HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 December 2010

HIROBRIZ BREEZHALER 150 micrograms, inhalation powder, hard capsules
B/10 with inhaler (CIP code: 494 108-2)
B/30 with inhaler (CIP code: 494 109-9)

HIROBRIZ BREEZHALER 300 micrograms, inhalation powder, hard capsules
B/10 with inhaler (CIP code: 494 110-7)
B/30 with inhaler (CIP code: 494 111-3)

Applicant: NOVARTIS PHARMA S.A.S.

indacaterol
ATC code: R03AC18

List I

Date of Marketing Authorisation: 30 November 2009

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Indacaterol

1.2. Indication

“HIROBRIZ BREEZHALER is indicated for maintenance bronchodilator treatment of airflow obstruction in adult patients with chronic obstructive pulmonary disease (COPD)".

1.3. Dosage

"Dosage
The recommended dose is the inhalation of the contents of one 150 microgram hard capsule once a day, using the HIROBRIZ BREEZHALER inhaler. The dosage should only be increased on medical advice.

The inhalation of the contents of one 300 microgram hard capsule once a day using the HIROBRIZ BREEZHALER inhaler has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The maximum recommended dose is 300 micrograms once daily.

HIROBRIZ BREEZHALER must be administered at the same time of the day each day.

If a dose is missed, the next dose must be taken at the regular scheduled time the next day.

Elderly patients
Maximum plasma concentration and overall systemic exposure increase with age but no dosage adjustment is required in elderly patients.

Children and adolescents
There is no specific indication for the use of HIROBRIZ BREEZHALER in the paediatric population (under 18 years).

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. There is no data available for the administration of HIROBRIZ BREEZHALER in patients with severe hepatic impairment.

Renal impairment
No dosage adjustment is required for patients with renal impairment.

Method of administration
For inhalation only.

HIROBRIZ BREEZHALER hard capsules must be administered only using the HIROBRIZ BREEZHALER inhaler.
HIROBRIZ BREEZHALER hard capsules must not be swallowed.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

R : Respiratory system
R03 : Drugs for obstructive airway diseases
R03A : Adrenergics, inhalants
R03AC : Selective beta-2-adrenoceptor agonists
R03AC18 : Indacaterol

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable medicines

Other long-acting inhalational beta-2 agonist bronchodilators indicated in the maintenance bronchodilator treatment of COPD:

Formoterol: FORADIL 12 µg per dose
FORMOAIR 12 µg per dose
ASMELOR NOVOLIZER 12 µg per dose
ATIMOS 12 µg per dose (not commercially available)
OXIS TURBUHALER 12 µg per dose (not commercially available)

Salmeterol : SEREVENT 25 µg per dose
SEREVENT DISKUS 50 µg per dose

2.2.2. Not strictly comparable medicines

Other inhalational bronchodilators indicated in the maintenance bronchodilator treatment of COPD:

- Long-acting anticholinergic inhalational bronchodilators:
Tiotropium: SPIRIVA 18 µg
SPIRIVA RESPIMAT 2.5 µg per dose

- Short-acting bronchodilators taken several times a day:
Ipratropium: ATROVENT 20 µg per dose
Oxitropium: TERSIGAT 100 µg per dose
Ipratropium + salbutamol: COMBIVENT 100/20 µg per dose
Ipratropium + fenoterol: BRONCHODUAL 100/40 µg per dose

- Long-acting beta-2 agonist bronchodilators combined with a corticosteroid:
budesonide + formoterol: SYMBICORT TURBUHALER 200/6 and 400/12 µg per dose
fluticasone + salmeterol: SERETIDE DISKUS 500/50 µg/dose

These proprietary drugs are reserved for patients with severe COPD and a history of repeated flare-ups who are suffering from significant symptoms despite undergoing maintenance treatment with a long-acting bronchodilator.

2.3. Medicines with a similar therapeutic aim

Other bronchodilator treatments:
- short-acting beta-2 agonists,
- theophylline and derivatives.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The pharmaceutical company has submitted:

- four studies aimed at demonstrating the superiority of indacaterol compared to placebo in terms of FEV1 after three months of treatment. Three of these studies also had an active comparator (tiotropium, formoterol or salmeterol).
- two studies versus an active comparator (salmoterol in one case and tiotropium in the other).

