HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

2 November , 2005

Spiriva 18 µg inhalation powder, hard capsule
Box of 3 blister packs each containing 10 capsules with inhaler (CIP: 368 692-0)

Spiriva 18 µg inhalation powder, hard capsule
Box of 9 blister packs each containing 10 capsules (CIP : 566 813-9)

Applicant: Boehringer Ingelheim International GmbH

Tiotropium bromide monohydrate

Date of marketing authorisation (AMM): 8 July 2005

Reason for application: inclusion on list of drugs reimbursed by social security and for hospital use

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tiotropium bromide monohydrate

1.2. Background

Spiriva is the first long-acting anticholinergic bronchodilator indicated for maintenance treatment of chronic obstructive pulmonary disease (COPD).

1.3. Indications

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

1.4. Dosage

The recommended dose of tiotropium bromide is inhalation of the contents of one capsule once daily with the HandiHaler device at the same time of day (for complete instructions for use see section 6.6).

The tiotropium bromide powder contained in the capsule should be inhaled with the HandiHaler device only.
Do not exceed the recommended dose.
Do not swallow the capsules.

Special populations

Elderly patients:

Elderly patients can use tiotropium bromide at the recommended dose.

Patients with renal failure:

Patients with renal failure can use tiotropium bromide at the recommended dose. For patients with moderate to severe renal impairment (creatine clearance $\leq$ 50 mL/min) see sections 4.4 and 5.2.

Patients with impaired liver function:

Hepatically impaired patients can use tiotropium bromide at the recommended dose (see section 5.2).

Paediatric patients:

The safety and efficacy of tiotropium bromide inhalation powder capsules in paediatric patients have not been established, it should therefore not be used in patients under 18 years of age.

2 SIMILAR DRUGS

2.1. ATC classification (2005)

R : Respiratory system
R03 : Drugs for obstructive airway diseases
R03B : Other drugs for obstructive airway diseases, inhalants
R03BB : Anticholinergics
R03BB04 : Tiotropium bromide

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

Tiotropium is a long-acting anticholinergic bronchodilator. Comparator medicines from the same therapeutic class as strictly defined are inhaled medicinal products which contain an anticholinergic. The other available anticholinergics are short-acting.
Other inhaled long-acting bronchodilators indicated as a maintenance treatment to relieve symptoms in patients with COPD, whether combined with a corticosteroid or not, are considered as comparator medicines.

- Anticholinergic bronchodilators:
  - ipratropium: Atrovent 20 µg/dose
  - oxitropium: Tersigat 100 µg/dose
  - salbutamol + ipratropium: Combivent 100/20 µg/dose
    Bronchodual 100/40 µg/dose
- Long-acting beta-2 agonist bronchodilators:
  - formoterol: Foradil 12 µg
    Oxis Turbuhaler 12 µg/dose
  - salmeterol: Serevent 25 µg/dose
    Serevent Diskus 50 µg/dose, inhalation powder
    Siserol 25 µg/dose (not marketed)
    Siserol Diskus 50 µg/dose (not marketed)

There are minor differences in the wording of the indications for the various medicinal products.
Short-acting anticholinergics are indicated as add-on therapy to a rapid-onset, short-acting beta-2 agonist to relieve symptoms of patients with COPD exacerbations and as a maintenance treatment to relieve symptoms of patients with reversible bronchospasm associated with COPD.
Foradil is indicated as a maintenance treatment to relieve symptoms in patients with asthma and other reversible airway obstruction.
Oxis Turbuhaler is indicated for the relief of broncho-obstructive symptoms in patients with COPD.
The medicinal products Serevent and Siserol are indicated as treatment to relieve symptoms in patients with COPD (N.B.: an inhaled corticosteroid does not necessarily have to be combined with a bronchodilator to treat COPD).

- Long-acting bronchodilators combined with a corticosteroid:
  budesonide + formoterol: Symbicort Turbuhaler 200/6 and 400/12 µg/dose
  fluticasone + salmeterol: Seretide Diskus 500/50 µg/dose

The indication for these combinations in COPD is restricted to symptom relief in patients with the severe forms (FEV_1 < 50 % of theoretical value), who have a history of repeated exacerbations and significant symptoms despite maintenance treatment with a bronchodilator.

