

The legally binding text is the original French version

## TRANSPARENCY COMMITTEE

### Opinion

### 17 April 2013

#### EKLIRA GENUAIR 322 MICROGRAMS, inhalation powder

B/1 inhaler with 60 doses (CIP: 34009 266 608 0 2)

Applicant: ALMIRALL

INN	Acclidinium bromide
ATC Code (2012)	R03BB05 (Anticholinergic, inhalant)
Reason for the request	<b>Inclusion</b>
List(s) concerned	<b>National Health Insurance</b> (French Social Security Code L.162-17) <b>Hospital use</b> (French Public Health Code L.5123-2)
Indication(s) concerned	<b>"EKLIRA GENUAIR is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)"</b>

<b>Actual Benefit</b>	<b>Insufficient Actual Benefit</b>
<b>Improvement in Actual Benefit</b>	<b>Not applicable</b>
<b>Therapeutic use</b>	<b>In the absence of a long-term clinical study comparing acclidinium bromide to another long-acting bronchodilator indicated as a symptomatic maintenance treatment for COPD, in particular tiotropium bromide, its closest comparator, the place of acclidinium bromide in the therapeutic strategy cannot be defined.</b>

## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

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Marketing Authorisation (procedure)	27/07/2012 (centralised procedure)	
Prescribing and dispensing conditions / special status	List I	
ATC Classification	2012	
	R	Respiratory system
	R03	Drugs for obstructive airway diseases
	R03B	Other drugs for obstructive airway diseases, inhalants
	R03BB	Anticholinergics
	R03BB05	Acclidinium bromide

## 02 BACKGROUND

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EKLIRA GENUAIR is an acclidinium bromide-based proprietary medicinal product, a new long-acting anticholinergic, indicated as a maintenance bronchodilator treatment for COPD. It is administered using the GENUAIR inhalation device, a pre-loaded and ready to use multi-dose powder inhaler.

This request for inclusion on the list of medicinal products refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services was done in parallel with that of an identical medicinal product, BRETARIS GENUAIR (applicant - MENARINI FRANCE).

## 03 THERAPEUTIC INDICATION

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"EKLIRA GENUAIR is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)."

## 04 DOSAGE

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"The recommended dose is one inhalation of 322 µg acclidinium twice daily.

If a dose is missed the next dose should be taken as soon as possible. However, if it is nearly time for the next dose, the missed dose should be skipped.

### *Elderly population*

No dose adjustments are required for elderly patients.

### *Renal impairment*

No dose adjustments are required for patients with renal impairment.

### *Hepatic impairment*

No dose adjustments are required for patients with hepatic impairment.

### Method of administration

For inhalation use."

## 05 THERAPEUTIC NEED

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The diagnosis and treatment of patients with COPD should include an assessment of the severity of COPD, based on symptoms (chronic cough, exercise induced dyspnoea, production of purulent sputum and exacerbations) and state of respiratory function.

There is no medicinal product that can prevent the progression of COPD towards chronic respiratory failure. Stopping smoking is the only measure likely to restore a normal decrease rate in FEV<sub>1</sub> values. Flu vaccine is also recommended. Pulmonary rehabilitation and respiratory physiotherapy may help to improve symptoms, quality of life and the ability to participate in daily activities.

Pharmacological treatment of stable COPD (other than for exacerbations) is based on the severity of the condition and response to treatment. Medicinal products used aim to minimise the symptoms and reduce the frequency and severity of exacerbations.

For chronic simple bronchitis (stage 0), there are no medicinal products recommended.

Inhaled bronchodilators, beta-2 agonists and anticholinergics, are the main symptomatic treatments for COPD. Short-acting inhaled bronchodilators (beta-2 agonists or anticholinergics), taken on demand, are recommended as first-line treatment.

In the case of multiple daily, administrations, long-term treatment with long-acting (LA) inhaled bronchodilators is recommended.

Three LA beta-2 agonists (formoterol, salmeterol and indacaterol) and one LA anticholinergic (tiotropium) have Marketing Authorisation in the symptomatic maintenance treatment of COPD. There is no difference in their efficacy.

Long acting oral theophylline, the use of which is limited by its narrowness therapeutic margins, is only proposed if the patient has difficulties using inhaled bronchodilators or if these products do not adequately improve their dyspnoea.

According to SPLF (2010)<sup>1</sup> and GOLD (2011)<sup>2</sup> guidelines, inhaled corticosteroids should only be used in conjunction with an LA bronchodilator in patients with severe to very severe COPD with a FEV<sub>1</sub> < 50%<sup>3</sup> of the theoretical value and repeated exacerbations. In France, only inhaled corticosteroids in a fixed combination with a LA beta-2 agonist have Marketing Authorisation in this indication. These fixed combinations have not demonstrated any effect on mortality (from all causes) and increase the risk of lower respiratory tract infections, in particular pneumonia.

Inhaled treatment with a LA bronchodilator alone or combined with an inhaled corticosteroid should only be continued if a benefit on symptoms is observed.

Systemic corticosteroids are not recommended.

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<sup>1</sup>Société de Pneumologie de Langue Française (The French-language Society of Pneumology). Recommandation pour la pratique Clinique: prise en charge de la BPCO (mise à jour 2009). Revue des maladies respiratoires. 2010; 27:522-48

<sup>2</sup>Global initiative for Chronic Obstructive Lung Disease: [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2011\\_Feb21.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf).

