COLLEGE TER BEOORDELING VAN GENEESMIDDELEN
MEDICINES EVALUATION BOARD

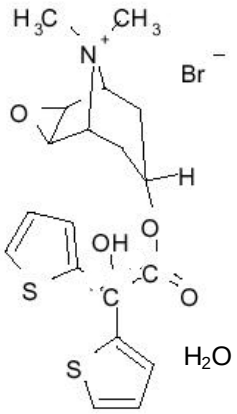
PUBLIC ASSESSMENT REPORT

Spiriva 18 µg, inhalation powder in hard capsules — RVG 26191

International Non-proprietary Name (INN) **tiotropium bromide**

Report version: 1st NPAR, original — Date 2002-05-21

GENERAL INFORMATION

Active substance:	tiotropium bromide monohydrate, equivalent to 18 µg tiotropium per capsule
Structural formula:	
Pharmacotherapeutic group: ATC code:	Anticholinergics R03BB04
Pharmaceutical dosage form	Inhalation powder in hard capsules
Route of administration:	Respiratory
Therapeutic indication:	Bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease (COPD)
Prescription information:	Prescription only
Marketing Authorisation Holder:	Boehringer Ingelheim International GmbH Ingelheim am Rhein, Germany
Date of first application:	18-12-2000
Application type/legal basis:	Directive 65/65/EEC, Article 4.8 (a)

Date of authorisation:	09-10-2001
Completion of Mutual Recognition Procedure (Directive 75/318/EEC):	2002-04-02
Countries recognising Dutch assessment:	Austria, Belgium, Denmark, Finland, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Norway, Portugal, Spain, Sweden, United Kingdom

ABSTRACT

On 2001-10-09, the Medicines Evaluation Board in the Netherlands issued a marketing authorisation for the medicinal product Spiriva 18 µg, which contains tiotropium.

The approved indication is bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The dosage is one capsule of inhalation powder a day. The special inhalation device, the HandiHaler, releases an amount of powder from each capsule equivalent to 10 µg tiotropium. The Summary of Product Characteristics (SPC, part IB1 of the dossier), adhered to this National Public Assessment Report, describes the conditions for the use of this product in detail. The product is presented as inhalation powder in hard capsules in blister pack and has a shelf life of 18 months when stored below 25 °C.

The preclinical pharmacodynamic studies clearly show that tiotropium is a potent bronchodilator without cardiovascular effects. Like ipratropium, tiotropium is a selective and reversible muscarine receptor antagonist. It is 1-3 times more potent than ipratropium, and has a marked longer duration of action Besides dry mouth and constipation, systemic anticholinergic effects of tiotropium do not occur after inhalation of therapeutically recommended dosages. Tiotropium has a low absolute oral bioavailability and is absorbed well in the lung. The drug is distributed broadly and rapidly in rats following intravenous and intratracheal administration. In humans, tiotropium is mainly excreted in urine, but in animal species, the excretion is more equally in urine and faeces. Metabolism is minor in humans, but much more pronounced in animal species (74 % versus 35-40 % parent excreted in urine). The elimination half-life of the drug is approximately 20 h in plasma and in most tissues in rats. In animal experiments, tiotropium has a low order of acute toxicity after oral administration or inhalation. After repeated doses anticholinergic effects occurred that affected the gastro-intestinal and the urinogenital tracts, the heart and eyes. Other relevant effects were mild irritation of the respiratory tract and prostatitis. Reproductive toxicity of tiotropium bromide was shown at maternally toxic dose levels. No genotoxic or oncogenic potential has been demonstrated.

Clinical trials investigated the efficacy and safety of Spiriva 18 µg in the treatment of patients with COPD. Four dose-ranging studies and ten pharmacokinetic studies were performed. Evidence for efficacy and safety was based on four large pivotal, one -year studies in which tiotropium was compared with either placebo or

ipratropium. Two other large studies of 6 months duration compared tiotropium with placebo and salmeterol
In pharmacodynamic studies tiotropium is well tolerated with known anticholinergic effects manifesting in healthy volunteers at some 2-8 times the recommended therapeutic dose of 18 µg. At therapeutic level, the anticholinergic effect is limited to dry mouth.
The absolute bioavailability of tiotropium after inhalation is about 20% and after oral administration only 2-3%. Distribution after inhalation is fast and the protein binding is about 72%. The terminal half-life was estimated on 4 to 5 days. Steady state is reached between 7 and 14 days.