2.2.2. Comparisons that have been carried out

Highest number of treatment days:
Anticholinergics: Combivent
Long-acting beta-2 agonists: Symbicort Turbuhaler (dosage 200/6 µg/dose + 400/12 µg/dose)

Most economical in terms of treatment costs:
Anticholinergics: Atrovent
Long-acting beta-2 agonists: Foradil 12 µg/dose

Most recently listed:
Anticholinergics: Bronchodual 100/40 µg/dose and Combivent 100 µg/dose (French Official Journal of 28/07/96)
Long-acting beta-2 agonists: Oxis Turbuhaler (French Official Journal of 31/05/2005)

2.3. Medicines with a similar therapeutic aim

Short-acting bronchodilators, beta-2 agonists and methylxanthines (theophylline) are used to treat the same condition.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

A total of 18 randomised, controlled, double-blind trials lasting 1–12 months were included in the dossier:
- 11 trials versus placebo
- 2 trials with the same protocol compared tiotropium with ipratropium
- 2 trials versus placebo and salmeterol
- 1 trial versus salmeterol
- 1 trial comparing the combination of tiotropium + formoterol with formoterol alone
- 1 trial versus placebo combined with pulmonary rehabilitation.

These trials included patients with moderate to severe COPD (see detailed information on the protocols in the Annex).

Results:

- Main results from trials versus placebo

  - **Trials versus placebo without rehabilitation**

Effect on postdose and predose forced expiratory volume in 1 second (FEV_1) (9 trials of 3 to 12 months' duration)

Trial	Duration (months)	N	Initial FEV_1 (mL)	Change in postdose FEV_1 (maximum effect) (mL)			Change in predose FEV_1 ° (residual efficacy) (mL)		
				tiotropium	placebo	tiotropium - placebo	tiotropium	placebo	tiotropium - placebo
205.117#	12	442	1010	**+260**	**+40**	**+220***	**+110**	**-50**	**+160***
205.128#	12	404	1000	**+260**	**+50**	**+210***	**+120**	**-30**	**+150***
205.214	12	1010	1380	**-**	**-**	**-**	**+90**	**-30**	**+120***
205.266	6	1829	1040	**-**	**-**	**-**	**+110**	**+20**	**+90***
205.256	9	554	1360	**-**	**-**	**-**	**+110**	**+10**	**+100***
205.130#	6	381	1060	**+320**	**+80**	**+240*(§)**	**+110**	**-30**	**+140***
205.137#	6	367	1110	**+270**	**+80**	**+190***	**+70**	**-30**	**+110***
205.284#	3	178	1020	**+275**	**+10**	**+265***	**+185**	**+1**	**+184***
205.257#	3	1639	1330	**+190**	**+63**	**+128***	**+93**	**+14**	**+79***

°: Predose: 23-24 hours post-inhalation
#: Predose FEV_1 = primary endpoint for the trial
§: postdose measured at 12 hours
*: significant difference

In 8 out of 9 trials tiotropium significantly improved predose or postdose FEV_1 compared with placebo. The improvement of about 200 mL (except in trial 205.257) is clinically relevant and was maintained at a level of 100 mL or higher at the end of the dosing interval (residual bronchodilator effect), except in trial 205.257.

Effect on postdose or predose forced vital capacity (FVC) (9 trials of 3 to 12 months' duration)
In the 9 trials tiotropium significantly improved FVC from 176 to 460 mL at maximum bronchodilator effect (postdose FVC) and from 116 mL to 300 mL at residual bronchodilator effect (predose FVC), compared with placebo.

Effects on resting inspiratory capacity (IC) (4 trials of 4 to 12 weeks' duration)
In these 4 trials tiotropium significantly improved postdose IC from 210 mL to 380 mL (4 trials) and predose IC from 100 mL to 220 mL (4 trials) compared with placebo.

Effects on dyspnoea: transition dyspnoea index focal score (TDI) (5 trials of 6 to 12 months' duration)
In 4 trials out of 5 tiotropium significantly improved TDI focal score by +1.02 to +1.21 (on a scale from –9 to +9), compared with placebo. These differences met the threshold of clinical relevance (difference of + 1). The effects observed can be considered as moderate.

Effects on exercise tolerance: improvement in exercise endurance time (2 trials of 6 weeks' duration)
An improvement in exercise endurance time was observed when tiotropium was compared with placebo (1.8 and 2.7 minutes, respectively). These differences are significant but with poor clinical relevance.

Effects on quality of life: SGRQ score (7 trials of 3 to 12 months' duration)
Quality of life improved significantly when patients were on tiotropium compared with placebo with a clinically relevant reduction in SGRQ score (≥ 4 points) in 4 out of 7 trials. The greatest differences (-6.50 and -6.52) were observed in the 2 trials involving the lowest numbers (about one hundred patients).