<sup>3</sup>Indication for FEV<sub>1</sub> < 60 % of the theoretical value for the combination salmeterol/fluticasone (see Marketing Authorisation)

## 06 CLINICALLY RELEVANT COMPARATORS

### 06.1 Medicinal products

INN	NAME Company	Indication <sup>4</sup>	aB (date of last Opinion)	IaB (date of Opinion)	Reimbursed Yes/no
<b>Same therapeutic class:</b> inhaled, long-acting, anticholinergic bronchodilators					
Tiotropium	<b>SPIRIVA 18 µg,</b> inhalation powder, hard capsule  Boehringer Ingelheim France	Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD)	Substantial (25/05/2011)	SPIRIVA shares a level IV improvement in actual benefit with long-acting, beta-2 agonist bronchodilators in the standard treatment of patients with COPD. (02/11/2005)	yes
	<b>SPIRIVA RESPIMAT 2.5 µg/dose,</b> solution for inhalation  Boehringer Ingelheim France		Substantial (25/05/2011)	SPIRIVA RESPIMAT 2.5 micrograms/dose, solution for inhalation, does not provide an improvement in actual benefit (IaB V) compared with SPIRIVA 18 µg, inhalation powder, hard capsule. (07/10/2009)	yes
<b>Other therapeutic class:</b> inhaled, short-acting, anticholinergic bronchodilators alone or in a combination					
Ipratropium	<b>ATROVENT 20 µg per dose,</b> actuation pressurised inhalation solution  Boehringer Ingelheim France	Symptomatic maintenance treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD).	Substantial (21/01/2007)	ATROVENT 20 µg/dose actuation pressurised inhalation solution with HFa does not provide an improvement in actual benefit (IaB V) compared with the formulation for ATROVENT 20 µg/dose actuation pressurised inhalation solution that contains CFCs (formulation currently discontinued). (31/01/2007)	yes
Ipratropium + salbutamol	<b>COMBIVENT 100/20 µg per dose,</b> actuation pressurised inhalation solution  Boehringer Ingelheim France	Symptomatic maintenance treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease, when a single bronchodilator is not satisfactory.	Substantial (25/04/2007)	The Committee does not see an improvement in actual benefit compared with the joint prescription of the two active ingredients alone. (14/06/1995)	yes
Ipratropium + fenoterol	<b>BRONCHODUAL 50/20 µg per dose,</b> actuation pressurised inhalation solution	Symptomatic maintenance treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease, when a single	Substantial (10/12/2008)	Absence of improvement in actual benefit (IaB V). (10/12/2008)	yes

<sup>4</sup>Uniquely in COPD

	Boehringer Ingelheim France	bronchodilator is not satisfactory.			
<b>Other therapeutic class:</b> inhaled, long-acting, beta-2 agonist bronchodilators					
formoterol	<b>ASMELOR NOVOLIZER 12 µg per dose,</b> inhalation powder  Meda Pharma	Symptomatic treatment of bronchial obstruction in patients presenting with chronic obstructive pulmonary disease (COPD) and requiring treatment with a long-acting bronchodilator.	Substantial (27/05/2009)	ASMELOR NOVOLIZER does not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators in patients with chronic obstructive pulmonary disease and requiring treatment with a long-acting bronchodilator. (27/05/2009)	yes
	<b>ATIMOS 12 µg per dose,</b> actuation pressurised inhalation solution  Chiesi SA	Symptomatic treatment of bronchial obstruction associated with chronic obstructive pulmonary disease.	Substantial (06/02/2008)	ATIMOS 12 micrograms/dose, actuation pressurised inhalation solution does not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators available in this indication. (06/02/2008)	yes  (not commercialised)
	<b>FORMOAIR 12 µg per dose,</b> actuation pressurised inhalation solution  Chiesi SA		Substantial (06/02/2008)	FORMOAIR 12 micrograms/dose, actuation pressurised inhalation solution does not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators available in this indication. (06/02/2008)	yes
	<b>FORADIL 12 µg per dose,</b> inhalation powder, hard capsule  Novartis Pharma SAS	Symptomatic treatment of bronchial obstruction associated with chronic obstructive pulmonary disease.	Substantial (29/02/2012)	No specific IAB for COPD.	yes
	<b>OXIS TURBUHALER 12 µg per dose,</b> Inhalation powder  Astra Zeneca	OXIS TURBUHALER is indicated for the symptomatic treatment of bronchial obstruction associated with COPD.	Substantial (13/01/2010)	OXIS TURBUHALER 12 µg per dose shares with salmeterol (SEREVENT and SISEROL 25 µg per dose and SEREVENT and SISEROL DISKUS 50 µg per dose) a minor improvement in actual benefit (level IV) in terms of efficacy compared with the standard treatment of patients with COPD, in the absence of a symptomatic maintenance treatment, and a minor improvement in actual benefit (level IV), compared with ipratropium (ATROVENT), in terms of use (reduction in the number of doses per day) enabling better treatment with possible clinical consequences. (15/09/2004)	yes (not commercialised)
	<b>HIROBRIZ BREEZHALER,</b> inhalation powder, hard capsule	ONBREZ BREEZHALER is indicated as a maintenance bronchodilator treatment for respiratory tract	Substantial (15/12/2010)	HIROBRIZ BREEZHALER 150 µg and 300 µg do not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators	yes
Indacaterol					

	Novartis Pharma SAS			indicated for COPD. (15/12/2010)	
	<b>ONBREZ BREEZHALER,</b> inhalation powder, hard capsule Novartis Pharma SAS	obstruction in adult patients with chronic obstructive pulmonary disease (COPD).	Substantial (15/12/2010)	ONBREZ BREEZHALER 150 µg and 300 µg do not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators indicated for COPD. (15/12/2010)	yes
	<b>OSLIF BREEZHALER,</b> inhalation powder, hard capsule Novartis Pharma SAS		Substantial (15/12/2010)	OSLIF BREEZHALER 150 µg and 300 µg do not provide an improvement in actual benefit (IAB V) compared with other long-acting bronchodilators indicated for COPD. (15/12/2010)	yes
Salmeterol	<b>SEREVENT 25 µg per dose,</b> Actuation pressurised inhalation suspension  Glaxo Smith Kline		Symptomatic treatment of chronic obstructive pulmonary disease (COPD).  N.B.: there is no need to systematically combine an inhaled corticosteroid with a bronchodilator in the treatment of chronic obstructive pulmonary disease.	Substantial (16/02/2011)	These medicinal products provide a minor improvement in actual benefit (level IV) in terms of efficacy compared with the standard treatment of patients with COPD in the absence of a symptomatic maintenance treatment and a minor improvement in actual benefit (level IV), compared with ipratropium (ATROVENT), in terms of use (reduction in the number of doses per day) enabling better treatment with possible clinical consequences. (07/04/2004)
		<b>SEREVENT DISKUS 50 µg per dose,</b> Inhalation powder  Glaxo Smith Kline	Substantial (16/02/2011)	yes	

\*therapeutic class

## 06.2 Other health technologies

Not applicable.

