HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
7 May 2014

ULTIBRO BREEZHALER 85 µg/43 µg, inhalation powder, hard capsule

B/6 hard capsules + 1 inhaler (CIP: 34009 275 662 4 0)
B/30 hard capsules + 1 inhale (CIP: 34009 275 664 7 9)

Applicant: NOVARTIS

INN	Indacaterol maleate, glycopyrronium bromide
ATC Code (2013):	R03AL04 (adrenergics in combination with anticholinergics)
Reason for the request	**Inclusion**
Lists concerned	**B/30 hard capsules: National Health Insurance** (French Social Security Code L.162-17) **B/6 hard capsules: Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"ULTIBRO BREEZHALER is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease."**

Actual benefit	**In patients with COPD:** - **<u>Substantial AB</u> only in patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination;** - **<u>Insufficient AB</u> for reimbursement by National Health Insurance in the other cases.**
Improvement in actual benefit	**ULTIBRO BREEZHALER fixed-dose indacaterol and glycopyrronium combination does not provide any improvement in actual benefit (IAB V, non-existent) compared with the free combination of its active ingredients administered separately in the population of patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.**
Therapeutic use	**ULTIBRO BREEZHALER fixed-dose indacaterol and glycopyrronium combination must be restricted to patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	19/09/2013 (centralised procedure)
Prescribing and dispensing conditions/special status	List I

ATC Classification	2013	
	R	Respiratory system
	R03	Drugs for obstructive airway diseases
	R03A	Adrenergics, inhalants
	R03AL	Adrenergics in combination with anticholinergics
	R03AL04	Indacaterol and glycopyrronium bromide

02 BACKGROUND

ULTIBRO BREEZHALER 85 µg/43 µg is the first proprietary medicinal product to combine two long-acting bronchodilator active ingredients - indacaterol (beta-2 agonist) and glycopyrronium bromide (anticholinergic).
These two active ingredients are available separately in the following proprietary medicinal products:

- ONBREZ BREEZHALER 150 and 300 µg, OSLIF BREEZHALER 150 and 300 µg and HIROBRIZ BREEZHALER 150 and 300 µg (not marketed) for indacaterol,
- SEEBRI BREEZHALER 44 µg for glycopyrronium bromide (recommended for reimbursement by the Transparency Committee on 24/07/2013).

The device used (BREEZHALER device) allows single-dose inhalation that does not require hand-lung coordination.

03 THERAPEUTIC INDICATIONS

"ULTIBRO BREEZHALER is indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease."

04 DOSAGE

"Dosage
The recommended dose is the inhalation of the contents of one capsule once daily using the ULTIBRO BREEZHALER inhaler.
ULTIBRO BREEZHALER is recommended to be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible on the same day. Patients should be instructed not to take more than one dose in a day.

Special populations

Elderly population
ULTIBRO BREEZHALER can be used at the recommended dose in elderly subjects (75 years of age and older).

Renal impairment
ULTIBRO BREEZHALER can be used at the recommended dose in patients with mild to moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, it should be used only if the expected benefit for the patient outweighs the potential risk (see sections 4.4 and 5.2[1]).

Hepatic impairment
ULTIBRO BREEZHALER can be used at the recommended dose in patients with mild or moderate hepatic impairment. There are no data available for the use of ULTIBRO BREEZHALER in patients with severe hepatic impairment therefore caution should be observed in these patients (see section 5.2[1])."

05 THERAPEUTIC NEED

The diagnosis and management of patients with COPD has to include assessment of the COPD severity stage based on the symptoms (chronic cough, exertional dyspnoea, phlegm production, exacerbations) and pulmonary function status.

Smoking cessation is the only measure likely to restore a normal rate of decline in the FEV1. Flu vaccination is recommended. Reconditioning and chest physiotherapy help improve the symptoms, quality of life and participation in activities of daily living, but no medicines can prevent COPD from turning into chronic respiratory failure.

Management of COPD with medicines (apart from exacerbations) is done in stages, depending on the severity stage and treatment response. The medicines used are aimed at diminishing the symptoms and reducing the frequency and severity of exacerbations.

According to the SPLF [The French-language Society of Pneumology] (2009),[2] no medicine is needed in the event of uncomplicated chronic bronchitis.

In patients with mild COPD (stage I) who are not daily inconvenienced by dyspnoea, the on-demand use of short-acting inhaled bronchodilators is usually sufficient.

Patients with moderate (stage II) to very severe (stage IV) COPD whose dyspnoea interferes with their activities of daily living must be proposed symptomatic maintenance treatment with a long-acting (LA) bronchodilators, beta-2 agonists or anticholinergics. Three LA beta-2 agonists (formoterol, salmeterol and indacaterol) and two LA anticholinergics (tiotropium and glycopyrronium) have Marketing Authorisation in the symptomatic maintenance treatment of COPD. Their efficacy is the same. In addition, aclidinium, another LA anticholinergic, also has Marketing Authorisation in this indication but the Transparency Committee considered that its place in the therapeutic strategy was not definable (lack of comparison with another LA bronchodilator). In patients at stage II to stage IV receiving symptomatic maintenance treatment with an LA bronchodilator, the treatment is completed in the event of a dyspnoeic attack due to an on-demand short-acting bronchodilator.

[1] From the SPC.
[2] Société de Pneumologie de Langue Française [French-language society of Pneumonology] Recommandation pour la pratique clinique : prise en charge de la BPCO (mise à jour 2009). Revue des maladies respiratoires 2010; 27: 522-48.

In the event of inadequate response to an LA bronchodilator, the combination of a beta-2 agonist and an LA anticholinergic may provide an additional benefit, after verifying the proper use of the inhalation system.

In the GOLD guidelines (2011[3]), the combination of an LA beta-2 agonist and an LA anticholinergic is a second-line treatment at all stages of the disease (stages I to IV), the first-line of treatment for each stage taking into account both the level of risk of exacerbation and the extent of symptoms (see the detail in the guidelines).

Inhaled corticosteroids are only recommended (SPLF 2009[2] and GOLD 2011[3]) when taken together with an LA bronchodilator in patients with an FEV1 < 50%[4] of the theoretical value and repeated exacerbations at severe (stage III) to or very severe (stage IV) exacerbations.. In France, only inhaled corticosteroids in a fixed-dose combination with an LA beta-2 agonist have Marketing Authorisation in this indication. These fixed-dose combinations have not been shown to have any effect on mortality (all causes combined) and increase the risk of lower respiratory tract infections, especially pneumonia.

Inhalation treatment with an LA bronchodilator alone or in combination with an inhaled corticosteroid should only be continued if it is seen to have a positive effect on the symptoms.