Effect on exacerbation rate (7 trials of 6 and 12 months' duration)
The 3 trials of 12 months' duration are the most relevant insofar as exacerbations occurred infrequently.
Two of these trials had the same protocol. Taken individually, they did not demonstrate any significant difference between tiotropium and placebo as regards exacerbation rate for all degrees of severity. Their combined analysis based on a total of 921 patients revealed a significant difference of 0.19 exacerbation/ patient/ year or 1 exacerbation prevented every 5 years.
In the 3rd trial, tiotropium significantly reduced by 0.32 the number of moderate to severe exacerbations per patient and per year compared to placebo, or 1 exacerbation was prevented every 3 years.
In 1 study of 6 months' duration involving 1829 patients where exacerbation rate was the primary endpoint, the difference of 0.20 exacerbation/patient/year noted in favour of tiotropium was statistically significant.
These differences, although statistically significant, are not clinically relevant.

Effect on the rate of hospitalisations for exacerbation (6 trials of 6 and 12 months' duration)
Three trials, 2 of them with the same protocol, included more than 1900 patients in total and lasted 12 months.
Taken individually, the twin studies did not show any significant difference between tiotropium and placebo as regards the hospitalisation rates due to exacerbation. When analysed together there was a significant difference of 0.16 hospitalisation per exacerbation/patient/year or 1 hospitalisation per exacerbation prevented every 6 years. This difference is not clinically relevant.
In the 3rd trial no significant difference was observed between the 2 groups.

Effects on the number of days on oral corticosteroid therapy (2 trials of 6 and 12 months' duration
In both trials the number of days on oral corticosteroid therapy was significantly lower on tiotropium than on placebo:
- 6.25 days on tiotropium and 7.40 days on placebo or a difference of 1.15 days in the trial lasting 6 months
- 11.9 days on tiotropium and 16.4 days on placebo or a difference of 4.5 days in the trial lasting 12 months.

- **Trial comparing tiotropium to placebo in combination with rehabilitation**

After 6 months of treatment, the 13 first weeks of which were combined with a respiratory rehabilitation program, exercise endurance time improved by 6.60 minutes in patients on tiotropium compared to placebo. At 13 weeks patients in the tiotropium group improved their exercise endurance time by 5.35 minutes compared to placebo (significant difference).

Similarly TDI focal score significantly improved in the tiotropium group compared to placebo. The difference of 1.67 unit in favour of tiotropium exceeds the threshold of clinical relevance by 1 unit.

➢ Main results from the trials versus an active comparator

- **Tiotropium versus ipratropium**

Two trials lasting 12 months compared tiotropium with ipratropium. Both trials were performed with the same protocol.

Impact on FEV_1
The impact of tiotropium on postdose FEV_1 was greater in 1 of the 2 trials (140 mL difference) and on predose FEV_1 in both trials (130 mL and 180 mL difference respectively). These differences are considered to be clinically relevant.

Impact on predose FVC (mL)
In both, trials improvement in residual FVC at the end of the dosing interval was significantly greater on tiotropium than on ipratropium with an intergroup difference of about 200 mL.

Impact on dyspnoea in everyday life A clinical relevant difference (+1.21 unit) in favour of tiotropium was observed in one trial only.

Impact on quality of life
A statistically significant and clinically relevant reduction in total SGRQ of ≥ 4 points in favour of tiotropium was observed in 1 trial out of 2.

Impact on exacerbations and hospitalisations for exacerbation
Exacerbation rate (including all degrees of severity) was significantly lower on tiotropium than ipratropium in 1 out of 2 trials. Combined analysis of both studies highlighted a significant and clinical relevant difference (0.23 exacerbation/patient/year) or 1 exacerbation prevented every 4.3 years in favour of tiotropium. In these trials no significant difference in hospitalisation rate for exacerbation was found.

- **Tiotropium versus salmeterol**

Effect on FEV_1 (mL)

Trial	Duration (months)	N	Initial FEV_1 (mL)	Change in postdose FEV_1 # (mL)			Change in predose FEV_1 § (mL)		
				tiotropium	salmeterol	tiotropium - salmeterol	tiotropium	salmeterol	tiotropium - salmeterol
205.130	6	405	1060	**+300**	**+210**	**+80***	**+110**	**+50**	**+50***
205.137	6	369	1110	**+270**	**+210**	**+70***	**+70**	**+50**	**+20 (NS)**
205.264	3	608	1051	**+262**	**+216**	**+46***	**+88**	**+71**	**+18 (NS)**

Postdose: 3 hours post-inhalation
§ Predose=tiotropium: 23-24 hours post-inhalation; salmeterol: 12 hours post-inhalation
* significant difference

In both trials which examined postdose FEV_1 the differences observed between tiotropium and salmeterol, although statistically significant, were not clinically relevant.

A significant but not clinically relevant difference in predose FEV_1 was observed in favour of tiotropium in 1 of the 3 trials.

There are no data on FEV_1 expressed as 24-hour area under the curve. This criterion becomes increasingly relevant when the 2 drugs are not administered according to the same schedule.