Studies in geriatric COPD patients showed no clinically significant difference in plasma concentrations than in younger patients. In patients with renal failure, renal clearance of unchanged tiotropium decreased proportional with the creatinine clearance.

The efficacy of tiotropium with respect to lung function, symptoms, quality of life, and exacerbations in patients with COPD is not only statistically significant but also clinically relevant. The efficacy of tiotropium is favourable in comparison with ipratropium and as least as good as salmeterol. Patient selection criteria provided the participation of "true" COPD patients, and the exclusion of asthma patients.

Safety data show that during tiotropium treatment anticholinergic events occur, especially dry mouth, more often than with ipratropium therapy. In most cases, the complaints of dry mouth are temporarily. Remarkable is a small increase in incidence of pharyngitis, sinusitis and moniliasis during tiotropium. This may be related to the drying of the mucous membranes.

The Medicines Evaluation Board, on the basis of the quality, efficacy and safety data submitted, considered that Spiriva can be consistently produced with sufficient quality, and that efficacy for the therapeutic indication, as well as safety, has been adequately shown.

SAMENVATTING

Op 9 oktober 2001 heeft het College ter beoordeling van geneesmiddelen Spiriva 18 µg geregistreerd. Dit inhalatiepoeder in harde capsules bevat het nieuwe werkzame bestanddeel tiotropium (als bromide).

De goedgekeurde indicatie is bronchusverwijder voor de onderhoudsbehandeling van COPD De dosering is één capsule met inhalatiepoeder per dag. Het speciale inhalatieapparaat, de HandiHaler, geeft het equivalent van 10 µg tiotropium aan poeder af uit elke capsule. De gedetailleerde voorwaarden voor het gebruik van het geneesmiddel staan beschreven in de Samenvatting van de kenmerken van het product (deel IB1 van het registratiedossier). Deel IB1 is bij dit rapport gevoegd.

Spiriva 18 µg is beschikbaar als inhalatiepoeder in harde capsules, verpakt in blisters. De houdbaarheidstermijn is 18 maanden bij maximaal 25 ºC.

Bij preklinisch farmacodynamisch onderzoek blijkt tiotropium een effectieve bronchodilatator zonder cardiovasculaire werking. Net als ipratropium is tiotropium

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een selectieve en reversibele muscarinereceptor antagonist. Het is 1-3 maal werkzamer dan ipratropium en heeft een duidelijk langere werking. Behalve een droge mond, treden systemische anticholinerge effecten niet op na inhalatie van therapeutisch werkzame doseringen. Tiotropium heeft bij onderzoek met dieren een lage absolute biologische beschikbaarheid en wordt in de longen goed geabsorbeerd. Na intraveneuze en intratracheale toediening bij ratten volgt uitgebreide en snelle verdeling. Bij de mens vindt voornamelijk uitscheiding in de urine plaats, bij dieren in zowel de urine als de feces. Het metabolisme is bij de mens van ondergeschikt belang, maar is bij dieren veel meer uitgesproken (74 % versus 35-40% onveranderd uitgescheiden in de urine). Bij ratten is de eliminatiehalfwaardetijd in plasma en de meeste weefsels ongeveer 20 uur.
Tiotropium heeft bij dierexperimenten een geringe mate van acute toxiciteit na orale toediening en inhalatie. Na herhaalde toediening traden anticholinerge effecten op in het gastrointestinale en urogenitale gebied, het hart en de ogen. Andere effecten van belang waren irritatie van de luchtwegen en prostatitis. Reproductietoxiciteit trad op bij dosisniveaus die toxisch waren voor het moederdier. Genotoxiciteit en carcinogeniteit zijn niet aangetoond.

Met klinisch onderzoek zijn de werkzaamheid en veiligheid van Spiriva 18 µg aangetoond bij patiënten met COPD. Er zijn vier onderzoeken naar de beste dosering uitgevoerd en tien farmacokinetische studies. Het bewijs voor werkzaamheid en veiligheid is gebaseerd op de vier voornaamste, omvangrijke klinische studies met de duur van één jaar. In deze studies is tiotropium vergeleken met placebo en ipratropium. In twee andere studies van een half jaar is tiotropium vergeleken met placebo en salmeterol.