Systemic corticosteroids are not recommended.
Sustained-action oral theophylline, whose use is limited owing to its narrow therapeutic margin, is only offered to patients who have trouble using inhaled bronchodilators or if the latter are insufficiently effective against their dyspnoea.

[3] Global initiative for Chronic Obstructive Lung Disease: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf.
[4] Indication for an FEV1 < 60% of the theoretical value for the salmeterol/fluticasone combination (see Marketing Authorisation).

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

ULTIBRO BREEZHALER is the only proprietary medicinal product combining a long-acting anticholinergic bronchodilator with a long-acting beta-2 agonist. The comparators are:

INN	NAME Company	Indication in COPD[5]	AB (date of last opinion)	IAB (date of opinion)	Reimbursement Yes/No
Inhaled long-acting anticholinergic bronchodilators					
Glycopyrronium	**SEEBRI BREEZHALER 44 µg** Inhalation powder, hard capsules Novartis Pharma SAS	Maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD).	Substantial (24/07/2013)	SEEBRI BREEZHALER 44 micrograms/dose, inhalation powder, hard capsule, does not provide any improvement in actual benefit (IAB V, non-existent) compared with SPIRIVA 18 µg, inhalation powder, hard capsule.	No (to date non-refundable, to date not marketed)
Tiotropium	**SPIRIVA 18 µg,** Inhalation powder, hard capsule Boehringer Ingelheim France	Maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).	Substantial (25/05/2011)	SPIRIVA shares the level IV improvement in actual benefit of long-acting beta-2 agonist bronchodilators in the standard management of patients with COPD. (02/11/2005)	Yes
	SPIRIVA RESPIMAT 2.5 µg/dose, solution for inhalation Boehringer Ingelheim France		Substantial (25/05/2011)	SPIRIVA RESPIMAT 2.5 micrograms/dose, solution for inhalation, does not provide any improvement in actual benefit (IAB V) compared with SPIRIVA 18 µg, inhalation powder, hard capsule. (07/10/2009)	Yes
Aclidinium	**BRETARIS GENUAIR 322 µg,** **EKLIRA GENUAIR 322 µg** Inhalation powder Menarini France		Insufficient (03/04/2013)	Not applicable	Not recommended by the TC

Inhaled long-acting beta-2 agonist bronchodilators					
Formoterol	**ASMELOR NOVOLIZER 12 µg per dose,** Inhalation powder Meda Pharma	Symptomatic treatment of bronchial obstruction in patients with chronic obstructive pulmonary disease (COPD) and requiring long acting bronchodilator treatment.	Substantial (27/05/2009)	ASMELOR NOVOLIZER does not provide any improvement in actual benefit (IAB V) compared with other long-acting bronchodilators in patients with chronic obstructive pulmonary disease requiring long acting bronchodilator treatment. (27/05/2009)	Yes
	ATIMOS 12 µg per dose, Inhalation solution in pressurised canister Chiesi SA	Symptomatic treatment of bronchial obstruction during chronic obstructive pulmonary disease.	Substantial (06/02/2008)	ATIMOS 12 micrograms/dose, inhalation solution in a pressurised canister does not provide any improvement in actual benefit (IAB V) compared with other long-acting bronchodilators available in this indication. (06/02/2008)	Yes (to date not marketed)
	FORMOAIR 12 µg per dose, Inhalation solution in pressurised canister Chiesi SA		Substantial (06/02/2008)	FORMOAIR 12 micrograms/dose, inhalation solution in a pressurised canister does not provide any improvement in actual benefit (IAB V) compared with other long-acting bronchodilators available in this indication. (06/02/2008)	Yes
	FORADIL 12 µg per dose, Inhalation powder in hard capsules Novartis Pharma SAS	Symptomatic treatment of bronchial obstruction during chronic obstructive pulmonary disease.	Substantial (29/02/2012)	No specific IAB in COPD.	Yes
	OXIS TURBUHALER 12 µg per dose, Inhalation powder AstraZeneca	OXIS TURBUHALER is indicated in COPD as symptomatic treatment for bronchial obstruction.	Substantial (13/01/2010)	OXIS TURBUHALER 12 µg per dose shares with salmeterol (proprietary medicinal products SEREVENT and SISEROL 25 µg per dose and proprietary medicinal products SEREVENT and SISEROL DISKUS 50 µg per dose) a minor improvement in actual benefit (level IV) in terms of efficacy compared with the usual therapeutic strategy for managing 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 methods of use (reduced number of daily intakes) allowing better management with possible clinical implications. (15/09/2004)	Yes (to date not marketed)
Indacaterol	**ONBREZ BREEZHALER,** Inhalation powder, hard capsule	ONBREZ/OSLIF/HIROBRIZ BREEZHALER is indicated for	Substantial (15/12/2010)	ONBREZ BREEZHALER 150 µg and 300 µg do not provide any improvement in actual	Yes

	Novartis Pharma SAS	maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD).		benefit (IAB V) compared with other long acting bronchodilators indicated in COPD. (15/12/2010)	
	OSLIF BREEZHALER, Inhalation powder, hard capsule Novartis Pharma SAS		Substantial (15/12/2010)	OSLIF BREEZHALER 150 µg and 300 µg do not provide any improvement in actual benefit (IAB V) compared with other long acting bronchodilators indicated in COPD. (15/12/2010)	Yes
	HIROBRIZ BREEZHALER, Inhalation powder, hard capsule Novartis Pharma SAS		Substantial (15/12/2010)	HIROBRIZ BREEZHALER 150 µg and 300 µg do not provide any improvement in actual benefit (IAB V) compared with other long acting bronchodilators indicated in COPD. (15/12/2010)	Yes (to date not marketed)
Salmeterol	**SEREVENT 25 µg per dose,** Inhalation suspension in pressurised canister GlaxoSmithKline	Symptomatic treatment of chronic obstructive pulmonary disease. N.B.: There is no reason routinely to combine an inhaled corticosteroid with a bronchodilator in the treatment of chronic obstructive pulmonary disease.	Substantial (16/02/2011)	These proprietary medicinal products provide minor improvement in actual benefit (level IV) in terms of efficacy in comparison with the usual therapeutic strategy for managing patients with COPD in the absence of symptomatic maintenance treatment and a minor improvement in actual benefit (level IV) compared with ipratropium (ATROVENT) in terms of methods of use (reduced number of daily intakes) allowing better management with possible clinical implications. (07/04/2004)	Yes
	SEREVENT DISKUS 50 µg per dose, Inhalation powder GlaxoSmithKline		Substantial (16/02/2011)		Yes

06.2 Other health technologies

Not applicable.