Effects on FVC

Trial	Duration (months)	N	Initial FVC (mL)	Variation in postdose FVC # (mL)			Variation in predose FVC § (mL)		
				Tiotropium	Salmeterol	Tiotropium - Salmeterol	Tiotropium	Salmeterol	Tiotropium - Salmeterol
205.130	6	405	2540	**+580**	**+410**	**+170***	**+230**	**+120**	**+110***
205.137	6	369	1110	**+530**	**+380**	**+140***	**+150**	**+100**	**+60 (NS)**
205.264	3	608	1051	**+493**	**+374**	**+120***	**+149**	**+85**	**+64***

Postdose: 3 hours post- inhalation, 205.264: AUC: 0-12 hours/12 hours
§ Predose=tiotropium: 23-24 hours post-inhalation; salmeterol: 12 hours post-inhalation
* significant difference

There was a significant difference in postdose FVC (+120 mL to +170 mL) in favour of tiotropium. However, these results have limited clinical relevance.

Tiotropium was significantly superior to salmeterol in impact on residual FVC at the end of the dosing interval in 2 out of 3 trials. The differences observed (+110 mL and +64 mL) are not clinically relevant.

Impact on dyspnoea TDI focal score (unit)

Trial	Duration (weeks)	N	Tiotropium	Salmeterol	Placebo	Difference tiotropium vs placebo	Difference salmeterol vs placebo	Difference tiotropium vs salmeterol
205.130	6	363	+0.39	-0.39	-0.63	**+1.02***	**+0.24 (NS)**	**+0.78***
205.137	6	325	+0.80	+0.35	-0.42	**+1.21***	**+1.26***	**-0.05 (NS)**

* significant difference

There was no statistically significant difference between triotropium and salmeterol on dyspnoea.

Impact on exercise tolerance: shuttle walking test (SWT)* (walking distance)

No significant difference was observed in either trial between tiotropium and salmeterol or between tiotropium and placebo on walking distance in the shuttle walking test.

Impact on quality of life

No significant difference was detected in either trial between tiotropium and salmeterol on quality of life evaluated by total SGRQ score.

Impact on exacerbations and hospitalisations due to exacerbations

In both trials no significant difference was observed between tiotropium and salmeterol either on exacerbation rate regardless of degree of severity or on hospitalisation rate due to exacerbation.

- **Tiotropium versus formoterol and tiotropium + formoterol combination**

In this trial tiotropium 18 µg alone was administered once daily, formoterol 12 µg alone twice daily and the tiotropium 18 µg + formoterol 12 µg combination once daily. As the formoterol dose recommended by the MA was 12 µg twice daily, the results obtained for the combination are not relevant.

Impact on $FEV_{1AUC24/24}$ (area under the curve over 24 hours/24 hours) versus formoterol
$FEV_{1AUC24/24}$ improved by 136 mL on tiotropium and by 95 mL on formoterol compared to baseline level. The inter-group difference (41 mL), although significant, is not clinically relevant.

Impact on predose FVC versus formoterol
No clinically relevant improvement in forced vital capacity was observed on tiotropium or formoterol (+17 mL on tiotropium and -57 mL on formoterol).

3.2. Undesirable effects

The most commonly reported undesirable effects in these trials were dry mouth (usually mild and transient), constipation, candidiasis, sinusitis, pharyngitis and epistaxis (nosebleeds).

Severe but rare cases of constipation and urinary retention have been reported.
It is important to note that renal function failure, prostatic hypertrophy, recent myocardial infarction and narrow angle glaucoma were criteria for exclusion from the trials. Tiotropium should be used with caution in cases of prostatic hypertrophy, bladder neck stenosis, narrow angle glaucoma and recent myocardial infarction. However, the population likely to be treated with tiotropium tends to consist of smokers and the elderly (>50 years), whose risk of urinary disorders, heart disease and glaucoma is higher.

In patients with moderate to severe renal failure (creatinine clearance ≤ 50 mL/min), the drug should be used only if expected benefit outweighs potential risk.

3.3. Conclusion

A large amount of clinical data on efficacy and safety of tiotropium is available (18 trials). These have been obtained from comparative, randomised, double-blind trials including 11 versus placebo. The patients included had moderate to severe COPD.

Tiotropium versus placebo:
The majority of trials comparing tiotropium to placebo (lasting 3 to 12 months) showed that tiotropium was superior in terms of FEV_1, FVC and inspiratory capacity (at peak of efficacy and at the end of the dosing interval). The effects observed were slight to moderate.

In parallel to the improvement in spirometric parameters the results showed a significant and clinically relevant improvement in terms of:
- dyspnoea (TDI focal score of 1.02 to 1.21, above the threshold of clinical relevance of 1.00)
- quality of life with a reduction of more than 4 points in total score on the St George's Respiratory Questionnaire in 4 trials out of 7.
- exercise tolerance (+1.8 min and +2.7 min improvement in exercise endurance time).

