HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion
5 November 2014

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

Applicant: VERTEX

INN	Ivacaftor
ATC code	R07AX02 (other respiratory system products)
Reason for the review	**Extension of indication** **New examination following submission of new data, in accordance with article R.163-12 of the French Social Security Code**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R".**

Actual Benefit	**In patients age 6 years and older and who have one of the following gating (class III) mutation in the CFTR gene G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R, the actual benefit is substantial.**
Improvement in Actual Benefit	**KALYDECO provides a substantial improvement in actual benefit (level II in the treatment of cystic fibrosis in patients age 6 years and older and who have one of the following gating (class III) mutation in the CFTR gene": G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.**
Therapeutic use	**Taking into account the data available, KALYDECO is a disease-modifying drug that must be prescribed as a first-line treatment to patients with cystic fibrosis ge 6 years and older who have one of the following gating (class III) mutation in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. The optimal treatment duration is unknown.**
Recommendations	**The Committee would like the data requested for patients with the G551D mutation to also be collected for the patients considered in this opinion. This would therefore involve collecting:** **In a comprehensive study targeting all French patients treated with KALYDECO (with their status regarding G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R mutations of the CFTR gene), the characteristics of all patients treated regardless of their age, and reporting the impact in terms of morbidity and mortality, in real-life practice, of this proprietary medicinal product. This study may be based, in particular, on data already collected in the registry of cystic fibrosis patients.** **The following will be collected, in particular, for all patients on KALYDECO regardless of their genetic status: values of the parameters described below, prior to starting treatment (with retrospective collection, if necessary), and during treatment:** **- the value of spirometry tests including FEV1 before treatment with KALYDECO, then the evolution of these tests every 24 weeks;** **- the number of pulmonary exacerbations before treatment with KALYDECO, then throughout the treatment;** **- the number of pulmonary exacerbations leading to antibiotic treatment (with a retrospective collection of this number before treatment with KALYDECO);** **- the number of pulmonary secondary infections leading to hospitalisation at home or in an institution (with a retrospective collection of this number before treatment with KALYDECO);** **- the number of adverse effects attributable to the treatment, and especially liver effects.** **The mean FEV1 value will also be collected at inclusion for patients with these CFTR gene mutations, then the mean change value every 24 weeks.** **The Transparency Committee wishes to reiterate that in the request for inclusion, it requested that the company report new available data each year, in particular those related to liver effects; this remains valid for patients involved in the extension of indication.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralized)	Initial date: 23 July 2012 Extension of indication: 26 June 2014 Additional studies requested by the CHMP: see opinion of 7/11/2012 Risk Management Plan (RMP) including, in particular, monitoring of the following potential risks (effects on liver function tests, cataracts, cardiac arrhythmias) and missing information.
Prescribing and dispensing conditions /special status	List I Orphan medicinal product (July 2008) Drug subject to initial 6-month hospital prescription, restricted to certain specialists (physicians experienced in the treatment of Cystic Fibrosis). 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

On 7 November 2012, the Transparency Committee recommended inclusion of KALYDECO 150 mg in "treatment of cystic fibrosis (CF) in patients aged 6 years and older who have the *CFTR-G551D* mutation" (substantial AB, IAB II).

This request for inclusion concerns:

- an extension of indication in patients who have one of the following gating (class III) mutation in the CFTR gene): G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R,
- submission for new clinical data at 3 years in patients with the G551D mutation (initial indication), for which the company does not request a change in the initially attributed AB and IAB (substantial/IAB II).

03 THERAPEUTIC INDICATION

"KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R".

04 DOSAGE

See SPC.