3.1.1. Placebo-controlled studies

❑ Study INHANCE 2335S

Comparators	Indacaterol 150 µg once daily Indacaterol 300 µg once daily Placebo Tiotropium 18 µg once daily
Method	Randomised study, double-blind except for the tiotropium group as it is technically impossible to manufacture a placebo that is identical to the active product.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 20 pack-years
Study duration	6 months
Total randomised cohort	1,683 (randomisation 1:1:1:1)
Primary efficacy endpoint	FEV1 24 hours after administration measured at three months
"Key" secondary endpoint	Non-inferiority and superiority to tiotropium in terms of FEV1 24 hours after administration measured at three months. Non-inferiority was demonstrated if the lower limit of the 95% CI was above the non-inferiority threshold of -0.055 L in the PP population.

Results:

The breakdown of participants in the various groups is shown in table 1.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 63.6 years. Their COPD was mild (4.4%), moderate (55.7%), severe (39.3%) or very severe (0.4%). Their average tobacco consumption was 49.7 pack-years. On inclusion, pre-bronchodilator FEV1 was 1.33 L and the reversibility of FEV1 after salbutamol was 15.5% on average.

Table 1: Breakdown of participants

	Indacaterol 150 µg	Indacaterol 300 µg	Tiotropium	Placebo	Total
Randomised patients (n)	420	418	420	425	1683
ITT population (n)	416	416	415	418	1665
PP population (n)	369	373	351	358	1451
% of patients completing the study	77.4	81.6	78.8	69.2	76.7

Primary efficacy endpoint**:**
After three months of treatment, indacaterol at doses of 150 µg and 300 µg was statistically superior to placebo in terms of FEV1 measured 24 hours after administration (for both doses, least squares means difference of 0.18 L, $p < 0.001$) (see table 2).

Table 2: Change in FEV1 24 hours after administration after three months of treatment (ITT population)

	Indacaterol 150 µg	Indacaterol 300 µg	Tiotropium	Placebo
FEV1 before first bronchodilator (L)	1.34	1.36	1.28	1.33
FEV1 24 hours after administration after three months (L)	1.46	1.46	1.42	1.28

Secondary endpoint:
After three months of treatment, indacaterol at doses of 150 µg and 300 µg was not inferior to tiotropium in terms of FEV1 measured 24 hours after administration: in the PP population, the lower limit of the 95% confidence interval of the least squares means difference (95% CI = [0.000; 0.008]) was above the non-inferiority threshold of - 0.055 L.

In addition, the statistical superiority of indacaterol was demonstrated versus tiotropium according to the same criterion ($p<0.05$); however, the least squares means differences observed in FEV1 24 hours after administration (0.050 L for the 150 µg dose and 0.040 L for the 300 µg dose versus placebo) are not clinically relevant (clinical relevance threshold of 0.100 L).

❑ Study INVOLVE 2334

Comparators	Indacaterol 300 µg once daily Indacaterol 600 µg once daily (off-label dosage) Placebo Formoterol 12 µg twice daily
Method	Randomised, double-blind study.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 20 pack-years
Study duration	12 months
Total randomised cohort	1,732 (randomisation 1:1:1:1)
Primary efficacy endpoint	Measurement of residual FEV1 24 hours after administration (indacaterol) and 12 hours after administration (formoterol) after three months Comparison with placebo
The secondary endpoints included	Percentage of days with "poor disease control" in a 12-month period. Poor disease control was defined by a symptom score of ≥ 2 (moderate to severe) for at least two of the five following symptoms: cough, wheezing, expectoration, colour of expectorate and shortness of breath. Comparison with placebo

Results:

The breakdown of participants in the various groups is shown in table 3.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 63.4 years. Their COPD was moderate in 50.9% of cases, severe in 43.2% of cases and very severe in 2.5% of cases. Their average tobacco consumption was 51.1 pack-years. On inclusion, pre-bronchodilator FEV1 was 1.34 L and the reversibility of FEV1 after salbutamol was 12.5% on average.

Table 3: Breakdown of participants

	Indacaterol 300 µg	Indacaterol 600 µg	Formoterol	Placebo	Total
Randomised patients (n)	437	428	435	432	1732
ITT population (n)	437	425	434	431	1727
Modified ITT population* (n)	405	396	400	399	1600
% of patients completing the study	77.3	76.2	74.3	68.3	74.0

* : ITT modified to exclude the Egyptian centre which had not complied with good clinical practice

Primary efficacy endpoint (modified ITT population):
After three months of treatment, indacaterol 300 µg was statistically superior to placebo in terms of residual post-administration FEV1 (for both doses, adjusted mean difference of 0.17 L, $p < 0.001$) (see table 4).