These effects are moderate however.

A statistically significant difference but with poor clinical relevance was highlighted in exacerbation rate (all degrees of severity) between the tiotropium and placebo groups.

When analysed individually, the three trials did not show any significant difference between tiotropium and placebo in hospitalisation rate due to exacerbation. Combined analysis of two of these three trials highlighted a statistically significant but not clinically relevant difference.

In two trials there was a statistically significant difference between tiotropium and placebo for number of days on oral corticosteroid therapy.

The value of combining tiotropium with pulmonary rehabilitation compared with rehabilitation combined with placebo was showed in one trial in terms of impact on exercise tolerance (endurance time increased by 6.6 minutes on tiotropium compared with placebo) and dyspnoea (improvement by 1.67 unit in TDI focal score). No data are available on any comparison with pulmonary rehabilitation combined with another bronchodilator.

Tiotropium versus ipratropium:
Tiotropium was compared with ipratropium in 2 trials. The impact of tiotropium was superior to that of ipratropium on residual FEV_1 and FVC at the end of the dosing interval in both trials and on FEV_1 and FVC at peak efficacy in 1 out of the 2 trials. As regards dyspnoea (TDI focal score) and quality of life (total SGRQ score) tiotropium was superior to ipratropium in 1 out of 2 trials. The differences observed were clinically relevant. No significant difference was observed between the 2 treatments for hospitalisation rate due to exacerbation.

Tiotropium versus salmeterol:
Three trials compared tiotropium to salmeterol. The results showed no clinically relevant difference between tiotropium and salmeterol on spirometry (FEV_1, FVC), dyspnoea, exercise tolerance, quality of life or hospitalisation rate for exacerbation.

Tiotropium versus formoterol:
Similarly no clinically relevant difference was highlighted between tiotropium and formoterol on FEV_1 and FVC (1 trial). No data are available versus formoterol for the other criteria.

Safety:
Undesirable effects are mainly cholinergic in nature and in particular include dry mouth and constipation, which may be severe. Special care should be taken with patients with narrow-angle glaucoma, history of recent myocardial infarct and prostatic hypertrophy or bladder neck stenosis because of the risk of urinary retention. In patients with moderate to severe renal failure (creatinine clearance ≤ 50 mL/min), the drug should be used only if expected benefit outweighs potential risk.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

COPD results in disability as well as marked deterioration in quality of life and may threaten life.

This medicinal product is classified as maintenance treatment to relieve symptoms of patients with COPD. It has no impact on long-term deterioration in lung function.

Benefit to public health:

COPD represents a substantial burden in terms of public health. The sub-population of patients who could benefit from tiotropium treatment represents a heavy burden. Therapeutic need is met by existing therapies intended to relieve symptoms.

When the data obtained in clinical trials and the available alternatives are considered, it is not expected that this medicinal product will have any impact in terms of morbidity and mortality.

As a result no public health benefit is expected for Spiriva.

The ratio of efficacy/undesirable effects is moderate.

This medicinal product is a first choice treatment in patients whose breathing difficulties have become permanent.
Treatment with the medicinal product should be continued only if patients feel that they benefit.

Alternative medicinal products exist.

The actual benefit from Spiriva is substantial.

4.2. Improvement in actual benefit

Spiriva shares the level IV improvement in actual benefit provided by long-acting beta-2 agonist bronchodilators in the management of patients with COPD.

4.3. Therapeutic use

4.3.1. Standard disease management

According to the *Société de pneumologie de langue française guidelines* (2003) and the international GOLD consensus, "Global Initiative for chronic Obstructive Lung Disease" (updated 2004): COPD is defined as a chronic and slowly progressive disease characterised by airflow limitation that is not fully reversible. Disease severity is classified into 3 stages by FEV_1 and FEV_1/FVC.

No drug treatment impacts on the long-term deterioration in lung function which is the specific characteristic of this disease. Stopping smoking, the only measure which can stop the progress of bronchial obstruction and delay airflow limitation, is a top priority at any stage of the disease (grade A).

The first steps also include detection and prevention of any respiratory professional exposure to industrial pollutants (grade A).
Rehabilitation and physiotherapy play an important part in managing patients with COPD.

Apart from exacerbations, the drugs used to treat COPD aim to decrease symptoms and reduce complications.

Bronchodilators (beta-2 agonists and anticholinergics) taken as rescue medication or as maintenance treatment are the main treatment to relieve symptoms of patients with COPD (grade A). Theophyllines can be used if patients find it difficult to use inhaled bronchodilators or if the improvement in their dyspnoea is insufficient, but these drugs have a narrow therapeutic index.