### ► Conclusion:

The most relevant comparator is tiotropium bromide (SPIRIVA 18 µg and SPIRIVA RESPIMAT).

## 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

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Country	REIMBURSED	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
USA	Yes	
Europe (Denmark, United Kingdom, Germany, Spain, Norway, Iceland, The Netherlands, Sweden, Finland, Portugal, Ireland and Italy)	Yes (community, hospital)	Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

## 08 ANALYSIS OF AVAILABLE DATA

- The request from the applicant is mainly based on a placebo-controlled efficacy clinical study (LAS34) and three safety clinical studies.
- Two other placebo-controlled studies have been carried out by the applicant. They will not be described below as their duration was shorter than that of the main 24 week study, which is the minimum duration required for studies of COPD according to EMA guidelines (CPMP/EWP/562/98).
- An active comparator-controlled efficacy study (LAS39) is available. This was a short-term study (6 weeks) that compared acclidinium bromide with tiotropium bromide and placebo. Since this study is the only one carried out versus a comparator active ingredient, it will be described below, however, given the short duration of the study, and the fact that the primary analysis for this study is only based on the comparison of acclidinium bromide with placebo, the results from this study can only be considered as exploratory.

Study	Type of study	Participants N	Population studied/ inclusion criteria	Treatment regimens	Primary endpoint	Secondary endpoint
<b>Efficacy studies</b>						
<b>LAS34 (ATTAIN)</b>	Comparative vs. Placebo, randomised, double-blind, 24 weeks.	828	Age $\geq$ 40 years Moderate to severe COPD (GOLD) Smoker or former smoker ( $\geq$ 10 packet years) $30\% \leq FEV_1 < 80\%$ of theoretical value $FEV_1/FVC < 70\%$	- AB 200 $\mu$ g - AB 400 $\mu$ g - Placebo  2 times/day	Morning pre-dose $FEV_1$	Maximum $FEV_1$ TDI score SGRQ, at Week 24
<b>LAS39</b>	Comparative vs. Placebo and tiotropium, randomised, double-blind, double-placebo 6 weeks.	441	Moderate to severe COPD (GOLD) Smoker or former smoker ( $\geq$ 10 packet years) $30\% \leq FEV_1 < 80\%$ of theoretical value $FEV_1/FVC < 70\%$	- AB 400 $\mu$ g 2 times/day  - Tio 18 $\mu$ g 1 time/day  - Placebo	$AUC_{0-24h}$ for $FEV_1$	$AUC_{12-24h}$ for $FEV_1$ , at Week 6
<b>Safety studies</b>						
<b>LAS35</b>	Randomised, double-blind, 52 weeks	605	Moderate to severe COPD Smoker or former smoker ( $\geq$ 10 packet years) $30\% \leq FEV_1 < 80\%$ of theoretical value $FEV_1/FVC < 70\%$	- AB 200 $\mu$ g - AB 400 $\mu$ g	Safety	Morning, pre-dose $FEV_1$
<b>LAS36</b>	Randomised, double-blind, 52 weeks	291		2 inhalations /day		
<b>LAS38B</b>	Randomised, open-label, 40 weeks	448		AB 400 $\mu$ g, 2 inhalations/day		

- Furthermore, the applicant carried out a network meta-analysis (unpublished study) to indirectly compare acclidinium bromide with other long-acting bronchodilators.



## 08.1 Efficacy

Study LAS34 (ATTAIN)	
<b>Primary study objective</b>	To evaluate the efficacy of aclidinium bromide versus placebo in patients with moderate to severe COPD.
<b>Method</b>	Comparative, randomised, double-blind placebo-controlled study, with a treatment period of 24 weeks.
<b>Inclusion criteria</b>	Age $\geq$ 40 years Moderate to severe COPD (GOLD classification) Smoker or formersmoker ( $\geq$ 10 packet years) $30\% \leq FEV_1 < 80\%$ of theoretical value $FEV_1/FVC < 70\%$
<b>Treatment groups</b>	- Aclidinium bromide: 200 $\mu$ g - Aclidinium bromide: 400 $\mu$ g - Placebo Administration 2 times/day  <b>NB:</b> only the dose of 400 $\mu$ g 2 times/day is recommended in the Marketing Authorisation, thus, only the results relating to this dosage are presented.
<b>Course of the study</b>	Treatment of patients over 24 weeks
<b>Associated treatments</b>	Salbutamol 100 $\mu$ g/dose if required Patients were permitted to continue with the treatment they were taking before starting the study.
<b>Primary efficacy endpoint</b>	Variation in morning, pre-dose $FEV_1$ compared with initial value after 24 weeks
<b>Secondary endpoints</b>	After 24 weeks: 1 - Variation in maximum $FEV_1$ (3 hours post-dose) compared with initial value. 2 - Dyspnoea: TDI focal score <sup>5</sup> 3 - Quality of life: SGRQ score <sup>6</sup>
<b>Statistical analysis</b>	Analysis of the ITT population. ANCOVA analysis of the primary efficacy endpoint and the maximum $FEV_1$ secondary endpoint (factors: treatment and sex of patient; covariates: initial value and age) Adjustment for test multiplicity by the Hochberg method: - for the analysis of several doses - for the analysis of the primary efficacy endpoint and the three secondary endpoints according to the numerical order above.

### Results:

A total of 828 patients were randomised, with 280 patients in the 200  $\mu$ g group, 272 in the 400  $\mu$ g group and 276 in the placebo group.

<sup>5</sup> **TDI (Transition Dyspnoea Index):** this score enables variations in dyspnoea compared with initial state to be evaluated.

With the **Baseline Dyspnoea Index (BDI)** it evaluates:

- disability linked to dyspnoea (functional reduction), which determines the impact dyspnoea has on the capacity to perform certain activities,
- the type of tasks resulting in dyspnoea,
- the importance of effort: the level of effort required to cause dyspnoea.

A difference of at least 1 unit is considered as the minimum clinically significant difference. Responders are patients with a variation in TDI  $\geq$  1 unit. Patients with a lower variation are considered as non-responders.