05 THERAPEUTIC NEED[1,2,3]

Cystic fibrosis is a serious genetic disorder characterised by an impairment of the CFTR (Cystic Fibrosis Transmembrane Regulator) protein. In the absence of the functional CFTR protein in the epithelial cell membranes, the sweat is abnormally salty and the mucous secretions abnormally viscous (responsible for stasis, obstruction, secondary infection in the lungs and exocrine pancreas, in particular).
Bacterial colonisation of the lungs occurs very early on in the natural history of the disease and progresses with time. It is responsible for the deterioration in lung function.
Usually progressive, the disease is often expressed in early childhood, sometimes from birth. The most common form combines respiratory effects and exocrine pancreatic effects (failure to absorb fats with steatorrhoea and/or constipation, delayed growth). The bronchopulmonary effects are responsible for most mortality and morbidity.

Patients with cystic fibrosis require intervention from a multidisciplinary team (treating doctor, specialist centres, paramedical team with a physiotherapist and a nurse), working in or in connection with a cystic fibrosis resource and specialist centre.

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

Symptomatic treatment is based on four types of complementary interventions that target symptoms:

- respiratory treatment: physiotherapy, inhaled dornase alfa, inhaled mannitol, antibiotic therapy,
- nutritional and digestive treatment,
- implementation of optimal prevention of pulmonary infections, meeting the vaccination schedule requirements,
- therapeutic education of patients.

To date, KALYDECO is the first treatment targeting the functional abnormalities of the CFTR protein that has shown efficacy in terms of short- and medium-term improvement of FEV1, the nutritional status of patients with the G551D mutation (weight gain), and the sweat chloride concentration, the biological marker of the disease.

[1] Conférence de consensus. Prise en charge du patient atteint de mucoviscidose. Pneumologie et infectiologie, novembre 2002.
[2] Bellon G. Cystic fibrosis. Encyclopédie Orphanet. April 2006. http://www.orphanet.fr.
[3] Guide ALD [Chronic conditions guide]. Mucoviscidose Protocole national de diagnostic et de soins pour une maladie rare. [Cystic fibrosis National diagnosis and treatment protocol for a rare disease.] HAS November 2006.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

To date, only symptomatic treatments are available for management of these patients:

- Respiratory treatment: inhaled dornase alfa (PULMOZYME), inhaled mannitol (BRONCHITOL[4]), inhaled corticosteroids and bronchodilators, antibiotic therapy in case of exacerbations or chronic infection,
- Nutritional treatment: fat-soluble vitamins (A, D, E, K), dietary minerals (iron, zinc, selenium), supplementation with sodium chloride and support and compensation for exocrine pancreatic insufficiency with pancreatic enzymes.

06.2 Other health technologies

Respiratory treatment is also based on daily respiratory physiotherapy.

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

◗ Conclusion

To date, as an alternative to Kalydeco, there are no medicinal products or other health technologies directly acting on the pathophysiological mechanism of cystic fibrosis

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
USA	YES 22/02/2014	Treatment of cystic fibrosis in patients aged 6 years and older, who have one of the following CFTR gene regulation defect mutations (class III): G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R
Canada	Under assessment	Treatment of cystic fibrosis in patients aged 6 years and older, who have one of the following CFTR gene regulation defect mutations (class III): G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N or S549R

[4] Still being assessed by the Transparency Committee.

08 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason forevaluation)	7 November 2012 Inclusion
Indication	Treatment of cystic fibrosis in patients aged 6 years and older, who have the *CFTR-G551D* mutation
SMR	Substantial
ASMR	KALYDECO provides a substantial improvement in actual benefit (level II) in the treatment of cystic fibrosis in patients aged 6 years and older and who have the G551D mutation in the CFTR gene (*CFTR-G551D* mutation).
Studies requested	The Transparency Committee would like the company to report new available data each year, in particular those related to liver effects.

09 ANALYSIS OF AVAILABLE DATA

In support of its application for extension of the indication of KALYDECO (ivacaftor) to other other gating (class III) mutation of the CFTR protein"
, the company has submitted a phase III clinical study (KONNECTION[5]), with the objective of comparing the efficacy of ivacaftor with placebo in terms of change in FEV1 (Forced Expiratory Volume in 1 Second) after two 8-week sequences in 39 patients.