Long-acting beta-2 agonists and anticholinergics are recommended for patients who use bronchodilators several times daily (grade C).

The benefit/risk ratio of inhaled corticosteroids in COPD has not been adequately assessed. An inhaled corticosteroid does not necessarily have to be combined with a long-acting bronchodilator to treat COPD. At present they are indicated, combined with a bronchodilator, in patients with severe to very severe COPD only (FEV_1 <50 % of the theoretical value) and repeated exacerbations). Systemic corticosteroids are not recommended.

Oxygen therapy is restricted to patients who experience daytime hypoxaemia (PaO_2 ≤55 mmHg) distant from an acute episode and despite receiving optimum treatment.

4.3.2. Therapeutic use of the medicinal product

Tiotropium is a long-acting anticholinergic bronchodilator recommended as maintenance treatment to relieve symptoms in patients with COPD which persist despite using a short-acting bronchodilator several times daily. Treatment should be continued only if patients feel they benefit from it.

4.4. Target population

According to the French epidemiological data available about 3.5 million persons have chronic bronchitis, which progresses to COPD in one out of three cases. As a result the target population in this indication is estimated to be approximately 1,150,000 patients.

4.5. Transparency Committee recommendations

Approval for inclusion on the list of reimbursable medicinal products and on the list of medicinal products approved for use by hospitals and various public services in the indications and at the dosage given in the Marketing Authorisation.

Packaging: suitable for conditions of prescription and supply.

Reimbursement rate: 65 %

ANNEX: Trial protocols

Trial	Duration	Total N	Tiotropium 18 µg 1x/d	Comparators	Inclusion criteria	Primary endpoint	Secondary endpoints
205.117 U99-3169 Casaburi 2002	1 year	470	279	Placebo	Relatively stable, moderately severe to severe bronchial obstruction (FEV_1≤65% of the theoretical value and FEV_1/FVC≤70%); age ≥40 years; smoking history (>10 pack-years)	Forced expiratory volume in 1 second measured predose (predose FEV_1) equivalent to the mean of 2 measurements of FEV_1 about 23-24 hours after inhalation	Transition dyspnoea index TDI (threshold of clinical relevance >1 unit); exacerbations and hospitalisations due to exacerbations; SGRQ quality of life questionnaire (Saint George's Respiratory Questionnaire: the threshold of clinical relevance is a reduction in total score ≥4 points); mean postdose and maximum postdose FEV_1; predose, mean postdose and maximum postdose forced vital capacity (FVC).
205.128 U99-3170-01 Casaburi 2002	1 year	451	271	Placebo			
205.214 U04-1252 Mistral Study: Dusser 2004a and b	1 year	1010	500	Placebo	Diagnosis of COPD with stable, moderate to severe bronchial obstruction, 30% ≤FEV_1 ≤65% of the theoretical value, FEV_1/FVC ≤70%; age ≥40 years; smoking history ≥ 10 pack-years; history of at least one exacerbation within the year but none in the 6 months prior to inclusion	Morning peak expiratory flow (MPEV) (weekly mean)	Incidence, severity and duration of exacerbations; number of days hospitalisation due to exacerbation; rescue medication; number of courses/days of antibiotics/corticosteroids; spirometry
205.266 U03-3575 Veterans Study Group: Niewoehner et al 2004	6 months	1829	914	Placebo	Relatively stable, moderately severe to severe bronchial obstruction (FEV_1 ≤60% of the theoretical value and FEV_1/FVC ≤70%); aged ≥40 years; smoking history (>10 pack-years)	% of patients with at least one exacerbation or one hospitalisation due to exacerbation	Number of exacerbations; number of hospitalisations due to exacerbation; time after which the first exacerbation/hospitalisation occurred; number of days of exacerbation/hospitalisation; number of days of oral corticosteroids/antibiotics for one exacerbation; predose FEV_1 and FVC and 90 mins. post-dose
205.256 Data on file Tonnel 2005	9 months	554	266	Placebo	Diagnosis of COPD: pre- and postbronchodilator FEV_1 between 20% and 70% of the theoretical value; age ≥40 years; smoking history >10 pack-years	% of responders to SGRQ (Saint George's Respiratory Questionnaire)	SGRQ scores; exacerbations; FEV_1, VC and IC (inspiratory capacity) measured 23-24hours post-dose
205.257 U03-1924	3 months	1639	1236	Placebo	COPD at different stages of severity	Mean 0-2 hrs and predose FEV_1 (according to stage of severity)	