Conclusion

All the free combinations of long-acting beta-2 agonist bronchodilators and long-acting anticholinergic bronchodilators among the medicines listed are clinically relevant comparators.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

ULTIBRO BREEZHALER has obtained a Marketing Authorisation in all the European countries. No information is as yet available on the status of reimbursement of ULTIBRO BREEZHALER in these countries.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company has submitted 8 randomised, double-blind, clinical efficacy studies (apart from the tiotropium arms):

- one 26-week pivot study versus indacaterol, glycopyrronium, tiotropium and placebo (A2303 SHINE)
- one 64-week pivot study versus glycopyrronium, tiotropium and placebo (A2304 SPARK)
- one 52-week pivot safety study versus placebo which studied efficacy as a secondary endpoint (2307 ENLIGHTEN)
- one non-inferiority study versus the free combination of indacaterol and glycopyrronium (A2326 BEACON): although short-term (4 weeks), this study will be described to the extent that it is the only one to have compared the fixed-dose indacaterol/glycopyrronium combination with the free combination of these active ingredients. However, these data should be considered as exploratory only.
- one 26-week study versus the free combination of tiotropium + formoterol (QUANTIFY)
- two crossover studies versus tiotropium and placebo (A2305 BRIGHT and A2322 BLAZE): these studies will not be described insofar as the treatment periods were very short-term (3 and 6 weeks)
- one study versus the fixed-dose fluticasone/salmererol combination (A2313 ILLUMINATE): this study will not be described below insofar as it predominantly included patients with moderate COPD (80 %) and 99.8 % of patients had no history of exacerbation and yet the fluticasone/salmeterol combination is restricted to patients with severe COPD with an FEV1 < 60 % of the theoretical value and a history of repeated exacerbations and significant symptoms despite maintenance bronchodilator treatment with long-acting bronchodilators.

8.1.1 Studies concerning superiority versus the components of the combination

	A2303 SHINE
Principal study objective	**Demonstrate the superiority of the fixed-dose indacaterol/glycopyrronium combination compared with each of the components of the combination in terms of the pre-dose FEV1 after 26 weeks in patients with moderate to severe COPD.**
Method	Comparative, randomised, double-blind study (except for the tiotropium group).
Study population	Age ≥ 40 years Moderate to severe COPD 30 % ≤ post-bronchodilator FEV1 < 80 % of the predicted value Use of tobacco (≥ 10 pack/years) Total symptom score ≥ 1 for at least 4 of the 7 days prior to randomisation
Treatment groups	▪ Fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination[6] ▪ Indacaterol 150 µg ▪ Glycopyrronium 50 µg ▪ Tiotropium 18 µg (administered open-label) ▪ Placebo Administration of treatments once/day
Course of the study	26-week duration
Treatments given in combination	Short-acting beta-2 agonist rescue treatment. Free-combination corticosteroids were continued throughout the study.
Primary efficacy endpoint	Pre-dose FEV1 after 26 weeks
Key secondary endpoints	Comparison with the placebo in terms of: ▪ Dyspnoea (TDI focal score[7]) ▪ Use of rescue medication (number of puffs) ▪ Quality of life (total SGRQ score[8])

Comment:
For technical reasons, the company was unable to manufacture a tiotropium placebo identical to those of the active product and therefore to carry out a double-blind study.
However, blinded administration of tiotropium was possible when using a third person to deliver treatments to and collect them from patients taking part in the clinical trials. This proved complicated to do over a very long period of time, which is why tiotropium was administered using a single-blind process in Study 2305 and 2322 and an open-label one in Study 2303 and 2304.

[6] For all the studies, the indacaterol 110 µg is equal to the dose dispensed through the mouthpiece of indacaterol maleate equivalent to 85 µg of indacacteol and the glycopyrronium 50 µg dose is equal to the dispensed dose of glycopyrronium bromide equivalent to 43 µg of glycopyrronium.

[7] **TDI ("Transition Dyspnoea Index"):** this score allows variations in dyspnoea to be evaluated in relation to the baseline value.
Using the **"Baseline Dyspnoea Index"** (BDI) it can evaluate:
- the level of disability associated with dyspnoea (functional impairment), which determines the impact of dyspnoea on the ability to perform certain activities,
- the type of tasks that bring on a dyspnoea attack,
- the amount of effort: level of effort required to cause dyspnoea.

A difference of at least 1 unit is regarded as the clinically significant minimum difference. Responders are subjects having a TDI ≥ 1 unit. Patients with a smaller variation are regarded as non responders.

[8] **SGRQ ("Saint George's Respiratory Questionnaire"):** quality of life questionnaire in the event of chronic airway obstruction. Three categories are evaluated: "Symptoms" (especially their frequency and severity), "Activity" (cause or consequences of dyspnoea) and "Impacts on daily life" (especially on professional life). Each category is independently assigned a score from 0 to 100, and the overall total gives the total score, also from 0 to 100 (a score of 0 signifies no limitation on quality of life). An improvement ≥ 4 points is considered to be clinically relevant.

Results:

A total of 2144 patients were randomised, comprising:
- indacaterol/glycopyrronium combination: n = 475
- indacaterol: n = 477
- glycopyrronium: n = 475
- tiotropium: n = 483
- placebo: n = 234

Most of the patients completed the study (89 %).
Patient characteristics at baseline were comparable between the groups.
The patients included were aged on average 63.9 years old, had moderate (63.6 %) or severe (36.4 %) COPD with an average pre bronchodilator FEV1 of 46.93 % of the predicted value, a post bronchodilator FEV1 reversibility of 20 % and had not had exacerbations during the previous year in 74.6 % of cases and were taking inhaled corticosteroids in 57.5 % of cases.

Primary efficacy endpoint:
After 26 weeks of treatment, the pre-dose FEV1 was higher in the indacaterol/glycopyrronium group than in the placebo (difference of 200 ml), indacaterol (difference of 70 ml) and glycopyrronium (90 ml) groups. Although statistically significant, these differences are lower than the clinical relevance threshold (< 100 ml) (see Table 1).
The pre-dose FEV1 was more significant in the indacaterol/glycopyrronium, indacaterol, glycopyrronium and tiotropium groups than in the placebo group with clinically relevant differences (see Table 1).

Secondary endpoints:

TDI focal score:
The TDI score was higher in the indacaterol/glycopyrronium, indacaterol, glycopyrronium and tiotropium groups than in the placebo group. This improvement reached the clinical relevance threshold (≥ 1) with the indacaterol/glycopyrronium combination only ($p < 0.001$). No difference was observed between the indacaterol/glycopyrronium groups and their comparators indacaterol, glycopyrronium and tiotropium.

Use of rescue treatment:
During the 26 weeks of treatment, the intake of rescue treatment was lower with the indacaterol/glycopyrronium combination than with the placebo (-0.96 puff/day; $p < 0.001$), indacaterol (0.30 puff/day; $p = 0.027$), glycopyrronium (-0.66 puff/day; $p < 0.001$) and tiotropium (- 0.54 puff/day; $p < 0.001$).