The secondary endpoints of the study did not include comparison with formoterol. For information, the difference in favour of indacaterol in terms of residual post-administration FEV1 of 0.10 L observed between indacaterol 300 µg once daily and formoterol 12 µg twice daily is statistically significant and meets the clinical relevance threshold.

Table 4: Change in residual post-dose FEV1 after three months of treatment (modified ITT population)

	Indacaterol 300 µg	Indacaterol 600 µg	Formoterol	Placebo
FEV1 before first bronchodilator (L)	1.33	1.32	1.35	1.37
Adjusted residual post-dose FEV1° after three months (L)	1.48* §	1.48*§	1.38*	1.31

*: p < 0.001 versus placebo
§: p < 0.001 versus formoterol
°: FEV1 24 hours after administration for indacaterol and FEV1 12 hours after administration for formoterol

Secondary endpoint (modified ITT population):
During the year of treatment, the percentage of days with poor disease control was 33.6% in the indacaterol 300 µg group, 30.0% in the indacaterol 600 µg group, 33.5% in the formoterol group and 38.3% in the placebo group. The differences observed versus placebo are statistically significant but of little clinical relevance.

❑ Study INLIGHT2 2336

Comparators	Indacaterol 150 µg once daily Placebo Salmeterol 50 µg twice daily
Method	Randomised, double-blind study.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 20 pack-years
Study duration	6 months
Total randomised cohort	1,002 (randomisation 1:1:1)
Primary efficacy endpoint	Measurement of residual FEV1 24 hours after administration (indacaterol) and 12 hours after administration (salmeterol) after three months Comparison with placebo
"Key" secondary endpoint	Measurements of quality of life score SGRQ after three months[1]

Results:

The breakdown of participants in the various groups is shown in table 5.

[1] Respiratory questionnaire devised at the Saint-George hospital: score scale with three areas: symptoms, activities and impact on social life. A total score ranging from 0 (best possible state) to 100 (worst possible state) is calculated from the scores for the three areas. A change of at least -4 points is regarded as clinically relevant.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 63.5 years. Their COPD was moderate in 53.6% of cases, severe in 42.6% of cases and very severe in 0.5% of cases. Their average tobacco consumption was 40.2 pack-years. On inclusion, pre-bronchodilator FEV1 was 1.34 L and the reversibility of FEV1 after salbutamol was 11.8% on average.

Table 5: Breakdown of participants

	Indacaterol 150 µg	Salmeterol	Placebo	Total
Randomised patients (n)	333	334	335	1002
ITT population (n)	330	333	335	998
% of patients completing the study	86.8	85.0	79.1	83.6

Primary efficacy endpoint (ITT population):
After three months of treatment, indacaterol 150 µg was statistically superior to placebo in terms of residual post-administration FEV1 (least squares means difference of 0.17 L, $p < 0.001$) (see table 6).

The difference in favour of indacaterol observed for the same criterion between indacaterol 150 µg once daily and salmeterol 50 µg twice daily is statistically significant but not clinically relevant (0.06 L).

Table 6: Change in residual post-dose FEV1 after three months of treatment (ITT population)

	Indacaterol 150 µg	Salmeterol	Placebo
FEV1 before first bronchodilator (LSM° in L)	1.34	1.35	1.32
Residual post-dose FEV1° after three months (LSM° in L)	1.45* §	1.39*	1.28

°: least squares mean
* : $p < 0.001$ versus placebo
§ : $p < 0.001$ versus salmeterol
°: FEV1 24 hours after administration for indacate rol and 12 hours after administration for salmeterol

Secondary endpoints (ITT population):
The SGRQ score was 36.4 in the indacaterol 150 µg group, 38.5 in the salmeterol group and 42.6 in the placebo group. The differences observed between indacaterol and placebo (-6.3 points) and between salmeterol and placebo (-4.2 points) are statistically significant and clinically relevant (clinical relevance threshold: -4 points).