Trial	Duration	Total N	Tiotropium 18 µg 1x/d	Comparators	Inclusion criteria	Primary endpoint	Secondary endpoints
205.215 U02-1622	3 months	100	46	Placebo	Age³40 years; diagnosis of COPD (FEV_1 ≤50% of the theoretical value, FEV_1/SVC ≤70%) and lung hyperinflation (RV ≥125% of the theoretical value)	FVC measured over 22-24 hours postdose	Changes in functional criteria FEV_1, FVC, SVC (slow vital capacity), IC; shuttle walking test; transition dyspnoea index; SGRQ score
205.218 U02-3256 Celli 2003	28 days	81	40	Placebo	Relatively stable bronchial obstruction with FEV_1 between 30% and 65% of the theoretical value; lung hyperinflation with FRC ≥ 120% of the theoretical value	Mean inspiratory capacity over 3 hours (IC 0-3hrs)	Predose and maximum postdose IC 0-3 hrs; functional residual capacity, vital capacity and FEV_1 (predose, maximum postdose, means 0-3 hrs)
205.131 U02-1202 O'Donnell, Flüge 2004	6 weeks	198	98	Placebo	COPD with FEV_1≤65% and lung hyperinflation with FRC ≥120%; age ≥40 and ≤70 years; smoking history >10 pack-years	Constant-load endurance time exercise test on a cycle ergo meter with a workload of 75% of peak work rate on D42 (2 hrs 15 post-dose)	Inspiratory capacity, current volume, residual volume resting and during exercise, functional residual capacity, vital capacity and FEV_1, Borg dyspnoea scale
205.223 U04-3016 O'Donnell 2004	6 weeks	261	131	Placebo	Stable, moderate to severe COPD with FEV_1 ≤65% and lung hyperinflation with FRC≥120% ; age ≥40 and ≤75 years; smoking history >10 pack-years	Constant-load endurance time exercise test on a cycle ergometer with a workload of 75% of peak work rate on D42 (2 hr 15 post-dose)	Inspiratory capacity resting and during exercise, functional residual capacity, forced vital capacity, Borg dyspnoea scale
205.230 U03-3251 Casaburi 2005	25 weeks 8 of which were for rehabil-itation	108	55	Placebo +rehabilitation	Diagnosis of COPD, FEV_1 ≤60% ; age ≥40 years; smoking history ≥10 pack-years	Endurance time measured on a treadmill at 80% of peak work rate	Dyspnoea, FEV_1, FVC, inspiratory capacity, functional residual capacity, quality of life (SGRQ)
205.284 U04-3374 Kesten 2004	3 months	196	100	Placebo	Diagnosis of COPD, FEV_1 ≤65% ; FEV_1/FVC ≤70%; age ≥40 years; smoking history ≥10 pack-years	Predose FEV_1 after 12 weeks of treatment	Other spirometric criteria, use of salbutamol as rescue medication, overall evaluation of symptoms
205.126 A U00-3113 Vincken 2002	1 year	288	191	**Ipratropium** (40µg 4X/d)	Relatively stable, moderately severe to severe bronchial obstruction (FEV_1 ≤65% of the theoretical value and FEV_1/FVC ≤70%); age ≥40 years; smoking history (>10 pack-years)	Predose FEV_1 equivalent to the mean of 2 measurements of FEV_1 23-24 hours after inhalation	Transition dyspnoea index (threshold of clinical relevance >1 unit); exacerbations and hospitalisations due to exacerbations; quality of life (SGRQ, threshold of clinical relevance: reduction >4 points); mean postdose and maximum postdose FEV_1; mean predose, mean postdose and maximum postdose FVC
205.126 B U00-3114 Vincken 2002	1 year	247	165	**Ipratropium** (40µg 4X/d)			

Trial	Duration	Total N	Tiotropium 18 µg 1x/d	Comparators	Inclusion criteria	Primary endpoint	Secondary endpoints
205.130 U01-1236-2 Donohue 2002 Brusasco 2003	6 months	623	209	Placebo **Salmeterol** (50µg 2X/d)	Relatively stable, moderately severe to severe bronchial obstruction (FEV_1≤65% of the theoretical value and FEV_1/FVC≤70%); age≥40 years; smoking history (>10 pack-years)	Predose FEV_1 equivalent to the mean of 2 measurements of FEV_1 about 23-24 hours after inhalation; a 50 mL difference between active treatment groups was defined as a clinically relevant dyspnoea index TDI (threshold of clinical relevance ≥1 unit)	Exacerbations and hospitalisations due to exacerbation; quality of life (SGRQ: clinically relevant reduction ≥4 points); endurance test (shuttle walking test); mean and postdose maximum FEV_1; predose, mean and maximum postdose FVC
205.137 U01-1231-02 Brusasco 2003	6 months	584	193	Placebo **Salmeterol** (50µg 2X/d)			
205.264 U03-3445 Briggs 2005	3 months	653	328	**Salmeterol** (50µg 2X/d)	COPD with FEV_1≤60% of the theoretical value and FEV1/FVC<70%	FEV_1 AUC 0-12 hrs/12 hrs and at peak (AUC: area under the curve)	
1184.3 U03-1209 Van Noord 2003	3 x 6 weeks (cross-over)	74	74	**Formoterol** (F) (12µg 2X/d) **Tiotropium (T) +formoterol (F)** (18µg 1x/f / 12µg 1x/d)	COPD with FEV_1<60% of the theoretical value and FEV_1/FVC≤70%	FEV_1 AUC 0-12 hrs/12 hrs FEV_1 AUC 0-24 hrs/24 hrs	FEV_1 AUC 12-24 hrs/12 hrs, FEV_1 0-3 hrs, predose FEV_1; FVC 0-3 hrs, predose FVC; morning and evening PEF; use of salbutamol,