<sup>6</sup> **SGRQ (Saint George's Respiratory Questionnaire) :** quality of life questionnaire in cases of chronic restriction of airways. Three categories are evaluated: "Symptoms" (especially their frequency and severity), "Activity" (cause or consequences of dyspnoea) and "Impact on daily life" (especially on professional life). Each category is independently given a score from 0 to 100 and the overall sum gives a total score, which also ranges from 0 to 100 (a score of 0 indicates no limitation in quality of life). An improvement  $\geq$  4 points is considered as clinically relevant.

The results were analysed in the ITT population, defined as the patients who took at least one dose of treatment and for whom there is an FEV<sub>1</sub> evaluation available at inclusion and at least one after. Numbers in the ITT population were as follows:

- acclidinium bromide 200 µg: n = 277
- acclidinium bromide 400 µg: n = 269
- placebo: n = 273

The demographic characteristics of the patients were comparable in the two groups. The mean age of patients was 62.4 years and these patients were predominately male (67.4%). They were smokers in 52.8% of cases and former smokers in 47.3% of cases. They had been smokers for a mean duration of 38.8 years and their mean tobacco consumption was 40.2 packets/year.

The severity of COPD was moderate for 68.1% of patients and severe for 31.9%. The mean disease duration was 6.8 years. During the year prior to inclusion, the majority of patients (65.3%) did not have any exacerbation and 34.7% had at least one exacerbation.

Previous treatments: before inclusion, 89.9% of patients were taking a treatment for COPD. The most commonly used treatments were: short-acting β<sub>2</sub>-mimetics (50.4%), ICS (38.1%), long-acting β<sub>2</sub>-mimetics (30.3%); anticholinergics (27.0%) and theophylline (20.9%). The use of these treatments was generally comparable between the treatment groups.

Concomitant treatments: 88.9% of patients had started a COPD treatment before the study, which they were permitted to continue with during the study: short-acting β<sub>2</sub>-mimetics (79.1%), inhaled corticosteroids (49.1%) and theophylline (18.2%).

Other permitted study treatments: ACE inhibitors, analgesics, PPI, statins, β-blockers, etc.

Some treatments could be started during the study: the most commonly used was salbutamol (18.6% to 20.2%, depending on the treatment group), which was permitted as a rescue treatment.

The use of these concomitant treatments, started before or during the study, was similar across the treatment groups.

#### Primary endpoint:

After 24 weeks of treatment the variation in morning pre-dose FEV<sub>1</sub> compared with the initial value was +0.055 l in the acclidinium bromide 400 µg group (2 times/day) and -0.073 l in the placebo group, which is a statistically significant (p < 0.0001) difference of +128 ml (CI<sub>95%</sub> = [85; 170]) in favour of acclidinium bromide (see Table 1). This difference is above the clinically relevant threshold of 100 ml.

#### Secondary endpoints:

##### *Variation in maximum FEV1 at 24 weeks:*

A statistically significant (p < 0.0001) and clinically relevant (> 100 ml) difference of 209 ml (CI<sub>95%</sub> = [163; 256]) was observed in favour of acclidinium bromide 400 µg compared with placebo (see Table 1).

##### *Focal TDI score after 24 weeks of treatment:*

The focal TDI score ranged from 1.94 points in the acclidinium bromide group and 0.94 points in the placebo group compared with the baseline value, which is a statistically and clinically relevant (≥ 1 unit) difference of 1.00 (CI<sub>95%</sub> = [0.43; 1.57]) (see Table 1).

The percentage of patients with a clinically relevant (≥ 1 unit) improvement in focal TDI score was 56.9% in the acclidinium bromide 400 µg group and 45.5% in the placebo group.

##### *Variation in SGRQ score at 24 weeks:*

The improvement in total SGRQ score was more significant in the acclidinium bromide 400 µg group than in the placebo group, with a difference of -4.63 points, which is statistically and clinically relevant (≥ 4 points) (see Table 1).

The percentage of patients with an improvement in SGRQ score ≥ 4 points was 57.3% in the acclidinium bromide group and 41.0% in the placebo group.

**Table 1:** results for the primary and secondary endpoints (study LAS34)

Endpoints	Aclidinium bromide 400 µg 2x/day N = 269	Placebo N = 273	Difference AB – placebo at 24 weeks 95% CI p
Initial values			
Initial FEV <sub>1</sub> (mean of least squares in l ± SD)	1.508 ± 0.525	1.500 ± 0.489	-
BDI score <sup>7</sup> (mean of least squares ± SD)	6.7 ± 2.1	6.7 ± 2.0	-
Total SGRQ score (mean of least squares ± SD)	47.4 ± 18.4	44.9 ± 16.7	-
Primary efficacy endpoint			
<b>Pre-dose variation in FEV<sub>1</sub> at 24 weeks (mean of least squares in l ± SD)</b>	<b>0.055 ± 0.016</b>	<b>-0.073 ± 0.016</b>	<b>0.128</b> <b>[0.085; 0.170]</b> <b>p &lt; 0.0001</b>
Secondary endpoints			
Post-dose variation in FEV <sub>1</sub> at 24 weeks (mean of least squares in l ± SD)	0.231 ± 0.017	0.022 ± 0.017	0.209 [0.163; 0.256] p < 0.0001
Focal TDI score at 24 weeks (mean of least squares)	1.94 ± 0.21	0.94 ± 0.21	1.00 [0.43; 1.57] p = 0.0006
Variation in focal SGRQ score at 24 weeks (mean of least squares ± SD)	-7.41 ± 0.82	-2.79 ± 0.82	-4.63 [-6.84; -2.42] p < 0.0001

<sup>7</sup> **BDI (Baseline Dyspnoea Index)** : enables the severity of dyspnoea at the start of the study to be evaluated