The company also submitted long-term data in patients with a G551D mutation (initial indication):
- Data at week 96 of the open-label follow-up study (PERSIST) of patients included in the two initial pivotal studies (STRIVE and ENVISION); results at week 48 were presented in the inclusion opinion of 7 November 2012.
- Observational data on the use of KALYDECO in real-life conditions of use (Hubert, Barry[6] and GOAL study available only as an abstract, which will not be discussed in this opinion)

09.1 Efficacy

9.1.1 Efficacy data in patients with other class III mutations (extension of indication): KONNECTION study

Method: phase III, randomised, double-blind, comparative study of ivacaftor (KALYDECO) 150 mgx2/day versus placebo in combination with standard therapies,[7] performed in patients with cystic fibrosis with a class III mutation, except for the *G551D CFTR* gene mutation, treated during two periods:
- Period 1 corresponds to a 20-week crossover phase; the primary efficacy endpoint was evaluated at 8 weeks (n=39).
- Period 2 corresponds to an open-label follow-up of patients scheduled until 36 weeks (n=36).

Inclusion criteria: patients with cystic fibrosis confirmed by a sweat chloride concentration ≥ 60 mmol/l or two genetic mutations characteristic of cystic fibrosis and a sinus-lung disease and:

[5] Kris De Boeck et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of Cystic Fibrosis 2014; 13: 674-80.
[6] Barry PJ et al. Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. Chest 2014; 146: 152-8.
[7] Dornase alfa (PULMOZYME), pancreatic replacement therapy, inhaled antibiotics, etc.

- one of the following class III CFTR mutations: G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D;
- a FEV1 ≥ 40% as a percentage of predicted value according to age, sex, and height during the observation period;
- be aged 6 years or older;
- a minimum weight of 15 kg.

Treatments:

Period 1

Sequence 1: ivacaftor 150 mg/day for 8 weeks, then 4-week washout, followed by placebo for 8 weeks (n=20).

Sequence 2: placebo for 8 weeks, then 4-week washout, followed by ivacaftor 150 mg/day for 8 weeks (n=19).

Period 2

Patients were treated with ivacaftor 150 mg/day until 36 weeks (n=36).

Primary efficacy endpoint: absolute change in FEV1 (as a percentage of predicted value) after 8 weeks of each of the treatment sequences of the 1st period.

Statistical analysis:

Analysis of the primary endpoint was based on a mixed-effects repeated measures model. The model includes the change from the baseline in each treatment period as a dependent variable; the sequence, treatments, treatment period and visit during the period as fixed effects; the mean FEV1 as a percentage of the predicted value and age as co-variables; and patients included in the sequence as random effects.

This model had the hypothesis of equal variances for the repeated measurements and equal co-variances between each pair of measurements for each of the patients.

Due to the use of a mixed-effects model, no imputation of missing data was performed.

Secondary endpoints, in particular:

- change in respiratory symptoms, assessed by a validated questionnaire[8] CFQ-R,[9]
- change in sweat chloride concentration ,
- evolution of body mass index (BMI).

Tertiary endpoints, in particular:

- number of clinical events (exacerbations, number of antibiotic treatments),
- duration of antibiotic treatment.

RESULTS: see Table (period 1: ITT analysis)

In total, 2/3 of patients included in the two study periods had an FEV1 > 70% and 1/3 an FEV1 < 70% for a mean age of about 23 years and weight based on age of 0.08 ± 1.11 points.

The mean FEV1 was 78.38%

G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R mutations were present in one to eight patients.

[8] 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.

[9] The CFQ-R is a specific questionnaire intended to assess the quality of life of adolescents and adults with cystic fibrosis. This questionnaire contains three modules (quality of life, symptoms and general health status) and is based on 44 items (see annex 1). The scores obtained are defined from the patients' responses. A change ≥ 4 points compared with baseline is considered clinically relevant in patients with stable cystic fibrosis (Quittner 2009) and ≥ 8.5 points for patients with exacerbations.

G970R mutation was also evaluated (four patients) but was not included in the Marketing Authorisation given the absence of clinically significant improvement in FEV1 observed after 8 weeks (absolute change in FEV1 of -1.5) and the decrease in sweat chloride level less than 5 mmol/l.

