestones/ exposure	Milestones/Calendar time	Study Status
Study VX08-770-102 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-770 in Subjects With Cystic Fibrosis and the G551D Mutation	Not applicable	2-Year follow-up of subjects who prematurely discontinued Final Report December 2013	Active, ongoing
Study VX08-770-103 A Phase 3, 2-Part, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Pharmacokinetics, Efficacy and Safety of VX-770 in Subjects Aged 6 to 11 Years With Cystic Fibrosis and the G551D Mutation	Not applicable	2-Year follow-up of subjects who prematurely discontinued Final Report June 2013	Active, ongoing
Study VX08-770-104 A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of VX-770 in Subjects Aged 12 Years and Older With Cystic Fibrosis who are Homozygous for the F508del-CFTR Mutation	Not applicable	2-Year follow-up of subjects who prematurely discontinued Final report December 2013	Active, ongoing
Study VX08-770-105 An Open-Label, Rollover Study to Evaluate the Long-Term Safety and Efficacy of VX-770 in Subjects With Cystic Fibrosis (Long-term safety and potential benefit of ivacaftor, enrolling subjects who participated in the Studies 102 and 103)	Not applicable	Interim Report annually (beginning with the first PSUR) Final Report December 2015	Active, ongoing
Study VX11-770-110 A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis who Have the R117H-CFTR Mutation	Not applicable	Final report September 2014	Active/ Started
Study VX12-770-111 A Phase 3, Two-Part, Randomized, Double-Blind, Placebo-Controlled, Crossover Study With an Open-Label Period to Evaluate the Efficacy and Safety of Ivacaftor in Subjects With Cystic Fibrosis Who Have a Non-G551D CFTR Gating Mutation	Not applicable	Final Report June 2015	Active/ Started
Long-term Safety Study An Observational Study to Evaluate the Long-Term Safety of Ivacaftor in Patients With Cystic Fibrosis	Not applicable	Annual Reports (December 2013, December 2014, December 2015, December 2016) Final Report December 2017	Planned **REQUESTED BY CHMP**
DDI study with digoxin An Open-Label Phase 1 Study in Healthy Adult Subjects to Examine the Effects of Ivacaftor (VX 770) on the Pharmacokinetics of Digoxin	Not applicable	Final Report December 2013	Planned
Study VX12-770-112: A Phase 3, open-Label, Roll-Over Study to Evaluate the Safety of Long-Term Ivacaftor Treatment in Subjects 6 Years of Age and Older with Cystic Fibrosis and a Non-G551D CFTR Mutation (2-year open-label extension study to evaluate the long-term safety and potential benefit of ivacaftor, enrolling subjects who participated in the Studies 110 and 111)	Not applicable	Final Report June 2017	Planned
Submission of an analysis of PK data with proposal for potential additional strengths of ivacaftor to be developed for use in modified	Not applicable	December 2012	Planned **REQUESTED**

Actions	Milestones/ exposure	Milestones/Calendar time	Study Status
dosing regimens in children 6 to 11 years of age, to avoid overexposure			**BY CHMP**
Submission of an analysis of PK data, including data from Study 110, on a need to perform a dose-finding study in children 6 to 11 years of age in order to develop a possible alternative dosing regimen to avoid overexposure	Not applicable	September 2014	Planned **REQUESTED BY CHMP**
Provisionally, apply for registration of presentations of ivacaftor with reduced strengths suitable for modified dosing (according to previously submitted analyses of PK data)	Not applicable	June 2016	Planned **REQUESTED BY CHMP**
Perform and submit a report of modelling and simulation of reduced ivacaftor strength dosing to inform on the potential daily dosing recommendations in patients receiving strong CYP3A inhibitors	Not applicable	June 2013	Planned **REQUESTED BY CHMP**
Perform and submit a report of modelling and simulation of reduced ivacaftor strength dosing in patients with moderate hepatic impairment to inform on potential daily dosing recommendations in patients with severe hepatic impairment	Not applicable	June 2013	Planned **REQUESTED BY CHMP**
Study VX-770-TX-025 Juvenile Toxicity Study in Rats	Not applicable	Final Report June 2012	Completed
Report regarding histologic examination of the eyes from head sections of the fetuses retained in alcohol from the rat embryo-foetal study	Not applicable	Final Report December 2012	Planned **REQUESTED BY CHMP**