	Study LAS39
<b>Primary study objective</b>	To evaluate the efficacy of acclidinium bromide versus tiotropium bromide in patients with moderate to severe COPD in terms of bronchodilation over 24 hours and at night.
<b>Method</b>	Comparative, randomised, double-blind study versus tiotropium bromide and placebo with double placebo and a treatment period of 6 weeks.
<b>Inclusion criteria</b>	Age $\geq$ 40 years Moderate to severe COPD (GOLD classification) Smoker or former smoker ( $\geq$ 10 packet years) $30\% \leq FEV_1 < 80\%$ of theoretical value $FEV_1/FVC < 70\%$
<b>Treatment groups</b>	- Acclidinium bromide: 400 $\mu$ g 2x/day - Tiotropium bromide: 18 $\mu$ g 1x/day - Placebo
<b>Course of the study</b>	Treatment of patients over 6 weeks
<b>Associated treatments</b>	Salbutamol 100 $\mu$ g/dose if required
<b>Primary efficacy endpoint</b>	Variation in area under the curve between 0 and 24 h ( $AUC_{0-24\ h}$ ) of post-dose $FEV_1$ after 6 weeks of treatment.
<b>Secondary endpoint</b>	Variation in area under the curve between 12 and 24 h ( $AUC_{12-24\ h}$ ) of post-dose $FEV_1$ after 6 weeks of treatment.
<b>Statistical analysis</b>	Primary analysis on the comparison of acclidinium bromide versus placebo (ITT population: patients who received at least one dose and had at least one evaluation, initial or post-dose). ANCOVA analysis (factors: treatment and sex of patient; covariates: initial $FEV_1$ value and age)

### **Results:**

A total of 414 patients were randomised, including 171 in the acclidinium bromide group, 158 in the tiotropium bromide group and 85 in the placebo group.

The results were analysed in the ITT population, defined as the randomised patients who took at least one dose of treatment and for whom there was an evaluation at inclusion or after the first dose available.

The demographic characteristics of the patients were comparable between the groups. Patients had a mean age of 61.8 years in the acclidinium bromide group and 62.8 years in the tiotropium bromide group and were predominately male (67.2%). They were smokers in 54.1% of cases and former smokers in 45.9% of cases. They had been smokers for a mean duration of 39.1 years and their mean tobacco consumption was 42.4 packets/year.

The severity of COPD was moderate for 65.4% of patients and severe for 34.6%. The mean disease duration was 8.7 years. During the year prior to inclusion, the majority of patients (69.3%) did not have any exacerbation and 24.9% had at least one exacerbation. The mean number of exacerbations during the previous year was 0.4.

On inclusion,  $FEV_1$  was 50.8% of the theoretical value in the acclidinium bromide group, 51.8% in the tiotropium bromide group and 50.3% in the placebo group.  $FEV_1$  reversibility was 12.6% for the whole study population.

#### **Primary efficacy endpoint** (see Table 2):

After 6 weeks of treatment, the increase in the area under the curve for normalised  $FEV_1$  over 24 hours ( $AUC_{0-24}$ ) post-dose was more significant with acclidinium bromide than with placebo, with a mean adjusted difference of 150 ml ( $p < 0.0001$ ).

A similar result was observed with tiotropium bromide compared with placebo: difference of 140 ml ( $p < 0.0001$ ).

No significant difference was observed between acclidinium bromide and tiotropium bromide.

### Secondary endpoint (see Table 2):

Furthermore, the increase in the area under the curve for normalised FEV<sub>1</sub> between 12 and 24 hours (AUC<sub>12-24</sub>) post-dose after 6 weeks of treatment was more significant with acclidinium bromide than with placebo, with a mean adjusted difference of 160 ml (p < 0.0001).

A similar result was observed with tiotropium bromide compared with placebo: difference of 123 ml (p < 0.0001).

No significant difference was observed between acclidinium bromide and tiotropium bromide.

**Table 2:** results (ITT population) for the primary efficacy and secondary endpoints (study LAS39)

Endpoints	Acclidinium bromide 400 µg 2x/day N = 171	Tiotropium bromide 18 µg 1x/day N = 158	Placebo N = 85
Initial values			
Initial FEV <sub>1</sub> (mean of least squares in l ± SD)	1.462 ± 0.481	1.543 ± 0.536	1.422 ± 0.521
Primary efficacy endpoint			
Variation in FEV <sub>1</sub> (AUC <sub>0-24h</sub> ) at 6 weeks (mean in l ± SD)	0.065 ± 0.017	0.055 ± 0.018	-0.085 ± 0.023
Difference compared with placebo CI <sub>95%</sub> p	0.150* [0.094; 0.205] p < 0.0001	0.140 [0.083; 0.196] p < 0.0001	-
Difference compared with tiotropium bromide CI <sub>95%</sub> p	0.010 [-0.036; 0.056] NS	-	-
Secondary endpoint			
Variation in FEV <sub>1</sub> (AUC <sub>12-24h</sub> ) at 6 weeks (mean in l ± SD)	0.032 ± 0.017	-0.006 ± 0.018	-0.128 ± 0.024
Difference compared with placebo CI <sub>95%</sub> p	0.160 [0.103; 0.217] p < 0.0001	0.123 [0.065; 0.181] p < 0.0001	-
Difference compared with tiotropium bromide CI <sub>95%</sub> p	0.037 [-0.010; 0.084] NS	-	-

\*: primary analysis

### Indirect comparison meta-analysis (unpublished)

In the absence of validated comparative clinical data versus another comparator active ingredient, the applicant carried out an indirect comparison through a network meta-analysis, the aim of which was the comparison with tiotropium bromide.

This study included randomised clinical studies published in the form of articles covering the period from January 1989 to July 2012 and recent abstracts presented at conferences (2009 - 2012).

The studies included a placebo arm and at least one active ingredient arm, acclidinium bromide or tiotropium bromide. The minimum study duration of those included was 12 weeks and the patients included had moderate to severe COPD.

The Bayesian model was used.

In total, 22 studies were included, 16 for tiotropium bromide 18 µg, 3 for tiotropium bromide 5 µg and 3 for acclidinium bromide (published LAS34 and LAS33 and unpublished LAS38A).

The endpoints measured at 12 and 24 weeks included variation in morning pre-dose FEV<sub>1</sub>, TDI dyspnoea score and variations in SGRQ quality of life score compared with placebo.

Only the results related to comparators used at the dose validated by the Marketing Authorisation and obtained at 24 weeks are presented below (see Table 3). No statistically significant difference was shown between acclidinium bromide and tiotropium bromide.

A non-inferiority analysis was supplied; however, the level of evidence for this approach is not sufficient to validate the non-inferiority of acclidinium bromide to tiotropium bromide, as it was performed a posteriori.