Table 7: Change in SGRQ score after three months of treatment (ITT population)

Least squares mean:	Indacaterol 150 µg	Salmeterol	Placebo
Baseline SGRQ (LSM°)	43.6	43.2	43.6
SGRQ after 3 months (LSM°)	36.4	38.5	42.6
Change in the SGRQ score (LSM°) compared to placebo	-6.3	-4.2	-

°: least squares mean

❑ Study INLIGHT1 2346

Comparators	Indacaterol 150 µg once daily Placebo
Method	Randomised, double-blind study.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 20 pack-years
Study duration	3 months
Total randomised cohort	416 (randomisation 1:1)
Primary efficacy endpoint	FEV1 24 hours after administration measured at three months.

Results:

The breakdown of participants in the various groups is shown in table 8.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 63.0 years. Their COPD was mild in 4.1% of cases, moderate in 56.7% of cases, severe in 38.5% of cases and very severe in 0.5% of cases. Their average tobacco consumption was 57 patient-years. On inclusion, pre-bronchodilator FEV1 was 1.3 L and the reversibility of FEV1 after salbutamol was 16.5% on average.

Table 8: Breakdown of participants

	Indacaterol 150 µg	Placebo	Total
Randomised patients (n)	211	205	416
ITT population (n)	211	204	415
% of patients completing the study	88.2	86.8	87.5

Primary efficacy endpoint (ITT population):
After three months of treatment, indacaterol 150 µg was statistically superior to placebo in terms of FEV1 measured 24 hours after administration (least squares means difference of 0.13 L, $p < 0.001$) (see table 9).

Table 9: Change in FEV1 24 hours after administration after three months of treatment (ITT population)

	Indacaterol 150 µg	Placebo
FEV1 before first bronchodilator (LSM° in L)	1.30	1.40
Post-dose FEV1 after three months (LSM° in L)	1.48*	1.35

°: least squares mean
* : $p < 0.001$ versus placebo

3.1.2. Studies versus active comparator

- **Study INSIST 2349**

Comparators	Indacaterol 150 µg once daily Salmeterol 50 µg twice daily
Method	Randomised, double-blind study.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 10 pack-years
Study duration	3 months
Total randomised cohort	1,123 (randomisation 1:1)
Primary efficacy endpoint	Measurement after three months of the standardised area under the curve of FEV1 for 12 hours after administration
The secondary endpoints included	At 3 months: - Residual FEV1 24 hours after administration for indacaterol and 12 hours after administration for salmeterol - TDI score - percentage of days on which no rescue treatment is used

Results:

The breakdown of participants in the various groups is shown in table 10.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 62.8 years. Their COPD was moderate in 53.2% of cases and severe in 45.9% of cases. Their average tobacco consumption was 44.8 patient-years. On inclusion, pre-bronchodilator FEV1 was 1.29 L and the reversibility of FEV1 after salbutamol was 14.4% on average.

Table 10: Breakdown of participants

	Indacaterol 150 µg	Salmeterol	Total
Randomised patients (n)	560	563	1123
ITT population (n)	558	562	1120
% of patients completing the study	91.3	92.9	92.1

Primary efficacy endpoint (ITT population):
After three months of treatment, indacaterol 150 µg was statistically superior to salmeterol in terms of the standardised area under the curve of FEV1 measured for 12 hours after administration (least squares means difference of 0.06 L, $p < 0.001$). However, the difference was not clinically relevant (see table 11).

Secondary endpoints (ITT population):
After three months of treatment, indacaterol 150 µg was statistically superior to salmeterol in terms of residual FEV1 after administration (least squares means difference of 0.06 L, $p < 0.001$). However, the difference was not clinically relevant (see table 12).

Table 11: Change in the area under the curve (AUC) of FEV1 12 hours after administration after three months of treatment (ITT population)

	Indacaterol 150 µg	Salmeterol
FEV1 AUC 12 h after initial administration (LSM° in L)	1.28	1.28
FEV1 AUC 12 h after administration after three months (LSM° in L)	1.47*	1.41

°: least squares mean
* : p < 0.001 versus salmeterol

Table 12: Change in residual FEV1 after administration after three months of treatment (ITT population)

	Indacaterol 150 µg	Salmeterol
FEV1 before first bronchodilator (LSM° in L)	1.29	1.29
Residual post-dose FEV1° after three months (LSM° in L)	1.41*	1.35

°: least squares mean
* : p < 0.001 versus salmeterol
°: FEV1 24 hours after administration for indacate rol and 12 hours after administration for salmeterol

The dyspnoea score (TDI, least squares mean) measured after three months' treatment was higher in the indacaterol group (2.78) than in the salmeterol group (2.14), a difference of 0.63 (95% CI = [0.30; 0.97]. This difference is statistically significant (p<0.001) but is below the clinical relevance threshold (clinical relevance threshold: 1 point). 69.4% of patients on indacaterol had an improvement in their score of ≥ 1 point, compared with 62.7% of patients on salmeterol (p = 0.014).