Table 1: Results of the primary and secondary endpoints after 8 weeks of treatment

	KALYDECO	Placebo	Difference [95% CI] p
	n=38	**n=37**	
Primary endpoint FEV1 (% predicted value) - initial mean value, - final mean value, - Absolute change in predicted FEV1	 76.37 83.71 +7.49	 79.34 76.04 -3.19	 **+10.68* [7.26; 14.10] p<0.0001**
Secondary endpoints - Change in BMI (kg/m^2)	0.679	0.016	+0.66 [0.34; 0.99] p<0.0001
- Change in sweat chloride concentration (mmol/l)	-52.28	-3.11	-49.17 [-56.95; -41.38] p<0.0001
- Change in respiratory symptoms (CFQ-R score)	8.94	-0.67	+9.61 [4.48; 14.73] p<0.0001

* corresponding to a change of 0.367 l

After 8 weeks of treatment, a greater improvement in the percentage of the predicted FEV1 value (primary endpoint) was observed with KALYDECO compared with placebo: +7.49 versus -3.19, difference +10.68 points, 95% CI [7.26; 14.10], p<0.0001.
Improvements greater than those observed with placebo were observed in the secondary endpoints, in particular:

- Change in BMI: gain of 0.66 kg/m^2 [0.34; 0.99], p<0.001.
- Respiratory symptoms reported by the patient (CFQ-R): gain of 9.61 points [4.48; 14.73] on a 100-point scale
- Sweat chloride concentration : decrease of 49.17 mmol [-56.95; -41.38], for a mean baseline concentration of 97.54 ± 18.58 mmol/l.

During the open-label follow-up period (period 2), after 24 weeks of additional follow-up, these effects were maintained:

- the mean predicted FEV1 **(primary efficacy endpoint)** was 88.37% (± 20.50), or a mean change compared with baseline of 13.53 points (± 810.18),
- the mean BMI was 23.48 (± 6.43), or a mean change compared with baseline of 1.26 kg/m^2 (± 0.76),
- The mean sweat chloride concentration was 33.50 mmol/l (± 30.30), or a mean change compared with baseline of -59.24 (± 32.57).

To assess the impact of treatment with KALYDECO on the use of antibiotics, tertiary analyses were planned; the number of exacerbations was not different after 20 weeks (10 events versus 10, NS), likewise for the number of exacerbations requiring treatment with antibiotics (3 versus 5, NS).

9.1.2 3-year efficacy data in patients with a G551D mutation (initial indication)

PERSIST study: Review of the data discussed in the opinion of 7/12/2012
"This open-label follow-up study included patients from the STRIVE study and the ENVISION study. It is currently ongoing and only an intermediate assessment report at week 48 for STRIVE-PERSIST and at week 24 for ENVISION-PERSIST is available. 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 which 143 patients were followed for 48 additional weeks (96 weeks total). After 48 weeks of additional open-label follow-up, the efficacy of KALYDECO on the absolute FEV1 value was maintained:
- *in patients who initially received placebo: +9.4%,*
- *in patients who initially received ivacaftor: +9.5%.*

The ENVISION-PERSIST study included 48 patients from the ENVISION study followed for 24 additional weeks (48 weeks total). After 24 weeks of additional open-label follow-up, the efficacy of KALYDECO on the absolute FEV1 value was maintained:
- *in patients who initially received placebo: +8.1%,*
- *in patients who initially received ivacaftor: +10.1%. "*

New data available at week 96:
After 48 weeks of additional open-label follow-up, the efficacy of KALYDECO on the absolute FEV1 value was maintained:
- in patients who initially received placebo (treated for 96 weeks with ivacaftor): +9.82% (SD 11.23),
- in patients who initially received ivacaftor (treated for 144 weeks with ivacaftor): +9.63% (SD 11.16).