**Table 3:** results at 24 weeks for pre- and post-dose FEV<sub>1</sub>, TDI score and variations in SGRQ score

Endpoint	Acclidinium bromide 400 µg 2x/day	Tiotropium bromide 18 µg 1x/day
<b>Variation in pre-dose FEV<sub>1</sub> at 24 weeks</b>		
Difference versus placebo (ml) 95% CI	127.80 [83.76; 172.30]	104.1 [93.25; 115.00]
Difference versus tiotropium (ml) 95% CI	23.72 [-21.83; 69.38]	-
<b>Variation in post-dose FEV<sub>1</sub> at 24 weeks</b>		
Difference versus placebo (ml) CI <sub>95%</sub>	206.00 [157.60; 254.40]	225.20 [186.40; 263.40]
Difference versus tiotropium (ml) CI <sub>95%</sub>	-19.21 [-78.21; 42.41]	-
<b>Variation in TDI score at 24 weeks</b>		
Difference versus placebo (ml) CI <sub>95%</sub>	1.00 [0.43; 1.57]	0.90 [0.67; 1.14]
Difference versus tiotropium (ml) CI <sub>95%</sub>	0.10 [-0.51; 0.71]	-
<b>Variation in total SGRQ score at 24 weeks</b>		
Difference versus placebo (ml) CI <sub>95%</sub>	-4.63 [-6.84; -2.42]	-2.65 [-3.23; -2.06]
Difference versus tiotropium (ml) CI <sub>95%</sub>	-1.98 [-4.26; 0.31]	-

## 08.2 Safety/ Adverse effects

### 8.2.1 Data from clinical studies

#### **Study LAS34 (ATTAIN): placebo-controlled study lasting 24 weeks**

A safety evaluation was a secondary objective of the study. Only the results for the 400 µg dose of acclidinium bromide 2 times/day are presented below.

The most common adverse events were: exacerbation of COPD (14.1% patients *versus* 20.5% with the placebo), headaches (12.3% *versus* 8.1%) and nasopharyngitis (11.2% *versus* 8.4%).

Other adverse events were reported in less than 5% of cases, including rhinitis (3.3% *versus* 2.6%) and diarrhoea (3.0% *versus* 1.1%).

There were very few adverse events considered as treatment-related: headaches (1.1%) and exacerbation (0.6%).

The incidence of anticholinergic type adverse events was low: dry mouth (0.4% with acclidinium bromide and placebo), palpitations (0.4% *versus* 0%), urinary tract infections (0.7% in both groups) and cystitis (0.4% *versus* 0%).

The most commonly reported severe adverse events were: COPD exacerbation (0.7% versus 3.7% with placebo), headaches (0.7% versus 1.1%), nasopharyngitis (0.7% versus 0.4%) and back pain (0.7% versus 1.1%).

The three deaths reported during the study (one in each of the groups) were not treatment-related.

#### **Study LAS39: placebo and tiotropium-controlled study lasting 6 weeks**

The adverse events reported during the study were comparable in nature and frequency between aclidinium bromide and tiotropium bromide except for headaches.

The most common ( $\geq 2\%$ ) adverse events were:

- nasopharyngitis (5.8% with aclidinium bromide and 5.7% with tiotropium bromide)
- headache (7.0% versus 3.8%)
- COPD exacerbation (2.3% versus 1.3%)
- cough (1.8% versus 1.9%)
- back pain (1.8% versus 1.3%)
- hypertension (0.6% versus 1.3%)

The incidence of adverse events of a severe intensity was  $< 2.5\%$  and no cases were treatment-related.

Furthermore, the incidence of serious adverse events was very uncommon ( $\leq 2.5\%$ ) and not treatment-related.

Anticholinergic effects were observed in less than 1.5% of patients.

#### **Safety study LAS35:**

This randomised, double-blind study evaluated the safety over 52 weeks of two doses of aclidinium bromide 200 and 400  $\mu\text{g}/\text{dose}$  twice daily in patients with moderate to severe COPD.

A total of 605 patients were included, with 602 who received at least one dose and who were included in the safety analysis population.

Disease duration was comparable in the two groups (8.0 years) and the mean number of exacerbations was 1.5/year.

#### **Results:**

Only the results concerning the 400  $\mu\text{g}$  dose 2x/day are presented below.

The mean treatment duration was 277.5 days, the median duration was 359.0 days and 56.4% of patients received treatment for 357 days or longer.

28 patients (9.6%) stopped the study prematurely, in 8 cases (2.7%) this was due to COPD exacerbation. The other adverse events that led to treatment discontinuation were isolated incidents (one observation per type of adverse event).

The most common adverse event was the occurrence of an exacerbation in 19.9% of patients.

Other adverse events that occurred in less than 5% of cases:

- nasopharyngitis and sinusitis, in 4.5% and 4.1% of cases (13 and 11 patients) respectively.
- cough, diarrhoea, dry mouth, upper respiratory tract infections, back pain and arthralgia occurred in less than 4% of patients.

The adverse events were light to moderate in intensity in 53.2% of cases; they were severe for 12.7% of patients:

The most common severe adverse event reported was COPD exacerbation, which occurred in 2.1% of cases (6 patients). Other reported severe adverse events were:

- pneumonia: 0.7% (2 patients);
- headache: 0.7% (2 patients);
- urinary tract infection: 0.3% (1 patient).

Four cases of serious adverse events were considered treatment-related:

- 1 case of COPD exacerbation;
- 1 case of acute heart failure;

- 1 case of fibrillation;
- 1 case of tracheobronchitis.

Anticholinergic effects (dry mouth, constipation) were observed in less than 3% of patients. Four cases of cardiac and cerebrovascular events were considered as treatment-related:

- 1 case of cyanosis;
- 1 case of acute heart failure;
- 1 case of auricular fibrillation;
- 1 case of ventricular extrasystoles.

The two deaths (one case for each dose) that occurred during the treatment period or in the 30 days after administration were not considered as treatment-related.

### **Safety study LAS36:**

This study, the primary objective of which was to evaluate the safety of aclidinium bromide, was a randomised, double-blind 52 week extension phase of the study (LAS33) that compared two doses of aclidinium bromide (200 and 400 µg 2 times/day) with placebo over 12 weeks in patients with moderate to severe COPD.

In the extension phase, patients treated with aclidinium bromide continued with their treatment and those who were initially on placebo were randomised to receive either 200 µg or 400 µg of aclidinium bromide 2 times/day. Only the results from the 400 µg dose 2 times/day are presented below.