Bij farmacodynamisch onderzoek met gezonde vrijwilligers bleek ipratropium goed te worden verdragen. Er traden bekende anticholinerge effecten op bij 2-8 maal de aanbevolen dosering van 18 µg (= 10 µg). Bij therapeutische doseringen is anticholinerge effect beperkt tot een droge mond.

De absolute biobeschikbaarheid van tiotropium is ongeveer 20% na inhalatie en slechts 2-3% na orale toediening. Na inhalatie vindt snelle distributie plaats en de eiwitbinding is ongeveer 72%. De terminale halfwaardetijd is geschat op 4 tot 5 dagen. De steady state wordt bereikt na 7 tot 14 dagen.

Onderzoek bij bejaarde patiënten heeft wat betreft plasmaspiegels geen verschil laten zien met jongere patiënten. Bij patiënten met nierinsufficiëntie nam de renale klaring van onveranderd tiotropium recht evenredig af met de creatinineklaring.

In het klinische onderzoek naar de werkzaamheid bleek Spiriva 18 µg effectief ten opzichte van placebo. De werkzaamheid van tiotropium met betrekking tot de longfunctie, symptomen, levenskwaliteit en exacerbaties bij patiënten met COPD is niet alleen statistisch significant maar ook klinisch relevant. De werkzaamheid van tiotropium is gunstig in vergelijking met die van ipratropium en ten minste zo goed als die van salmeterol. Door de criteria voor de patiëntenselectie bestonden de vergelijkingsgroepen uit "echte" COPD-patiénten en waren astmapatiënten uitgesloten. De gemeten werkzaamheidvariabelen waren de longfunctie, kwaliteit van leven, symptomen en het optreden van exacerbaties.

De gegevens over de veiligheid van de behandeling met tiotropium laten zien dat er anticholinerge effecten als bijwerking optreden, voornamelijk droge mond. In de

meeste gevallen zijn de klachten over een droge mond voorbijgaand. Opmerkelijk is een kleine toename van faryngitis, sinusitis en monoliasis tijdens de behandeling met tiotropium. Dit kan te maken hebben met het uitdrogen van slijmvlies-membranen.

Het College ter beoordeling van geneesmiddelen heeft op basis van de overgelegde gegevens geconstateerd dat Spiriva 18 µg met constante, voldoende kwaliteit kan worden geproduceerd. De werkzaamheid en veiligheid bij de gestelde indicatie zijn voldoende bewezen.

SCIENTIFIC DISCUSSSION

INTRODUCTION

Spiriva 18 µg inhalation powder in hard capsules contains 22.5 µg of the new active substance tiotropium bromide monohydrate, corresponding with 18 µg tiotropium. Spiriva is intended for the long term once daily maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD). Tiotropium is a specific, anti-cholinergic substance, with a very slow dissociation from the muscarinic receptors, which results in a long lasting bronchodilation.

Spiriva should be inhaled using the so-called HandiHaler. The HandiHaler is a breath-actuated device with a high resistance. The capsules are inserted individually and pierced. The device releases an amount of powder equivalent of 10 µg tiotropium from each capsule. The recommended dosage of tiotropium is one capsule (18 µg) once daily at the same time of day.

Apart from tiotropium, the following medicinal products are registered in the Netherlands for the treatment of COPD patients; the short-acting anti-cholinergic bronchodilator ipratropium bromide, several beta $_2$-sympaticomimetics (salbutamol, terbutaline, fenoterol, salmeterol, formoterol), theophylline and fluticasone.

A full dossier supported the application. The clinical part contains ten pharmacokinetic studies, eight pharmacodynamic studies, four large pivotal clinical one-year studies, two large salmeterol-compared 6-months studies, and four additional studies.

CHEMICAL-PHARMACEUTICAL ASPECTS

Composition

Spiriva is an inhalation powder in a hard gelatine capsule. Each capsule contains 22.5 µg tiotropium bromide monohydrate, corresponding to 18 µg tiotropium. The excipient lactose monohydrate is a very common ingredient in powders for inhalation. The capsules have a light green colour with black imprint and are packed in a blister made of polyvinylchloride and a protective aluminium layer. One blister-card consists of two 5-cavity blisters joined along a perforated line. An aluminium

peel-off foil covers the cavities. The blister allows taking one capsule at a time, so the other capsules remain protected from moist air.