Similarly, the following was observed:
- maintenance of the improvement in respiratory symptoms quantified by the CFQ-R:
  - in patients who initially received placebo (treated for 96 weeks with ivacaftor): +10.05 points (SD 15.25),
  - in patients who initially received ivacaftor (treated for 144 weeks with ivacaftor): +7.83 points (SD 19.38).
- maintenance of the improvement in BMI:
  - in patients who initially received placebo (treated for 96 weeks with ivacaftor): +1.12 kg/m^2 (SD 1.52),
  - in patients who initially received ivacaftor (treated for 144 weeks with ivacaftor): +1.26 kg/m^2 (SD 1.99).

Barry et al study
This is a follow-up (before-after) of patients included in a compassionate-use programme conducted in the UK and Ireland in which 31 patients whose FEV1 was < 40% were included and followed for 90 to 270 days after the start of treatment with ivacaftor.
The follow-up shows:
- an improvement from 26.5% to 30.7% of the predictive FEV1 value,
- a median weight increase from 49.8 to 51.6 kg,
- a reduction in IV antibiotics: from 23 days/year to 0 days/year.

Given the methodology of this study, the results should be interpreted with caution.

09.2 Adverse effects

9.2.1 Data from clinical studies

In the KONNECTION study, after 8 weeks (period 1), adverse events were observed in 28/38 patients (73.7%) in the KALYDECO group and 31/37 (83.8%) patients in the placebo group. The most common adverse events (≥ 3 %) were:
- lung infection, pulmonary exacerbation of cystic fibrosis: 9 patients versus 11 patients,

- cough: 6 versus 7 patients,
- headache: 3 versus 5 patients,

During period 2, adverse events were observed in 15/18 patients (83.3%) in the KALYDECO group and 15/18 (83.3%) patients in the placebo group (43.6%). The most common adverse events (> 10%) were:

- lung infection, pulmonary exacerbation of cystic fibrosis: 8 patients versus 5 patients,
- cough: 2 versus 3 patients.

In the PERSIST study, after 96 weeks of treatment, 176/191 patients (91.7%) including 22 (11.5%) related to the treatment. The most common adverse events were:

- pulmonary exacerbation of cystic fibrosis: 44.7%,
- cough: 26.2%,
- upper respiratory infection: 29.1%,
- headaches: 16.5%.

9.2.2 PSUR data

This summary of international pharmacovigilance data covers the period between 23/07/2012 and 23/01/2014 (PSUR 1, 2 and 3).

PSUR 1: 23/07/2012 to 23 January 2013
During this period, patient exposure to treatment is estimated at 6719 patients per day in Europe (127,924 patients/day in the United States).
During this period, 158 adverse events were reported, including 11 serious ones including primarily pulmonary exacerbations of cystic fibrosis.
No new signal was detected during PSUR No. 1.

PSUR 2: 24 January 2013 to 23 July 2013:
During this period, patient exposure to treatment is estimated at 81,130 patients per day in Europe (154,260 patients/day in the United States).
During this period, 191 adverse effects were reported including 41 serious ones.
During the period covering PSUR No. 2, a new hypersensitivity signal was detected based on two hypersensitivity reports related to ivacaftor.

PSUR 3: 24 July 2013 to 23 January 2014:
During this period, patient exposure to treatment is estimated at 126,256 patients per day in Europe (138,439 patients/day in the United States).
During this period, 151 adverse effects were reported including 38 serious ones.
During this period, a new haemoptysis signal was observed after the first analysis of data from the long-term PASS study.
The validity of this observation was not established due to the limitations of this preliminary analysis (numerous biases, numerous events of haemoptysis prior to treatment).
This signal will be further assessed during the next PSURs, future clinical studies and in the next analysis of the PASS study.

Liver function:
Research on adverse effects impacting liver function was **specifically** performed for each of the three PSURs.

In PSUR No. 1:
One American case of spontaneous reporting of fatal liver failure in a 55-year old woman was reported.
Similarly, 10 cases of liver disorders were reported, including 9 cases of increased liver enzymes.

In PSUR No. 2:
In this PSUR, 23 cases of abnormal liver function tests were observed, mostly mild to moderate and an ALAT or ASAT level greater than 5 times the normal limit was reported in 8 patients.