Table 1: **Pre-dose FEV1 after 26 weeks of treatment (L) (ITT populations)**

		Pre-dose FEV1 (L)			Difference between the treatments			
Treatment	**n**	**LMS**	**SD**	**Comparison**	**LMS**	**SD**	**95% CI**	**p**
Ind/Gly	442	1.45	0.010	Ind/Gly - PBO	0.20	0.017	(0.17; 0.24)	< 0.001
				Ind/Gly - Ind	0.07	0.014	(0.05; 0.10)	< 0.001
				Ind/Gly - Gly	0.09	0.014	(0.06; 0.11)	< 0.001
				Ind/Gly - Tio	0.08	0.013	(0.05; 0.10)	< 0.001
Indacaterol	435	1.38	0.010	Ind - PBO	0.13	0.017	(0.10; 0.16)	< 0.001
Glycopyrronium	424	1.36	0.010	Gly - PBO	0.12	0.017	(0.08; 0.15)	< 0.001
Tiotropium	446	1.37	0.010	Tio - PBO	0.13	0.017	(0.09; 0.16)	< 0.001
Placebo (PBO)	191	1.25	0.015					

LSM: least squares mean; SD: standard deviation; CI: confidence interval

SGRQ score:
After 26 weeks, a statistically significant improvement in the SGRQ score compared with the placebo was observed with the indacaterol/glycopyrronium combination only. However, the observed difference (-3.01) was lower than the clinical relevance threshold (difference of at least 4 points).

	A2304 SPARK
Principal study objective	**Demonstrate the superiority of the fixed-dose indacaterol/glycopyrronium combination compared with glycopyrronium in terms of the frequency of exacerbations in patients with severe to very severe COPD.**
Method	Comparative, randomised, double-blind study (except for the tiotropium group).
Study population	Age ≥ 40 years Severe to very severe COPD Post-bronchodilator FEV1 < 50 % of the predicted value Use of tobacco (≥ 10 pack/years) ≥ 1 exacerbation of COPD over the previous year
Treatment groups	▪ Fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination ▪ Glycopyrronium 50 µg ▪ Tiotropium 18 µg (administered open-label) Administration of treatments once/day
Course of the study	64-week duration
Treatments given in combination	Short-acting beta-2 agonist rescue treatment. Free-combination corticosteroids were continued throughout the study.
Primary efficacy endpoint	Comparison with glycopyrronium in terms of frequency of moderate to severe exacerbations[9] during the 64 weeks of treatment.
Secondary endpoints included:	▪ Comparison with tiotropium in terms of frequency of moderate to severe or severe only exacerbations during the 64 weeks of treatment. ▪ Pre-dose FEV1 after 64 weeks

Results:

A total of 2224 patients were randomised, comprising:
- indacaterol/glycopyrronium combination: n = 741
- glycopyrronium: n = 741
- tiotropium: n = 742

The study drop-outs concerned 25 % of patients, mainly because of adverse effects (7.8 %), withdrawal of consent (5.7 %), inadequate efficacy (4.0 %) and death (3.0 %).
Patient characteristics at baseline were comparable between the groups.
The patients included were aged on average 63.3 years old, had very severe (79 %) or severe (21 %) COPD with an average pre bronchodilator FEV1 of 32.27 % of the predicted value and post bronchodilator FEV1 reversibility of 18 %.

[9] *Definition of exacerbations*
A COPD exacerbation was defined by a worsening of the following over at least two consecutive days:
- two or more major symptoms: dyspnoea, sputum volume, purulence of sputum
- OR any of the major symptoms combined with an increase in the severity of any of the minor symptoms: sore throat, common cold (rhinorrhoea and/or nasal congestion), fever without any other cause, cough, wheezing.

Definition of moderate to severe exacerbations
- An exacerbation was considered moderate if it required use of systemic corticosteroids or antibiotics or both.
- An exacerbation was considered severe if hospitalisation was necessary. A visit to the emergency department for more than 24 hours was considered hospitalisation.

An independent adjudication committee reviewed all the exacerbations prior to the main analysis.

During the previous year, 76.2 % of patients had had an exacerbation, 22.3 % at least 2 exacerbations and 1.5 % had not had any.
The patients were taking inhaled corticosteroids in 75.3 % of cases.

Primary efficacy endpoint:
The annual frequency of moderate to severe exacerbations was lower with indacaterol/glycopyrronium than with glycopyrronium: 0.84 versus 0.95 exacerbations/year, i.e. a difference of 0.11 exacerbation/year, RR = 0.88, 95% CI= [0.77; 0.99], p = 0.038.

Secondary endpoint:
Exacerbations:
No significant difference was observed between indacaterol/glycopyrronium and tiotropium and between glycopyrronium and tiotropium in terms of the annual frequency of moderate to severe exacerbations and in terms of the frequency of severe exacerbations.

Pre-dose FEV1:
At 64 weeks, the pre-dose FEV1 was 1.05 l with the indacaterol/glycopyrronium combination, 0.98 l with glycopyrronium and 0.99 l with tiotropium, i.e. differences of 70 ml between the combination and glycopyrronium and 60 ml between the combination and tiotropium that were statistically significant (< 0.001) but not clinically relevant.

8.1.2 Study versus placebo

	A2307 ENLIGHTEN
Principal study objective	**Evaluate the tolerability and safety of use of the fixed-dose indacaterol/glycopyrronium combination versus placebo in terms of the frequency of adverse events in patients with moderate to severe COPD.**
Method	Placebo-controlled comparative randomised (2:1) double-blind study.
Study population	Age ≥ 40 years Moderate to severe COPD 30 % ≤ post-bronchodilator FEV1 < 80 % of the predicted value Use of tobacco (≥ 10 pack/years) Total symptom score ≥ 1 for at least 4 of the 7 days prior to randomisation
Treatment groups	▪ Fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination ▪ Placebo Administration of treatments once/day
Course of the study	52-week duration
Treatments given in combination	Short-acting beta-2 agonist rescue treatment. Free-combination corticosteroids were continued throughout the study.
Primary efficacy endpoint	Frequency of adverse events
Secondary endpoints included:	Pre-dose FEV1 after 52 weeks

Results:

A total of 339 patients was included, of whom 226 in the indacaterol/glycopyrronium group and 113 in the placebo group.
The patients completed the study in 86.5 % of cases.