Immediately before use, the patient has to place one capsule into the HandiHaler, a modernised version of the Inhalator Ingelheim. The HandiHaler-device is specially developed for Spiriva. By pushing a knob, the capsule is pierced and the contents are aerosolised by vibration energy created by the inhalation airflow of the patient. The suitability of this inhaler has adequately been demonstrated.

Active substance

Tiotropium bromide monohydrate is a white to yellowish white powder. The substance is sparingly soluble in water and soluble in methanol. Tiotropium bromide is a quaternary ammonium salt and there is no other ionisable functional group on the molecule. The active substance is not optically active. The specification of tiotropium bromide monohydrate includes requirements for identity, appearance of aqueous solution, content, related substances, residual solvents, water content and particle size distribution, amongst others. The limits for related substances are low and are toxicologically justified. The specification of the active substance is supported by scientific information regarding the route of synthesis.

Other ingredients

Lactose monohydrate and gelatine comply with the requirements of the European Pharmacopoeia. The two substances are TSE safe. For lactose, limits for the particle size distribution have been adopted.

Product development and finished product

Development pharmaceutics

When using the HandiHaler the delivered dose appears to be about 10 µg. The fine particle dose (< 5 µm) is about 3 µg, determined with the Andersen Cascade Impactor at a flow rate of 39 litres/minute (pressure drop 4.0 kPa).

The active substance can be hydrolysed due to the presence of an ester bond. In addition, gelatine is susceptible to water loss, leading to brittleness of the capsules. The composition of the gelatine capsule has been optimised in order to lower the water content without causing brittleness. Before packaging, the water content of the filled capsules is conditioned. Furthermore, the blister pack shows adequate protective properties towards influence of moisture. Finally, an in-use stability study showed acceptable quality of the product 9 days after opening.

Manufacture

The manufacturing process consists of sieving and mixing of the ingredients, followed by encapsulating. Before packaging, the water content of the filled capsules is conditioned. The production process is adequately validated.

Specification of the finished product

The most relevant requirements of the finished product are tests on identity of the active substance, uniformity of content, related substances, uniformity of delivered dose, fine particle dose, water content and microbiological purity. The limits for related substances are toxicologically justified. The upper and lower limits for the fine particle dose are based on the clinical trial batches, taking into account the

results obtained in the stability trials. The specification of the finished product is adequate in order to guarantee a satisfactory quality of the finished product. Analysis results of production scaled batches show compliance with the finished product specification.

Stability and shelf life of the finished product

The shelf life is 18 months when stored at below 25°C, in Al/PVC/Al blister. Stability results obtained with production scaled batches have shown that within this period the quality of the product remains acceptable. Degradation of the active substance is the shelf life limiting factor. When stored at 30°C/70% RH and 40°C/75% RH out of specification results are already observed after 6 months of storage.

PRECLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

Pharmacodynamics (see also section 5.1 of the SPC)

Tiotropium bromide is a potent bronchodilator. Tiotropium has a marked longer duration of action than ipratropium and acts like ipratropium as a selective and reversible muscarinic receptor antagonist does. Receptor selectivity was determined using membrane preparations from stable transfected cell lines expressing the gene for individual human muscarinic receptor (hm1 to hm3). Receptor selectivity was determined also in time- dependent binding studies to human muscarinic receptor subtypes (hm1-hm5) expressed in Chines Hamster Ovary (CHO) cells. The anticholinergic activity was tested in vitro using isolated guinea pig trachea contracted by methacholine or electric field stimulation (EFS), isolated ciliated cells from guinea pig trachea stimulated by methacholine, as well as human bronchi under EFS. In vivo tiotropium antagonised acetylcholine-induced bronchospasm in guinea pigs, rabbits and dogs in a dose and time dependent manner. General pharmacodynamic studies have shown that, besides dry mouth, several systemic anticholinergic effects of tiotropium do not occur after inhalation of therapeutic effective dosages. In human pharmacology studies, tiotropium is well tolerated with known anticholinergic effects. The effects were manifest in healthy volunteers at some 2-8 times the recommended therapeutic dose of 18 µg. Effects at doses closer to the therapeutic dose are primarily dry mouth of tolerable intensity.