In PSUR No. 3:
In this PSUR, 9 cases were reported, of which:
- 2 cases reported in France involved potential cirrhosis (10-year-old girl) with portal hypertension and a hepatocellular lesion, and a hepatic cytolysis under treatment with oestro-progestatives (26-year-old woman),
- 7 cases involved an abnormal liver function tests, including 1 with a slight elevation in bilirubin.

9.2.3 SPC data

According to the SPC, "The most common adverse reactions experienced by patients who received ivacaftor in the pooled placebo-controlled Phase III studies were: abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo)."

09.3 Summary & discussion

Main efficacy results
The application for extension of the indication of KALYDECO (ivacaftor) in the treatment of cystic fibrosis in patients aged 6 years and older who have one gating (class III) mutation in the CFTR gene (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R) is based on a phase III, randomised, double-blind study comparing ivacaftor to placebo, conducted in 39 patients ≥ 6 years.
The primary efficacy endpoint was absolute change in FEV1 (as a percentage of the predicted value) compared with baseline after 8 weeks (crossover). During the second period of the study, all patients were treated with KALYDECO and followed for 24 weeks.

In total, 2/3 of patients included had an FEV1 > 70% and 1/3 had an FEV1 < 70% for a mean age of about 23 years.
After 8 weeks of treatment, a greater improvement of the percentage of the predicted FEV1 value (primary endpoint) was observed with KALYDECO compared with placebo: +7.49 versus -3.19, difference +10.68 points, 95% CI [7.26; 14.10], p<0.0001.
Improvements greater than those observed with placebo were observed in secondary endpoints, in particular:
- Change in BMI: gain of 0.66 kg/m^2 [0.34; 0.99], p<0.001.
- Respiratory symptoms reported by the patient (CFQ-R): gain of 9.61 points [4.48; 14.73] on a 100-point scale.
- Sweat chloride concentration: reduction of 49.17 mmol [-56.95; -41.38], for a mean baseline concentration of 97.54 ± 18.58 mmol/l.

During the open-label follow-up period (period 2), after 24 weeks of additional follow-up, these effects were maintained:

- the mean predicted FEV1 value **(primary efficacy endpoint)** was 88.37% (± 20.50), or a mean change compared with baseline of 13.53 points (± 810.18),
- the mean BMI was 23.48 (± 6.43), or a mean change compared with baseline of 1.26 kg/m^2 (± 0.76),
- The mean sweta chloride concentration was 33.50 mmol/l (± 30.30), or a mean change compared with baseline of -59.24 (± 32.57).

The new data related to patients with a G551D mutation (initial indication) is based on the data at week 96 of the open-label follow-up study (PERSIST) of patients included in the two initial pivotal studies (STRIVE and ENVISION), whose results at week 48 were presented in the Transparency Committee opinion dated November 7, 2012.
The results at week 96 show a long-term maintenance of the benefit of KALYDECO on the absolute change in FEV1 (as a percentage of the predicted value), improvement of respiratory symptoms quantified by the CFQ-R, and BMI.

Main safety results

According to the SPC, "The most common adverse events experienced by patients who received ivacaftor in the pooled placebo-controlled Phase III studies were: abdominal pain (15.6% versus 12.5% on placebo), diarrhoea (12.8% versus 9.6% on placebo), dizziness (9.2% versus 1.0% on placebo), rash (12.8% versus 6.7% on placebo), upper respiratory tract reactions (including upper respiratory tract infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion, and nasopharyngitis) (63.3% versus 50.0% on placebo), headache (23.9% versus 16.3% on placebo) and bacteria in sputum (7.3% versus 3.8% on placebo).".
No new adverse event was reported in patients with one of the other class III mutations.

Main points of discussion and missing data

In patients with one of the class III mutations, except for the G551D mutation, the available data are limited to 24 weeks, which does not allow the benefit of the medicinal product on the overall treatment of the disease and its evolution, or on safety, to be evaluated in the longer term.