The patients included were aged on average 62.6 years old.
The characteristics of patients at baseline were not comparable between the groups in terms of severity of COPD, which was more severe in the indacaterol/glycopyrronium group: 68 % of moderate forms and 31.1 % of severe forms in the indacaterol/glycopyrronium as opposed to 80.5 % of moderate forms and 18.6 % of severe forms in the placebo group. As expected, the intake of

inhaled corticosteroids was more significant in the indacaterol/glycopyrronium (45.8 % versus 38.9 %) group.
The pre-dose FEV1 as a percentage of the predicated value was 49.6 % in the indacaterol/glycopyrronium group and 52.3% in the placebo group. The post-bronchodilator FEV1 reversibility was 15.7 % on average in the two groups.

After 52 weeks, the pre-dose FEV1 was higher with the indacaterol/glycopyrronium combination than with the placebo: 1.67 l versus 1.52 l, i.e. a difference of 0.15 l ($p < 0.001$) that is clinically relevant.

8.1.3 Non-inferiority study versus the free combination of components of the fixed-dose indacaterol/glycopyrronium combination

	A2326 BEACON
Principal study objective	**Demonstrate the non-inferiority of the fixed-dose indacaterol/glycopyrronium combination compared with the free combination of the components of the combination in terms of the pre-dose FEV1 in patients with moderate to severe COPD.**
Method	Non-inferiority, comparative, randomised, double-blind study.
Study population	Age ≥ 40 years Moderate to severe COPD 30 % ≤ post-bronchodilator FEV1 < 80 % of the predicted value Use of tobacco (≥ 10 pack/years) Total symptom score ≥ 1 for at least 3 days prior to randomisation
Treatment groups	▪ Fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination ▪ Free indacaterol 150 µg + glycopyrronium 50 µg combination Administration of treatments once/day
Course of the study	28-day duration After being weaned off ongoing treatments (apart from inhaled corticosteroids) over 7 days, the patients received the free indacaterol 150 µg and glycopyrronium 50 µg combination open-label in one dose per day for 14 days in order to stabilise them for the baseline FEV1 value, and to ensure their compliance and measure their symptoms. After this period, the symptomatic patients were randomised to two treatment groups.
Treatments given in combination	Short-acting beta-2 agonist rescue treatment. Free-combination corticosteroids were continued throughout the study.
Primary efficacy endpoint	Pre-dose FEV1 after 28 days
Statistical analysis	The fixed-dose combination could be considered as non-inferior to the free combination of active ingredients if the lower limit of the 95 % confidence interval of the difference between the treatments were higher than the pre-defined non-inferiority threshold of 100 ml with a study power of 90 %. Analysis of the per protocol (PP) population

Results:
A total of 193 patients was included, of whom 90 in the fixed-dose indacaterol/glycopyrronium combination and 103 in the free indacaterol + glycopyrronium combination.

The per protocol population in the analysis included 84 patients in the fixed-dose indacaterol/glycopyrronium combination and 97 in the free indacaterol + glycopyrronium combination.

Patient characteristics at baseline were comparable between the groups.
The patients included were aged on average 64.9 years old, had moderate (59.6 %) or severe (40.4 %) COPD with an average pre bronchodilator FEV1 of 44.7 % of the predicted value and

post bronchodilator FEV1 reversibility of 23.6 % and were taking inhaled corticosteroids in 64.8 % of cases.

After 28 days of treatment, in the PP population, the pre-dose FEV1 was 1.460 L with the fixed-dose combination and 1.432 L with the free combination of active ingredients, i.e. a difference of -0.005 L, $_{95\%\ CI}$= [-0.051; 0.040].
The lower limit of the $_{95\%}$ CI of the difference between the treatments being higher than -100 ml, it can be concluded that the fixed-dose combination is non-inferior compared with the free combination of indacaterol and glycopyrronium in terms of the pre-dose FEV1 after 28 days.

8.1.4 Study of non-inferiority versus the free formoterol + tiotropium combination

	QUANTIFY
Principal study objective	**Demonstrate the non-inferiority of the fixed-dose indacaterol/glycopyrronium combination compared with the tiotropium + formoterol combination in terms of quality of life in patients with moderate to severe COPD.**
Method	Non-inferiority, comparative, randomised, double-blind, triple placebo study.
Study population	Age ≥ 40 years Moderate to severe COPD 30 % ≤ post-bronchodilator FEV1 < 80 % of the predicted value FEV1/FVC < 70 % Use of tobacco (≥ 10 pack/years)
Treatment groups	▪ Fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination 1 x/day ▪ Free formoterol 12 µg 2 x/day + tiotropium 18 µg 1 x/day combination
Course of the study	26-week duration Triple placebo (three inhalations in the morning, one in the evening)
Treatments given in combination	Short-acting beta-2 agonist rescue treatment. Free-combination corticosteroids were continued throughout the study.
Primary efficacy endpoint	▪ SGRQ-C score (non-inferiority analysis)
Secondary endpoints included:	▪ SGRQ-C score (superiority analysis) ▪ TDI score ▪ Pre-dose FEV1
Statistical analysis	The fixed-dose combination could be considered as non-inferior to the free combination of active ingredients if the lower limit of the 95 % confidence interval of the difference between the treatments were higher than the pre-defined non-inferiority threshold of 4 points with a study power of 90 %. Analysis of the per protocol (PP) population

Results:

A total of 934 patients were randomised, of whom 476 patients in the indacaterol/glycopyrronium group and 458 in the formoterol + tiotropium group.
The size of the per protocol population is as follows:

- indacaterol/glycopyrronium: n = 376
- formoterol + tiotropium: n = 374

Patient characteristics were comparable between the groups.
The patients were aged 62.9 years old on average, had moderate (56.7 %) or severe (42.3 %) COPD and an average post-bronchodilator FEV1 of 53.2 % of the predicated value. The majority of patients (86.4 %) had not had any exacerbations during the previous year and 41.2 % were taking inhaled corticosteroids.

The SGRQ-C score (score from 0 to 100) at baseline was 44.84 points in the indacaterol/glycopyrronium group and 44.59 points in the formoterol + tioptropium group.

Primary efficacy endpoint:
After 26 weeks, the SGRQ-C score was -3.54 points with the fixed dose indacaterol/glycopyrronium combination and 2.77 points with the free formoterol + tiotropium combination, i.e. a difference of -0.77 points, $CI_{95\%}$ = [-2.48; 0.93]. It can be concluded that the fixed-dose indacaterol/glycopyrronium combination is non-inferior compared with the free formoterol + tiotropium combination insofar as the lower limit of the $_{95\%}$ CI of the difference between the treatments is higher than the pre-defined non-inferiority threshold (-4 points).
The non-inferiority was confirmed in the analysis on the ITT population.

Secondary endpoints (ITT population):
The analysis of the superiority in terms of the SGRQ-C score did not show any significant difference between the treatments.

After 26 weeks, the TDI score was 1.13 in the indacaterol/glycopyrronium group and 0.75 in the formoterol + tiotropium group without any significant difference between the groups.