Pharmacokinetics

Absorption, distribution, metabolism and excretion

Oral absorption was low in mice, rats, and rabbit (< 19 %) and higher in dogs (46 %). Absorption after single intratracheal instillation in rats was high in the lung (96 %)

The protein binding of tiotropium bromide was much lower in animal species (16-22 %) compared to humans (71 %).

A broad and rapid distribution was observed in rats following single intravenous and intratracheal administration of ^{14}C-labelled tiotropium.

Drug-related radioactivity crossed the placenta and tissue organ concentrations in the foetus were lower than in maternal tissue. Drug-derived radioactivity was

excreted in the milk of lactating rats resulting in milk: plasma ratios of 0.4 (0.5 h) to 18 at 24 h. Approximately 1.9 % of the dose was excreted in the milk over two days. The main metabolites N-methylscopine and dithienylglycolic acid were found in all species. Metabolism occurred mainly in the liver. There was no evidence of enzyme induction and no evidence of drug interactions. Metabolism of the drug seems to be a much more important clearance mechanism in animal species than in human.
Excretion in human was mainly renal but in animal species approximately 30-40 % of the dose was excreted in faeces.

Pharmacokinetics after a single dose/repeated administration
In single dose studies, terminal elimination half-life of the parent compound was ≤ 20 hours in all studied species (mice, rats, rabbits and dogs). Only small amounts of drug-derived radioactivity were eliminated from tissues of the rat with half-lives longer than 20 hours. Repeated dose studies showed no accumulation of parent drug in plasma and dose-proportional increase in plasma C_{max} levels following inhalation.

Toxicology

Dose extrapolation
The total tiotropium bromide dose achieved in the inhalation toxicology studies usually exceeded the human therapeutic dose. Based on $C_{max,}$ the exposure ratio varied from 1-5 (in the low dose group of a 52-week study in rats) to 5110-18600 (in the high dose group in a 13-week study in mice).

Single dose toxicity
Tiotropium bromide monohydrate has low toxicity in rats and mice after oral administration. Inhalation of tiotropium bromide at dose levels of 40.43 mg/kg (mice), 334.5 mg/kg (rat, the highest dose level), and 3.6 mg/kg (dog, the highest dose level) has shown low toxicity and caused no deaths. A dose of 131 mg/kg (mice) was toxic and did cause deaths.

Repeated dose toxicity
Most adverse effects observed in the repeated dose studies were the result of the systemic effects of a potent anticholinergic agent.

Gastro-intestinal tract
A species and strain-specific effect was noted in Fisher-F344 rats. Tiotropium bromide inhalation administration caused food impaction in the proximal oesophagus, caused by diminished salivation and followed by asphyxiation In CD-1 mice, inhalation doses of tiotropium bromide, similar to those intended for clinical use, caused swollen abdomens. Dilatation of the intestinal tracts, ultimately causing premature death, was associated with reactive mucosal hyperplasia and inflammation. Dry mouth and obstipation may be considered as the clinically relevant counterparts in humans.

Heart.
Tachycardia, a known anticholinergic effect was observed in many studies.

Eyes
As expected, tiotropium bromide caused reduced tear secretion and mydriasis. In the 13- and 52-week rat inhalation studies cataracts were noted. These cataracts

were probably related to long-term eye exposure occurring in the inhalation tubes, allowing the compound to cross the corneal epithelium and enter the eye.

Urinogenital tract

In rats, proteinaceous deposits and lithiasis were found in the bladder, in some cases related with minimal cystitis, diffuse hyperplasia of the transitional epithelium and prostatitis.

Respiratory tract and lungs

In rodents, an increased incidence of rhinitis, and a number of changes in the nasal cavity and larynx were observed. These included focal squamous metaplasia, focal inflammatory cell infiltrates, focal goblet cell hyperplasia, and inflammatory exudate in anterior and posterior lumens. From these findings, it may be concluded that tiotropium bromide is a mild irritant to the respiratory tract in rodents.

Reproduction studies

Reproductive toxicity of tiotropium bromide was studied in rats and rabbits. In all inhalation reproductive toxicity studies, maternal toxicity was observed. In rat fertility studies, maternal toxicity was accompanied by reduced ovulation and implantation rates, resulting in reduced litter sizes. In rat and rabbit embryo/foetotoxicity studies maternal toxicity was followed by embryo/foetotoxicity. In peri/postnatal developmental rat studies, maternal toxicity was associated with total litter loss, lower pup weights, delayed sexual maturity, and delays in development of startle and air righting reflexes.