During the three months of treatment, the consumption of rescue treatments was significantly less in patients taking indacaterol (-1.64 puffs per day) than in patients taking salmeterol (-1.45 puffs a day, i.e. one less puff every five days; p = 0.048). Patients taking indacaterol had significantly more days without rescue treatment (62.5%) than those taking salmeterol (58.2%; p = 0.025).

❑ Study INTENSITY 2350

Comparators	Indacaterol 150 µg once daily Tiotropium 18 µg once daily
Method	Randomised, double-blind, non-inferiority study.
Inclusion criteria	Age ≥ 40 Moderate to severe COPD with post-bronchodilator FEV1 < 80% and ≥ 30% of the predicted value, and a post-bronchodilator FEV1/FVC ratio of < 70% Tobacco consumption ≥ 10 pack-years
Study duration	3 months
Total randomised cohort	1,598 (randomisation 1:1)
Primary efficacy endpoint	FEV1 24 hours after administration measured at three months Non-inferiority study: indacaterol was regarded as not inferior to tiotropium if the lower limit of the 95% confidence interval of the difference between treatments was above the non-inferiority threshold of -0.055 L.
The secondary endpoints included	At 3 months: - FEV1 24 hours after administration (superiority test) - dyspnoea (TDI score[2]) - use of rescue treatments - quality of life (SGRQ score) Superiority analysis for all these criteria

Results:

The breakdown of participants in the various groups is shown in table 13.

The characteristics of patients in the groups were similar on inclusion.
The mean age of the patients was 63.5 years. Their COPD was moderate in 62.0% of cases and severe in 37.0% of cases. Their average tobacco consumption was 42.5 pack-years. On inclusion, pre-bronchodilator FEV1 was 1.36 L and the reversibility of FEV1 after salbutamol was 13.9% on average (14.5% after ipratropium).

Table 13: Breakdown of participants

	Indacaterol 150 µg	Tiotropium	Total
Randomised patients (n)	797	801	1598
ITT population (n)	794	799	1593
PP population (n)	599	624	1223
% of patients completing the study	92.5	92.4	92.4

Primary efficacy endpoint (PP population):
After three months, indacaterol 150 µg was not inferior to tiotropium in terms of FEV1 measured 24 hours after administration: in the PP population, the lower limit of the 95%

[2] Transition Dyspnoea Index: Score ranging from -9 to +9. A change of ≥ 1 is regarded as clinically relevant

confidence interval of the least squares means difference (95% CI = [-0.02; 0.02]) was above the non-inferiority threshold of - 0.055 L (see table 14).

Table 14: Change in FEV1 24 hours after administration after three months of treatment

	Indacaterol 150 µg	Tiotropium	Difference Indacaterol - tiotropium	test
PP population				
PP population: FEV1 24 h after administration after three months (LSM°in L)	1.44	1.43	0.002	95% CI = [-0.02; 0.02]

Secondary endpoints (ITT population):

After three months of treatment indacaterol 150 µg was not inferior to tiotropium, but indacaterol 150 µg was not found to be superior to tiotropium in respect of FEV1 measured 24 hours after administration (p=0.850)

The dyspnoea score (TDI, least squares mean) measured after three months' treatment was higher in the indacaterol group (2.01) than in the tiotropium group (1.43), a difference of 0.58 (95% CI = [0.28; 0.87]. This difference is statistically significant (p<0.001) but is below the clinical relevance threshold (clinical relevance threshold: 1 point). 57.9% of patients on indacaterol had an improvement in their score of ≥ 1 point, compared with 50.1% of patients on tiotropium (p < 0.001).