After 26 months, the pre-dose FEV1 was higher in the indacaterol/glycopyrronium group compared with the formoterol + tiotropium (165 ml versus 98 ml, $p < 0.001$) group. However, the observed difference (68 ml) is not clinically relevant.

08.2 Safety/Adverse effects

8.2.1 Clinical studies

52-week pivot safety study versus placebo: Study 2307 ENLIGHTEN

A total of 339 patients was included, of whom 226 in the indacaterol/glycopyrronium group and 113 in the placebo group.
The median length of exposure to treatment was 365 days in the indacaterol/glycopyrronium and placebo groups, and on average 337 days in the indacaterol/glycopyrronium group and 313 days in the placebo group.
Treatment was discontinued early due to serious adverse events in 5.3 % of the indacaterol/glycopyrronium group and 2.7 % of the placebo group.

The overall incidence of adverse events was 57.8 % in the indacaterol/glycopyrronium group and 56.6 % in the placebo group.
The most common adverse events in the two groups were the COPD exacerbations (28 % with the indacaterol/glycopyrronium combination versus 25.7 % with the placebo), and then the following were less common:

- Cough: 8.0 % versus 6.2 %
- Viral infections: 8.0 % versus 13.3 %
- Viral lower respiratory tract infections: 6.7 % versus 3.5 %
- Viral upper respiratory tract infections: 5.3 % versus 8.0 %
- Bacterial upper respiratory tract infections: 4.9 % versus 4.4 %
- Pyrexia: 4.4 % compared with 0.9 %

Serious adverse events:
Serious adverse events were observed in 12.4 % of patients in the indacaterol/glycopyrronium group and 8.8 % of patients in the placebo group.
The proportion of patients who had at least one serious adverse event was 16.4 % in the indacaterol/glycopyrronium group and 10.6 % in the placebo group.
The most common serious adverse event was a COPD exacerbation in 6.8 % of patients in the indacaterol/glycopyrronium group and 5.2 % of those in the placebo group, followed by pneumonia (confirmed on an x-ray) reported in 3.6 % of patients in the indacaterol/glycopyrronium group only.

No significant difference was shown between the two groups for serious respiratory adverse events: 4.9 % versus 1.8 % (p = 0.264).
In two patients (COPD exacerbation and pneumonia in one and COPD exacerbation in the other), the events were suspected to be linked to the indacaterol/glycopyrronium combination.

Five patients had six serious adverse events of cardio-cerebral vascular origin (2.2 %) in the indacaterol/glycopyrronium group only, among whom two patients had a major adverse event. However, no significant difference was shown between the groups in terms of the incidence of serious cardio-cerebral vascular events.

Death:
Five patients died during the study or over the 30 days of follow-up: four (1.8 %) in the indacaterol/glycopyrronium group and one (0.9 %) in the placebo group. No deaths were attributed to study treatments: indacaterol/glycopyrronium combination or placebo.

Adverse events of particular interest:
In the indacaterol/glycopyrronium group, five patients (2.2 %) had arrhythmia and three patients (1.3 %) had a reduction in urinary flow or urinary retention.

64-week Study A2304 SPARK versus glycopyrronium and tiotropium
The overall incidence of adverse events was 93 % with the indacaterol/glycopyrronium combination, 93.8 % with glycopyrronium and 93.1% with tiotropium.
The most common adverse events were COPD exacerbations (87.1 % to 88 % in the three groups).
The other adverse events > 10 % were bacterial upper respiratory tract infections, rhinopharyngitis and viral upper respiratory tract infections.
The incidence of other adverse events ≤ 10 % (particularly cough, bronchitis, pneumonia, hypertension, upper respiratory tract infections, pyrexia and urinary tract infection) was similar in the three groups.

The incidence of all cardio-cerebral vascular events was similar in the three groups (6 % in the indacaterol/glycopyrronium group and 6.8 % in the glycopyrronium and tiotropium groups), mainly atrial fibrillation (1.1 to 1.5 %) and heart failure (from 0.4 to 1.1 %).

The incidence of serious adverse events was similar between the three groups: 22.9 % with the indacaterol/glycopyrronium combination, 24.2 % with glycopyrronium and 22.4 % with tiotropium.
Serious cardio-cerebral vascular adverse events were observed in 3.7 % of patients in the indacaterol/glycopyrronium group, 3.4 % of those in the glycopyrronium group and 3.5 % of those in the tiotropium group.

8.2.2 Warnings in the SPC

ULTIBRO BREEZHALER caused adverse effects similar to those observed with the individual components of the combination. As it contains indacaterol and glycopyrronium, the adverse effects of the same type and severity as those associated with each of the components can be expected with the combination.

The safety profile is characteristic of that which is observed with anticholinergics and beta-2-adrenergics, components of the combination. The other most common adverse effects frequently linked to the product (reported in at least 3 % of patients with ULTIBRO BREEZHALER and also more often than with the placebo) were a cough and oropharyngeal pain (including throat irritation).

The adverse effects considered very common (≥ 1/10) are upper respiratory tract infections.
The adverse effects considered common (≥ 1/100 and < 1/10) are: nasopharyngitis, urinary tract infection, sinusitis, rhinitis, vertigo, headaches, cough, pharyngeal pain including throat irritation, dyspepsia, dental caries, gastroenteritis, musculoskeletal pain, fever, chest pain.

8.2.3 Risk Management Plan

Several adverse events are identified as adverse events of particular interest and undergo special supervision as part of the Risk Management Plan (RMP) for the fixed-dose indacaterol/glycopyrronium combination.

Risks related to the pharmacological effects of long-acting beta-2 agonists (including indacaterol):

- Identified risks and interactions: QTc prolongation, ischaemic cardiopathy, myocardial infarction, cardiac arrhythmia (brady- and tachyarrythmia), heart failure, cerebral vascular events, hyperglycaemia, hypokalaemia, drug interaction with CYP3A4 inhibitors.
- Potential risks and interactions: intubation, hospitalisation and death due to events related to asthma in asthmatics (off-label), medication error; drug interaction with P glycoprotein inhibitors, subpopulation suffering from a uridine diphosphate glucuronyltransferase (UGT1A1) deficiency, combination of medicines known to prolong the QTc interval, sympathomimetic agents, medicines linked with hypokalaemia, beta-blockers.

Risks related to the pharmacological effects of long-acting anticholinergics (including glycopyrronium):

- Significant risks identified: angle-closure glaucoma, bladder obstruction and urinary retention, use in patients with severe renal impairment or end-stage renal disease.
- Potential significant risks: atrial fibrillation.