### **Results:**

Patients who finished the initial study could be included in the extension phase. A total of 291 patients (of the 561 randomised in the initial study) were included, and 289 received at least one dose of treatment and were included in the safety analysis population.

Disease duration was 7.9 years and the mean number of exacerbations during the previous year was 1.5. The percentage of patients with a history of smoking was 56.6%.

In the two treatment groups, a total of 33 patients (11.4%) discontinued the study due to an adverse event. This affected 14 patients (9.2%) in the aclidinium bromide 400 µg group. The most common adverse event leading to treatment discontinuation was COPD exacerbation, which occurred in 2 patients (1.3%). Other adverse events that led to treatment discontinuation were isolated cases (one observation per type of adverse event).

Two cases were treatment-related; these were cough in one case and a cerebral haemorrhage in the other.

The most common adverse event was the occurrence of exacerbations of COPD in 21.7% of patients. Other adverse events that occurred in more than 5% of patients were:

- nasopharyngitis (7.9%);
- urinary tract infection (5.9%);
- upper respiratory tract infection (5.3%).

The most commonly reported severe adverse event was an exacerbation of COPD, which occurred in 4.6% of patients. Other severe adverse events reported in less than 2% of cases were pneumonia in 1.3% and in 0.7% of patients back pain, cough, hypertension, influenza and abdominal pain.

Two serious adverse events were considered as treatment-related: one case of hypertension and one case of cerebral haemorrhage.

Anticholinergic type adverse events were observed at a frequency of < 6%; only a single case of dry mouth and one of urinary tract infection were associated with treatment.



Two patients had a treatment-related cardiac event: one case of congestive heart failure and one case of first degree atrioventricular block.

One case of cerebral haemorrhage considered as serious and treatment-related was reported and led to study discontinuation.

Two deaths occurred during the study (one for each dose); they were not considered as treatment-related.

### **Safety study LAS38B:**

This study, the primary objective of which was to evaluate the safety of acclidinium bromide, is a non-comparative 40 week extension phase of the study (LAS38A) that compared two doses of acclidinium bromide (200 and 400 µg 2 times/day) with placebo over 12 weeks in patients with moderate to severe COPD.

In the extension phase, all patients were treated with 400 µg 2x/day acclidinium bromide. Three groups with the following treatment sequences were defined:

- placebo : placebo – acclidinium bromide 400 µg
- 200-400 : acclidinium bromide 200 µg – 400 µg
- 400-400 : acclidinium bromide 400 µg – 400 µg

Patients who finished the initial study could be included in the extension phase. A total of 448 patients (out of the 544 randomised in the initial study) received at least one dose of treatment during the open-label phase and were included in the safety analysis population.

### **Results:**

All patients included had moderate to severe COPD, however, disease duration and severity was higher in the 400-400 group where disease duration was 8.6 years and the percentage of patients with severe COPD was 53.1%. In the placebo and 200-400 groups, disease duration was 7.6 and 7.7 years and the percentage of patients with severe COPD was 37.4% and 45.5%, respectively.

In addition, the percentage of patients who had at least one exacerbation during the previous year appeared to be slightly higher in the 400–400 group: 25.2% versus 21.8% and 21.4% in the two other groups.

The mean number of exacerbations during the year prior to inclusion in patients who had exacerbations was homogeneous between the groups (1.5 per year for the whole population).

Mean tobacco consumption was 54.3 packet-years and comparable in the three groups. There were fewer active smokers in the acclidinium bromide 400 µg – 400 µg group (48.3% versus 56.5% and 53.2% in the other two groups).

In summary, in the three treatment sequences, 34 patients (7.6%) stopped the study due to an adverse event. The most common adverse event leading to treatment discontinuation was an exacerbation of COPD, which occurred in 7 patients (1.6%). The other adverse events that led to treatment discontinuation were isolated incidents (one or two observations per type of adverse event).

Eight cases were treatment-related: these were cough for 2 patients, dyspnoea, abdominal pain, myocardial ischaemia, nightmares, palpitations and ventricular tachycardia, for 1 patient for each event.

There were no cases of treatment discontinuation as the result of an exacerbation of COPD that were treatment-related.

The most common adverse event was the occurrence of exacerbations of COPD in 18.1% of patients.

Upper respiratory tract infections occurred in 5.8% of patients. Other adverse events occurred in less than 5% of cases.

Severe adverse events were observed in 11.2% of patients, the most common being an exacerbation of COPD in 2.7% of patients. Other severe adverse events were observed in less than 1% of patients.

The adverse events were regarded as treatment-related in 8.3% of patients for: cough, headache, nausea, dyspnoea and diarrhoea.

Serious adverse events were observed in 49 patients (10.9%), including two that were regarded as being treatment-related:

- one case of influenza occurred between Day 26 and Day 40 in one patient treated with the aclidinium bromide 200 µg – 400 µg sequence;
- one case of myocardial ischaemia between Day 79 and Day 115 in one patient treated with the aclidinium bromide 200 µg – 400 µg sequence.

Anticholinergic effects were observed in less than 3% of patients, the most common being urinary tract infection (2.5%) and constipation (1.3%). In the majority of cases, these effects were not considered as being treatment-related.

Among the six cardiac adverse events reported, three were considered as being treatment-related:

- one case of palpitations (aclidinium bromide 200 µg – 400 µg sequence)
- one case of myocardial ischaemia (aclidinium bromide 200 µg – 400 µg sequence)
- one case of ventricular tachycardia (aclidinium bromide 400 µg – 400 µg sequence)

## 8.2.2 Summary of product characteristics

The common ( $\geq 1/100$  to  $< 1/10$ ) adverse effects referred to in the SPC are headaches (6.6%), nasopharyngitis (5.5%), sinusitis, cough and diarrhoea.

Cardiac adverse effects (linked to anticholinergic effects of aclidinium bromide) are uncommon, however, it is stated that "EKLIRA GENUAIR should be used with caution in patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the "New York Heart Association". Such patients were excluded from the clinical trials and these underlying conditions may be affected by the anticholinergic mechanism of action."

Furthermore, given its anticholinergic activity, aclidinium bromide should be used with caution in patients with symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma (even though direct contact of the product with the eyes is very unlikely).