The data available at week 96 for patients with the G551D mutation seems to confirm the results initially observed at week 24, in terms of FEV1, respiratory syndromes and BMI in particular, but the impact of the treatment of the evolution of the patients' disease remains unknown.

09.4 Planned studies

The company has reported four studies in progress:

- KONTINUE study (study 112): Open-label extension study of the KONNECTION study.
- Study R117H: submission of an extension of the Marketing Authorisation indication for the R117H mutation is planned for mid-2014.
- KIWI study: Study in patients aged 2 to 5 years with a class III mutation; submission of an extension of the Marketing Authorisation is planned for the fourth quarter of 2014.
- Study H: Study in patients aged 0 to 2 years with a class III mutation is planned for 2015.

010 THERAPEUTIC USE

The management of patients with cystic fibrosis requires the intervention of a multidisciplinary team (treating doctor, specialist centres, paramedical team with a physiotherapist and a nurse). Treatment is symptomatic and necessarylife-long. It is based on complementary interventions, in particular respiratory treatment, nutritional treatment and therapeutic education.

Respiratory treatment is based on:
- daily respiratory physiotherapy,
- aerosol therapy, with:
  - inhaled dornase alfa (PULMOZYME), which moderately improves respiratory function and the number of exacerbations requiring intravenous antibiotic therapy. It must be followed by a 30-minuted respiratory physiotherapy session. Inhaled mannitol (BRONCHITOL) can also be used.
  - The data available do not allow systematic prescription of inhaled corticosteroids and bronchodilators to be recommended. A beta-2-mimetic can be offered in the event of exacerbations, in the long term during a stable period (with regular re-assessment of the clinical benefit), or in nebulisation with short-acting beta-2-mimetics before starting the physiotherapy session, to improve bronchial drainage.

antibiotic therapy is necessary in the event of an exacerbation or chronic infection, in successive courses or in long-term treatment.

The other treatments for respiratory disorders in cystic fibrosis are a short course of oral corticosteroids, 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 cases of allergic pulmonary aspergillosis.

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

Nutritional treatment 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 compensation of exocrine pancreatic insufficiency by providing pancreatic extracts.

Therapeutic use of KALYDECO:
The efficacy of KALYDECO which has already been demonstrated in patients with cystic fibrosis age 6 years and older who have the CFTR gene G551D mutation, in particular in terms of short- and medium-term improvement of FEV1, was also demonstrated in patients with other class III gating mutations (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R). Furthermore, it is the same for respiratory symptoms, weight and BMI, as well as the sweat chloride concentration, biological markers of the disease. These data were confirmed in the longer term (up to 144 weeks) in patients with the G551D mutation.
The consequences of these results on the evolution of the disease in patients are unknown, but it seems that established pulmonary lesions cannot heal.
Finally, based on the lack of data on long-term morbidity and mortality, the benefit of the medicinal product in the overall management of the disease and its evolution remain to be shown.
Taking account of all of these elements, KALYDECO is a disease-modifying drug that should be prescribed as a first-line treatment in patients with cystic fibrosis age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene : G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. The optimal treatment duration is unknown.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

- Cystic fibrosis is a serious disease which is prematurely 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.

In patients with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene : G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R, the efficacy of KALYDECO was shown in terms of improvement in absolute change in FEV1 (as a percentage of the predicted value), respiratory symptoms reported by the patient (CFQ-R), BMI and sweat chloride concentration after two 8-week treatment periods

In patients with cystic fibrosis with at least one copy of the G551D mutation, the efficacy of KALYDECO demonstrated in terms of improvement in absolute change of FEV1 (in percentage of theoretical value), respiratory symptoms (CFQ-R), weight, BMI and sweat chloride concentration at 24 weeks is confirmed until 144 weeks.