08.3 Summary & discussion

The fixed-dose indacaterol/glycopyrronium 110 µg/50 µg was compared with each of the components of the indacaterol (150 µg) and glycopyrronium (50 µg) combination in a 26-week randomised, double-blind study in 2144 patients with moderate to severe COPD. The study also included a tiotropium 18 µg group and a placebo group. The treatments were administered once a day double-blinded apart from tiotropium.
After 26 weeks, all the active treatments were superior to the placebo in terms of pre-dose FEV1 with clinically relevant differences (> 100 ml): 200 ml for the indacaterol/glycopyrronium combination, 130 ml for indacaterol, 120 ml for glycopyrronium and 130 ml for tiotropium.
The indacaterol/glycopyrronium combination was superior to each of the components of the combination (main analysis) and to tiotropium in terms of the pre-dose FEV1. However, the differences observed were not clinically relevant: 70 ml versus indacaterol, 90 ml versus glycopyrronium and 80 ml versus tiotropium.
In the case of secondary endpoints, that is the TDI focal score, the use of rescue treatment and the SGRQ-C score, a significant difference was shown between the indacaterol/glycopyrronium combination and each of the components of the combination only in rescue treatment: -0.30 puff/day versus indacaterol ($p = 0.027$), -0.66 puff/day versus glycopyrronium ($p < 0.001$).

The fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination was compared with glycopyrronium 50 µg in terms of the frequency of moderate to severe exacerbations in a 64-week randomised, double-blind study in 2224 patients with severe to very severe COPD who had had at least one COPD exacerbation the previous year. The study also included a tiotropium 18 µg arm administered open label.
After 64 weeks, the annual frequency of moderate to severe exacerbations was lower with indacaterol/glycopyrronium than with glycopyrronium: 0.84 versus 0.95 exacerbations/year, i.e. a difference of -0.11 exacerbations/year, RR = 0.88, 95 % CI= [0.77; 0.99], $p = 0.038$.
No significant difference was observed in terms of the moderate to severe exacerbations and in terms of the frequency of severe exacerbations between the indacaterol/glycopyrronium combination and tiotropium on the one hand, and between glycopyrronium and tiotropium on the other.
In terms of pre-dose FEV1, the indacaterol/glycopyrronium combination was superior to glycopyrronium (+70 ml) and tiotropium (+60 ml) but the differences observed are not clinically relevant.

The non-inferiority of the fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination compared with the free combination of these same active ingredients (indacaterol 150 µg + glycopyrronium 50 µg) was demonstrated in terms of pre-dose FEV1 in a randomised, double-blind study after 4 weeks of treatment in 193 patients with moderate to severe COPD: difference of 5 ml, 95% CI = [-51; 40] with a non-inferiority threshold of 100 ml (PP population).

The non-inferiority of the fixed-dose indacaterol/glycopyrronium 110 µg/50 µg combination compared with the free formoterol 12 µg 2 x/day + tiotropium 18 µg 1 x/day combination was demonstrated in terms of quality of life evaluated by the SGRQ-C score after 26 weeks of treatment in a randomised, double-blind, triple placebo study in 934 patients with moderate to severe COPD: difference of 0.77 points, $_{95\%\ CI}$= [-2.48; 0.93] with a non-inferiority threshold of - 4 points (PP population).

The results of these two non-inferiority studies should be interpreted with caution insofar as the non-inferiority thresholds recorded correspond with the clinical relevance thresholds usually accepted in the superiority studies when they should have been lower and insofar as these studies do not comprise a placebo arm to assure of the internal validity of the study.

The safety of the indacaterol/glycopyrronium combination was evaluated in a randomised, double-blind safety study versus placebo lasting 52 weeks in 339 patients with moderate to severe COPD.
The most common adverse events in the two groups were COPD exacerbations (28 % with the indacaterol/glycopyrronium combination versus 25.7 % with the placebo), and viral and bacterial infections particularly of the upper and lower respiratory tracts (24.9 % versus 28.8 %) with a cough (8.0 % versus 6.2 %) and fever (4.4 % versus 0.9 %) occurring less often. No significant difference was shown between the two groups for serious respiratory adverse events: 4.9 % versus 1.8 % (p = 0.264). In two patients (COPD exacerbation and pneumonia in one and COPD exacerbation in the other), the events were suspected to be linked to the indacaterol/glycopyrronium combination.
No significant difference was shown between the groups in terms of the incidence of serious cardio-cerebral vascular events.
In the indacaterol/glycopyrronium group, five patients (2.2 %) had arrhythmia and three patients (1.3 %) had a reduction in urinary flow or urinary retention.

In addition, in the longest efficacy study of 64 weeks, which compared the indacaterol/glycopyrronium combination with glycopyrronium and tiotropium, the most common adverse events were COPD exacerbations (from 87.1 % to 88 % in the three groups). The other common adverse events in the indacaterol/glycopyrronium group were similar to those observed in the safety study, particularly infections, cough, fever and similar to those observed in the glycopyrronium and tiotropium groups.
The incidence of all cardio-cerebral vascular events, including the serious ones, was similar in the 3 groups.

In all, the safety profile observed with the indacaterol/glycopyrronium combination is that of the two components, of anticholinergic and beta-2 adrenergic type.
The RMP provides plans in particular the monitoring of significant risks related to beta-2 adrenergic effects (cardio-cerebral vascular effects, hyperglycaemia, hypokalaemia) and to identified (angle-closure glaucoma, bladder obstruction and urinary retention, use in patients with severe renal impairment or end-stage renal disease) and potential (atrial fibrillation) anticholinergic effects.
The most common adverse effects linked to the product reported in at least 3 % of patients with the indacaterol/glycopyrronium combination and also more often than with the placebo were a cough and oropharyngeal pain (including throat irritation).
The other adverse effects considered common (≥ 1/100 and < 1/10) are: nasopharyngitis, urinary tract infection, sinusitis, rhinitis, vertigo, headaches, cough, pharyngeal pain including throat irritation, dyspepsia, dental caries, gastroenteritis, musculoskeletal pain, fever, chest pain.

08.4 Planned studies

The pharmacovigilance plan of the RMP includes two post authorisation studies:

- Utilisation study of the indacaterol/glycopyrronium combination in Europe (DUS) from the multinational database to evaluate the characteristics of patients newly treated with the indacaterol/glycopyrronium combination, focusing on the prevalence of off-label use and use in the conditions associated with the warnings and precautions of use for this combination.

- Post-authorisation safety study (PASS, Post Authorisation Safety Studies) to evaluate the relative risk of the various adverse events occurring in new COPD patients treated with indacaterol/glycopyrronium compared with new COPD patients taking comparator treatments for COPD.
  The risks covered in this study are: ischaemic cardiopathy, myocardial infarction, cardiac arrhythmia (brady- and tachyarrythmia), heart failure, cerebral vascular events, diabetes, angle-closure glaucoma, bladder obstruction and urinary retention, bronchospasm and atrial fibrillation.