## 08.3 Summary & discussion

A randomised, double-blind study lasting 24 weeks, compared aclidinium bromide 400 µg 2 times/day with placebo in 828 patients with moderate to severe COPD. Patients could take a symptomatic treatment when required (salbutamol 100 µg/dose) and they were permitted to continue to take treatments that they were taking prior to starting the study.

The primary efficacy endpoint was variation in pre-dose FEV<sub>1</sub> compared with its initial value. Variation in post-dose FEV<sub>1</sub> compared with its initial value, dyspnoea measured using the focal TDI score and variation in SGRQ quality of life score measured at 24 weeks were all secondary endpoints. Prioritisation of these four tests was included in the study protocol.

After 24 weeks of treatment, aclidinium bromide was superior to placebo for:

- variation in morning, pre-dose FEV<sub>1</sub> compared with its initial value: +0.055 l versus -0.073 l, which is a difference of +128 ml that is statistically significant (CI<sub>95%</sub> = [85; 170]; p < 0.0001) and clinically relevant (> 100 ml)
- secondary endpoints:
  - post-dose FEV<sub>1</sub>: difference of 209 ml (CI<sub>95%</sub> = [163; 256]; p = 0.0006) clinically relevant (>100 ml)
  - Focal TDI score: difference of 1.00 point (CI<sub>95%</sub> = [0.43; 1.57]), achieving the clinical relevance threshold (1 point)

- Variation in SGRQ score: difference of -4.63 points (CI<sub>95%</sub> = [-6.84; -2.42]; p < 0.0001) achieving the clinical relevance threshold (4 points).

Only exploratory clinical data were provided to compare acclidinium bromide with tiotropium bromide. These are results from a short-term randomised study (6 weeks) with the primary analysis based on a comparison with placebo. These results could not be taken into consideration.

A network meta-analysis was carried out by the applicant to make an indirect comparison of acclidinium bromide with tiotropium bromide. This meta-analysis did not show a statistically significant difference between the two products. A non-inferiority analysis was provided, however, the level of evidence for this approach is not sufficient to validate the non-inferiority of acclidinium bromide to tiotropium bromide, as it was performed a posteriori.

The most commonly observed adverse effects with acclidinium bromide were headaches (6.6%), nasopharyngitis (5.5%), sinusitis, cough and diarrhoea.

Anticholinergic type adverse effects were uncommon in the clinical studies, however, it is recommended that acclidinium bromide is used with caution in patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the "New York Heart Association" and in patients with symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma.

In conclusion, acclidinium bromide has shown a modest efficacy versus placebo, achieving the minimum clinical relevance thresholds for variation in pre-dose FEV<sub>1</sub>, dyspnoea and quality of life.

Its safety is what is expected of medicinal products of this pharmacological class.

However, the Committee notes that there is no relevant and methodologically valid data available comparing it with other long-acting bronchodilators, even though they have been available on the market in the treatment of COPD for several years, in particular tiotropium bromide, its closest comparator (Marketing Authorisation in 2006). Furthermore, the efficacy of acclidinium bromide on exacerbations and hospitalisations due to exacerbation has not been investigated, either as a primary efficacy or secondary endpoint (exploratory endpoints). Therefore, it is not possible to assess the performance of this new long-acting, anticholinergic bronchodilator as compared to the existing therapeutic arsenal.

## 09 THERAPEUTIC USE

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In the absence of a long-term clinical study comparing acclidinium bromide with another long-acting bronchodilator indicated as a maintenance treatment for COPD, specifically tiotropium bromide, its closest comparator, the therapeutic use of acclidinium bromide cannot be defined.

## 010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

### 010.1 Actual benefit

COPD is a debilitating, potentially life-threatening condition, which can lead to a marked deterioration in quality of life.

This medicinal product is a symptomatic maintenance therapy for COPD.

The effects at 24 weeks versus placebo on morning pre-dose FEV<sub>1</sub>, dyspnoea (TDI score) and quality of life (SGRQ score) achieved the accepted minimum clinical relevance thresholds. Efficacy on exacerbations and hospitalisations due to exacerbation has not been investigated, either as primary efficacy or secondary endpoints, even though these are both important criteria in judging the clinical benefits for the patient. The efficacy/adverse effects ratio is moderate.

In the absence of a long-term clinical study comparing acclidinium bromide with another long-acting bronchodilator indicated as a symptomatic maintenance treatment for COPD, specifically tiotropium bromide, its closest comparator, the place of acclidinium bromide in the therapeutic strategy, cannot be defined.

There are alternative treatments available, in particular tiotropium bromide, another long-acting anticholinergic bronchodilator taken once daily (as opposed to twice daily for acclidinium bromide). The non-inferiority of acclidinium bromide compared with these alternative treatments was not demonstrated in a clinical study with a direct comparison and a sufficient duration.

► Public health benefit:

COPD is a disease with a high prevalence, responsible for significant morbidity (disability, exacerbations, complications, co-morbidities), mortality, a marked change in quality of life of patients and a significant and increasing need for care, which is a public health priority. Furthermore, there is a persistent high level of under-diagnosis in France.

The public health burden of COPD is therefore substantial.

Improvement in the management of COPD is a public health need which is already an established priority (objective 75 of Law No. 2004-806 of 9 August 2004 on Public Health policy aiming to reduce the functional limitations and restrictions in activity and consequences on quality of life, Programme of actions in favour of COPD 2005 – 2010, Plan for the improvement of the quality of life of patients with chronic conditions, Prevention plan by the reduction of exposure to smoking).

Given the data from presented clinical studies, essentially based on the exploration of respiratory function, the impact on public health criteria such as exacerbations, hospitalisations and mortality can not be established. Although a significant and clinically relevant improvement in quality of life was noted (improvement in overall SGRQ score > 4 points), this improvement was not demonstrated versus an active comparator.

Thus, it is not expected that EKLIRA GENUAIR will provide any additional impact on morbidity, mortality or quality of life compared with other existing treatments.

Consequently, EKLIRA GENUAIR does not present a public health benefit.

**Taking account of these points, the Committee considers that the actual benefit of EKLIRA GENUAIR 322 µg is insufficient in the Marketing Authorisation indication.**

**The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.**