- To date, there is no other 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 benefits:

In terms of public health, while cystic fibrosis is a serious disease which is incurable to date, its burden is moderate because of its low prevalence. In the indicationconsidered, the burden is low given the restricted number of patients with one of the following gating (class III) mutations in the CFTR gene : G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

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

Given the results observed for FEV1 and respiratory function symptoms, a moderate impact on the symptoms presented by patients treated is expected. In the absence of conclusive data on morbidity and quality of life data (only the results on the respiratory symptoms of the CFQ-R scale were presented), the impact of KALYDECO on morbidity and quality of life cannot be quantified.

. Furthermore, the ability to transpose the results of these clinical trials to current practice is only partially ensured in the extension of indication that is the subject of this opinion, due in particular to the non-inclusion of patients with a FEV1 < 40% (severe patients) and the absence of long-term data.

KALYDECO therefore constitutes a partial response to the identified public health need.

Consequently, in view of the available data and considering the low number of patients concerned, it is expected that the proprietary medicinal product KALYDECO will have a low public health benefit in patients with cystic fibrosis who have one of the following gating (class III) mutations in the CFTR gene :G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

Consequently, the Committee considers that the actual benefit of KALYDECO is substantial in the extension of the Marketing Authorisation indication "treatment of cystic fibrosis (CF)

in patients age 6 years and older who have one of the following gating (class III) mutations in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R".
The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the extension of indication and at the dosages in the Marketing Authorisation.

Given the new data submitted, the Committee considers the opinion issued in the indication "treatment of cystic fibrosis in patients age 6 years and older with the G551D mutation" to be unchanged.

◗ Proposed reimbursement rate: 65%

011.2 Improvement in actual benefit (IAB)

KALYDECO offers a substantial improvement in actual benefit (level II) in the treatment of cystic fibrosis in patients age 6 years and older and who have one of the following gating (class III) mutation in the CFTR gene: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.

011.3 Target population

The target population of KALYDECO is patients age 6 years and older with cystic fibrosis who have one of the following gating (class III) mutation in the CFTR gene : G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R, who have not received a transplant.

It can be estimated on the basis of the following factors:

- According to the French Cystic Fibrosis Registry, 172 patients over 6 years of age have at least one of the class III mutations, of which 19 have received a transplant.
- Considering that this registry covers only 88% of the French population, extrapolation allows the number of patients to be estimated at 192 patients, including 160 over 6 years of age and 21 who have received a transplant.

The target population of KALYDECO is therefore a maximum of 160 patients.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Not appropriate for the prescribing conditions. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, it recommends that for treatments of 1 month, the size of packaging should be standardized and correspond to 30-days worth of tablets.

◗ Request for data
The Committee would like the data requested for patients with the G551D mutation to also be collected for the patients considered in this opinion. This would therefore involve collecting the following:
In a comprehensive study of all French patients treated with KALYDECO (including their status regarding G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R mutations of the CFTR gene), the characteristics of all treated patients regardless of their age, and reporting the impact in terms of morbidity and mortality, in real-life practice, of this proprietary medicinal product. This study may be based, in particular, on data already collected in the registry of cystic fibrosis patients.

The following will be collected, in particular, for all patients on KALYDECO regardless of their genetic status: values of the parameters described below, prior to starting treatment (with retrospective collection, if necessary), and during treatment:
- the value of spirometry tests including FEV1 before treatment with KALYDECO, and the evolution of these tests every 24 weeks;
- the number of pulmonary exacerbations before treatment with KALYDECO, and throughout the treatment;
- the number of pulmonary exacerbations leading to antibiotic treatment (with a retrospective collection of this number before treatment with KALYDECO);
- the number of pulmonary secondary infections leading to hospitalisation at home or in an institution (with a retrospective collection of this number before treatment with KALYDECO);
- the number of adverse effects attributable to the treatment, and especially liver effects.
The mean FEV1 value will also be collected at inclusion for patients with these CFTR gene mutations, then the change in mean value every 24 weeks.

The Transparency Committee wishes to reiterate that in the request forfirst-time registration , it requested that the company report new available data each year, in particular those related to liver effects; this remains valid for patients involved in the extension of indication.

◗ Exception drug status
The Committee wishes to reiterate that this medicinal product has exception drug status.