09 THERAPEUTIC USE

ULTIBRO BREEZHALER fixed-dose indacaterol and glycopyrronium combination must be restricted to patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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 entails handicap, a marked deterioration in the quality of life, and it can be life-threatening.

◗ This proprietary medicinal product is intended as symptomatic maintenance treatment for COPD. It has no impact on the long-term decline in pulmonary function.

◗ This proprietary medicinal product combines two long-acting bronchodilators - indacaterol (beta-2 agonist) and glycopyrronium (anticholinergic). This fixed-dose combination showed its superiority compared with the placebo in terms of improvement in pre-dose FEV1 and dyspnoea (TDI focal score). However, the effects obtained in terms of control of the symptoms and reduction in exacerbations by adding these two long-acting bronchodilators from two different pharmacological classes compared with a long-acting bronchodilator as monotherapy, although statistically significant, are not clinically relevant. Adverse effects of the anticholinergic and beta-2 adrenergic type were not very common in the studies. However, their monitoring and evaluation should be continued and the precautions of use set out in the SPC need to be respected.
The efficacy/adverse effects ratio is modest.

◗ This proprietary medicinal product, a fixed dose indacaterol and glycopyrronium combination, must be restricted to patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.
Treatment with this proprietary medicinal product should not be continued unless the patient feels to be deriving benefit from it.

◗ Alternative medicinal products exist.

◗ Public health benefit:

The public health burden of COPD is considerable.

Improvement in the treatment of COPD is a public health need which is an established priority (GTNDO [National Technical Group for the Definition of Public-Health Objectives] priorities,[10] French Public Health Law[11]). However, for the symptomatic treatment of COPD, the therapeutic need is covered by existing symptomatic therapies.

On the basis of the data available from the clinical trials and in view of the available alternatives, it is not expected that this proprietary medicinal product will have an additional impact on morbidity and mortality.

Consequently, it is not expected that the proprietary medicinal product ULTIBRO BREEZHALER will benefit public health.

Taking account of these points, the Committee considers that the actual benefit of ULTIBRO BREEZHALER in patients with COPD is:

[10] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public-Health Objectives] (DGS [Directorate-General for Health]-2003).
[11] Public Health Law 2004*: Law No. 2004-806 of 9 August 2004 on public health policy [DREES [Directorate for Research, Surveys, Assessment and Statistics] indicator report - July 2005].

- **<u>Substantial</u> only in patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination ;**
- **<u>Insufficient</u> for reimbursement by National Health Insurance in the other cases.**

The Committee recommends:

- **inclusion of the medicine ULTIBRO BREEZHALER in a box of 30 capsules on the list of medicines refundable by National Health Insurance and**
- **inclusion of the medicine ULTIBRO BREEZHALER in a box of 6 capsules on the list of medicines approved for hospital use**

in the maintenance bronchodilator treatment to relieve the symptoms of adult patients with moderate to very severe COPD only when the symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65 %**

010.2 Improvement in actual benefit (IAB)

ULTIBRO BREEZHALER fixed-dose indacaterol and glycopyrronium combination does not provide any improvement in actual benefit (IAB V, non-existent) compared with the combination of these active substances administered separately in the population of patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.

010.3 Target population

The target population of ULTIBRO BREEZHALER is defined by the adults patients with moderate to very severe COPD whose symptoms are already controlled by the separately administered indacaterol and glycopyrronium combination.

Epidemiological data on the prevalence of COPD are not very numerous. It was estimated at 7.5 % in a study performed in a population of over 40 years of age coming for consultation to a health examination centre within a preventative context,[12] which, based on the French population aged over 40 years old (INED [French National Institute of Demographic Studies] 2012 data), represents 2,470,000 patients with COPD.

According to the European epidemiological data,[13,14,15] the prevalence of COPD depending on the stage of severity can be estimated at around 40 % for mild stages, 45 % for moderate stages and 15 % for severe to very severe stages, i.e. a total of 60 % for moderate to very severe stages, which represents 1,482,000 patients.

There are no epidemiological data allowing the prevalence to be estimated of patients with moderate to very severe COPD inadequately controlled by a long-acting bronchodilator as monotherapy and requiring dual therapy of two long-acting bronchodilators.
According to data from clinical studies of ONBREZ BREEZHALER (indacaterol) and SEEBRI BREEZHALER (glycopyrronium), the percentage of patients treated with indacaterol,

[12] Fuhrman C, Delmas MC, SPLF epidemiology and clinical research group. Épidémiologie descriptive de la bronchopneumopathie chronique obstructive (BPCO) en France. Rev Mal Respir 2010; 27(2): 160-8.
[13] BEH – Roche – BPCO n°27 – 28 July 2007.
[14] Hoogendorn et al. Severity distribution of COPD in Dutch general practice. Respir Med 2006; 100: 3-6
[15] Pena et al. IBERPOC multicenter epidemiological study. CHEST 2000; 118(4): 981-9.

glycopyrronium or tiotropium as monotherapy who had a response in terms of FEV1 or TDI score not achieving the clinical relevance threshold was 40 to 60 %, i.e. 590,000 to 890,000 patients. Consequently, the population of patients with moderate to very severe COPD who have failed to respond to monotherapy, being as a result able to be treated with the free combination of two long acting bronchodilators, such as the free combination of indacaterol and glycopyrronium, can be estimated at between 590,000 and 890,000 patients. Only a fraction of this population will have COPD symptoms controlled by the free combination of indacaterol and glycopyrronium and may benefit from the fixed-dose indacaterol/glycopyrronium combination.

For information, according to the data from the EGB [general sample of beneficiaries] extrapolated to the French population,[16] the number of adult patients (apart from one patient under 18 years of age) who had at least one co dispensing[17] of a long acting anticholinergic bronchodilator and a long-acting inhaled beta 2 agonist bronchodilator between 01 September 2012 and 31 August 2013 is estimated at 123,927 ($_{95\%\ CI}$= [116,657 to 131,198]).

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

Request for data

The Committee wishes to be kept informed of the results of the observational and safety studies requested in the Risk Management Plan.

[16] The EGB is a representative sample of people in France covered by national insurance. It contains anonymous information on the reimbursed services, the demographic characteristics of the recipients and the chronic diseases since 2003. The extrapolation of data from the EGB [general sample of beneficiaries] to the French population was carried out by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01/01/2012 (n = 602,199) in relation to the French population on 01/01/2012 (n = 65,585,857). The extrapolation coefficient obtained is 1/108.91.

[17] Co-dispensing was defined as same-day dispensing of an anticholinergic bronchodilator and a long-acting inhaled beta-2 agonist bronchodilator.