*Placebo = standard treatment: patients were allowed to take short and long-acting beta-2 agonists (rescue medication) during the study [study 205.266], as well as inhaled corticosteroids (stable dosage), oral corticosteroids (<10 mg/d of prednisone equivalent) and theophyllines.

Rating scales:

Transition dyspnoea index (TDI). TDI measures changes in baseline dyspnoea index (BDI) over time. It includes domains of functional impairment, magnitude of the task and magnitude of effort causing dyspnoea. Each domain is rated from 0 (severe dyspnoea) to 4 (no dyspnoea). TDI measures changes in score in each domain compared to baseline ranging from +3 (major improvement) to -3 (major deterioration).

The focal score is obtained from the sum of all domains rated from 0 to 12 (BDI) with changes ranging from +9 to -9 (TDI). An increase in focal score of at least 1 unit represents the minimum difference in clinical relevance. This change may signify that patients who were breathless when walking on level ground or when washing become breathless when climbing a slope or carrying a light weight on level ground.

Modified Borg scale:

This scale rates breathlessness experienced during a standardised level of exercise. It is a non-linear, open scale ranging from 0 to 10, used in standardised conditions and based on psychometric data which rates the severity of dyspnoea experienced by patients (0 = nothing at all; 10 = maximum). The Borg scale was used to rate improvement in dyspnoea at maximum exercise (bicycle ergometry or walked distance) or at during an endurance test at sub-maximum constant load (bicycle ergometry).

"St-George's hospital Respiratory Questionnaire" (SGRQ):

This questionnaire measures changes over time in quality of life associated with health status in patients with chronic airways disease. The scale consists of 50 questions and 76 weighted responses in 3 domains: symptoms, activity and psychosocial impact. The total SGRQ score is rated from 0 to 100, 100 being greatest deterioration in quality of life. A 4-point difference is considered to be clinically relevant. A difference of this kind may mean that patients do not walk more slowly than other persons, are not breathless when washing or dressing, are capable of carrying a load upstairs, can do housework without stopping to rest, can go out for pleasure, can go upstairs without stopping, dress and wash in less time.

Definition of exacerbations:

Trial	Exacerbation	Mild exacerbation	Moderate exacerbation	Severe exacerbation
205.117 205.128 205.126A et B	Appearance or worsening of at least 2 symptoms (cough, dyspnoea, sputum, wheezing) persisting for at least 3 days and reported by the investigator as an undesirable effect.			
205.214	Change in treatment: -↑ß-2 agonist -antibiotic -corticosteroid or ↑corticosteroid -bronchodilator or ↑bronchodilator And at least 1 of the following symptoms in the last 24 hours : -↑dyspnoea -↑cough (frequency and severity) -↑sputum production - purulent sputum -fever<38℃ -X-ray abnormalities	Change in treatment with less than 3 of the symptoms given	Exacerbation which is neither mild or severe	Hospitalisation required Or ↓FEV_1 or PEV <30% compared to baseline for 2 consecutive days or ↓$Pa0_2$≥10 mmHg or $Pa0_2$≤60 mmHg or ↑$PACO_2$≥5 mmHg or $PaCO_2$≤45 mmHg
205.256	Acute sustained deterioration in patients' condition (compared to their stable condition and exceeding the normal day-to-day variations) requiring a change in drug treatment.			
205.266	Appearance or worsening of at least 2 of the respiratory symptoms (cough, sputum, wheezing, dyspnoea, chest tightness) persisting for at least 3 days: And antibiotic and/or systemic corticosteroid treatment and/or hospitalisation	Antibiotic treatment but no need for hospital visit.	Hospital visit including emergency visit or systemic corticosteroid treatment but without hospital admission.	Admission to a department other than an emergency department or an emergency department visit for more than 24 hours.
205.130 205.137	Combinations of several pulmonary events reported as undesirable for at least 3 days.			