The quality of life score (SGRQ, least squares mean) measured after three months treatment was higher in the indacaterol group (37.1) than in the tiotropium group (39.2), a difference of -2.1 (95% CI = [-3.3; -1.0]. This difference is statistically significant (p<0.001) but is below the clinical relevance threshold (clinical relevance threshold: difference of 4 points). 50.5% of patients on indacaterol had an improvement in their score of ≥ 4 points, compared with 42.5% of patients on tiotropium (p < 0.001).

During the three months of treatment, patients on indacaterol took significantly fewer puffs of rescue treatment per day (-1.40) than those on tiotropium (-0.85, or one fewer puff every 1.8 days; p<0.001).
The percentage of days on which no rescue treatment was used was higher in the indacaterol group (46.1%) than in the tiotropium group (41.4%; p=0.004).

3.2. Tolerance

The adverse effects most frequently observed (≥ 1/100, < 1/10) in patients taking indacaterol are: rhinopharyngitis, upper respiratory tract infections, sinusitis, diabetes and hyperglycaemia, headache, ischaemic cardiopathies, cough, laryngopharyngeal pain, rhinorrhoea, respiratory tract congestion, muscular spasms, peripheral oedema.

The study with the longest duration of treatment (INVOLVE, 12 months) compared indacaterol to formoterol. The most common adverse events were rhinopharyngitis (16.7%), cough (7.3%), lower respiratory tract infection (6.2%), muscular spasms (5.3%), upper respiratory tract infections (4.8%) and dyspnoea (3.9%). A similar incidence of these adverse events was observed with formoterol.

In the study versus salmeterol (INSIST), the most common adverse events were infections (9.8% with indacaterol and 10.3% with salmeterol), gastrointestinal disorders (5.9% vs. 6.9%), general disorders such as asthenia, peripheral oedema, pain and fever (3.2% vs.

2.8%), exacerbations of COPD (4.5% vs. 5.7%), headache (3.6% in both groups), cough (3.4% vs. 2.5%) and muscle contractions (2.0% vs. 1.4%).

In the study versus tiotropium (INTENSITY), the most common adverse events were exacerbations of COPD (10.7% with indacaterol and 8.3% with tiotropium), cough (4.7% vs. 3.4%) and rhinopharyngitis (4.5% vs. 4.6%).

3.3. Conclusion

In four randomised, double-blind placebo-controlled studies carried out on patients with an average age of 63 suffering from moderate to severe COPD (FEV1 after bronchodilator administration < 80% and ≥ 30% of the predicted value, and FEV1/FVC ratio after bronchodilator administration of < 70%), indacaterol (150 µg or 300 µg once daily) was superior to placebo in terms of FEV1 measured 24 hours after administration after three to six months of treatment. The difference observed, which ranged from 0.13 to 0.18 L depending on the study, was above the clinical relevance threshold of 0.10 L.

Two randomised double-blind studies compared indacaterol (150 µg once daily) to salmeterol (50 µg twice daily) in one study and to tiotropium (18 µg once daily) in the other study. The populations were similar, and the endpoints were FEV1 measured 24 hours after administration. Indacaterol 150 µg was statistically superior to salmeterol after three months' treatment, but the difference is not clinically relevant. Indacaterol was not inferior to tiotropium, but superiority was not demonstrated.

For the secondary endpoints, statistically significant differences in favour of indacaterol were observed for:
- the percentage of patients with an improvement in quality of life of ≥ 4 points on the SGRQ score; this was higher for the indacaterol group than for the tiotropium group
- the percentage of patients with an improvement in dyspnoea of ≥ 1 point on the TDI score; this was higher for the indacaterol group than for the salmeterol and tiotropium groups
- lower consumption of rescue treatments in the indacaterol group compared to the salmeterol group (one fewer puff every five days) and the tiotropium group (one fewer puff every 1.8 days).

The improvement in the SGRQ score (difference between indacaterol and tiotropium) was statistically significant but not clinically relevant, as was the difference in the TDI score between indacaterol on the one hand and salmeterol and tiotropium on the other hand.

Indacaterol was found to have a similar tolerance profile to its comparators (formoterol, salmeterol and tiotropium).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

COPD causes disability, a marked deterioration in quality of life and can be life-threatening.

This proprietary drug is intended for maintenance symptomatic treatment of COPD. It has no effect on the long-term decline in lung function.

Public health benefit:

The public health burden of COPD is high.

Improving the management of COPD is a public health need according to priorities defined in the GTNDO[3] and the Public Health Act[4].

However, as regards the symptomatic management of COPD, the therapeutic need is met by existing symptomatic treatments.

In the light of the clinical data available and the alternatives that are available, this proprietary drug is not expected to have any additional impact in terms of morbidity and mortality.

Consequently, the proprietary drug HIROBRIZ BREEZHALER is not expected to have any public health benefit.

The efficacy/adverse effects ratio is average.

This proprietary drug is a first-line treatment for patients who have developed permanent respiratory difficulties.
Treatment with this proprietary drug must be continued only if the patient is benefiting from it.

Alternative medicinal products exist.

The actual benefit of HIROBRIZ BREEZHALER 150 µg and 300 µg is substantial.

4.2. Improvement in actual benefit

HIROBRIZ BREEZHALER 150 µg and 300 µg provide no improvement in actual benefit (IAB V) compared to the other long-acting bronchodilators indicated for COPD.

4.3. Therapeutic use

4.3.1. Therapeutic strategy[5]

The diagnosis and management of patients suffering from COPD must include an assessment of the severity of their COPD based on examination of the symptoms (chronic cough, effort-induced dyspnoea, production of purulent expectorate, exacerbations) and functional respiratory tests.

No drug can stop COPD developing into chronic respiratory insufficiency. Stopping smoking is the only action which may restore normal FEV1 reduction rhythm. Patients should be vaccinated against influenza. Exercise-based rehabilitation and respiratory physiotherapy help to improve symptoms, quality of life and allow patients to participate more in everyday activities.

Drug treatment for stable COPD (except when the condition flares up) is staged according to the degree of severity and the response to treatment. The drugs used aim to relieve the symptoms and reduce the frequency and severity of flare-ups.

The main symptomatic treatment for COPD consists of bronchodilators, beta-2 agonists and anticholinergics in inhalational form. Short-acting inhalational bronchodilators (beta-2 agonists or anticholinergics), used when required, are recommended as the first-line treatment.

[3] Groupe Technique National de Définition des Objectifs [National Technical Objective Definitions Group] (DGS [Department of Health]-2003)
[4] 2004 Public Health Act*: Act no. 2004-806 of 9 August 2004 on Public Health policy *[rapport_DREES_indicateurs - juillet 2005]*
[5] SPLF. Clinical practice guideline: management of COPD (updated in 2009). *Revue des maladies respiratoires* [Journal of Respiratory Diseases] 2010; 27:522-48

Long-acting (LA) bronchodilators are recommended when continuous treatment of symptoms is necessary, i.e. when the patient's dyspnoea persists even though he or she uses a short-acting bronchodilator several times a day.
Two long-acting beta-2 agonists (formoterol and salmeterol) and one long-acting anticholinergic (tiotropium) are available. They are equally effective.
These three pharmaceutical products form part of the continuous symptomatic first-line treatment of COPD.

Long-acting theophylline can be used in the case of patients who have difficulty in using inhalational bronchodilators, or if the latter substances are insufficiently effective in improving dyspnoea. Their use is restricted by their narrow therapeutic range.

Inhalational corticosteroids may be used only in conjunction with a long-acting bronchodilator in patients suffering from severe COPD with an FEV1 level of <50% of the theoretical value and repeated flare-ups. They have not been shown to be effective in controlling mortality (all causes), and increase the risk of lower respiratory tract infections, especially pneumonia.

Patients should only be kept on treatment with a long-acting bronchodilator, or a combination of a long-acting bronchodilator and an inhalational corticosteroid, if their symptoms are seen to improve.
Corticoids administered via a general route are not recommended.

Oxygen therapy is administered only to patients with diurnal hypoxaemia ($PaO_2 \leq 55$ mmHg) when not suffering an acute attack and despite optimum treatment.

4.3.2. Therapeutic use of the proprietary drug

Indacaterol is a long-acting beta-2 agonist bronchodilator recommended for the maintenance treatment of COPD symptoms which persist even though the patient uses a short-acting bronchodilator several times a day. It must only be continued if the patient benefits.

4.4. Target population

According to the French epidemiology data available, around 3.5 million people are thought to suffer from chronic bronchitis, which evolves into COPD in around a third of cases. Consequently, the target population for this indication can be estimated at around 1,150,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%