Mutagenic potential

Standard in vitro and in vivo genotoxicity tests did not indicate any genotoxic potential of tiotropium bromide or any of the relevant impurities or degradation products.

Carcinogenic potential

Tiotropium bromide showed no carcinogenic potential.

Local tolerance

Repeated dose toxicity studies and oncogenicity studies in rats and mice produced evidence that tiotropium bromide has mild local irritant properties for the respiratory tract. This is discussed in the section on repeated dose toxicity.

CLINICAL ASPECTS

Four dose-ranging studies and ten pharmacokinetic studies were performed. In most of these studies, other inhalation devices than the HandiHaler have been used. Equivalence of the predecessing device and the HandiHaler has been demonstrated. Evidence for efficacy and safety was based on four large pivotal, one -year studies in which tiotropium was compared with either placebo or ipratropium. Two other large studies of 6 months duration compared tiotropium with placebo and salmeterol.

Clinical pharmacodynamics

Three single dose studies showed a dose related bronchodilator effect of inhaled tiotropium of ± 24 hours. Furthermore, these studies exhibited general dose ordering with evidence of a plateau at the highest doses, i.e. 40 to 160µg tiotropium bromide. In the range of 10 to 40 µg, dose-dependent increases in effectiveness were generally seen, and 10µg always was the least effective dose

A multiple dose study showed that all doses were more efficacious than placebo. The trough FEV_1 increased after one week and remained the same during the further 3 weeks.

The difference between the 9 and 18 µg dose is twice as large as the difference between the 18 and 36 µg dose. Within one week, lung function reached a steady state. Furthermore, there was no difference in bronchodilator effect between the time of dosing (a.m. or p.m.). The study with the HandiHaler showed that COPD patients with varying degrees of disease severity could generate sufficient inspiratory flow rates to use the HandiHaler properly. Safety evaluation showed trends with respect to dry mouth and overall reported adverse events when 36 µg was compared with 18 µg

Clinical pharmacokinetics (see also section 5.2 of the SPC)

Ten pharmacokinetic studies were submitted. In two pharmacodynamic studies also a limited number of pharmacokinetic parameters were estimated

Absolute bioavailability.
Pharmacokinetics of tiotropium was studied in healthy male volunteers after administration by different routes. After oral administration of a 64 µg solution, plasma concentrations were regularly below the limit of quantitation (2.5 pg/ml).

Pharmacokinetics after single oral, intravenous and inhalation doses of tiotropium (geometric mean and CV)

Administration route and dose	N	C_{max} pg/ml	AUC_{0-2h} pg.h/ml	AUC_{0-8h} pg.h/ml
Intravenous 14.4 µg	11	378 (25)	143 (19)	186 (25)
Oral solution 64 µg	12	2.4 (88)	--	--
Inhalation powder 108 µg	11	65 (58)	40 (39)	93 (28)

From the normalised excretion data extrapolated to infinity, an absolute bioavailability after inhalation of 19.5% was calculated. After oral administration, the absolute bioavailability was estimated to be 2 – 3%. The terminal elimination half-life from the urine excretion data was similar for the different routes and was estimated to range from 116 to 137 h.

Pharmacokinetics after i.v. dosing
In a study to examine changes in vital and laboratory variables as well as to assess the incidence of adverse events after intravenous dosing additional,

pharmacokinetic data were also determined. Two subsequent doses of respectively 2.4, 4.8. 9.6 and 14.4 µg were given. During intravenous infusion, over 15 min the plasma levels showed a very steep increase, already after 7 min the plasma levels were close to maximum. After the end of infusion, concentrations decreased also very rapidly 15 min after infusion. Concentrations were then below 10% of the maximal concentrations. The maximum concentration and the AUC are more or less dose proportional. The excretion in urine seems to be a little higher after administration of higher doses. Renal clearance based on the excretion data of 0-4h after administration was about 650 ml/min for the9.6 and 14.4 µg dose groups.

Pharmacokinetics after oral administration

In a single dose tolerance study, the pharmacokinetics after oral administration was investigated. At each dose level (8, 16, 32 and 64 µg tiotropium cation) six volunteers received orally the active drug with 300 ml water and two the placebo. The testing of each dose level was separated by at least 4 days. Plasma concentrations above the limit of quantitation (3 pg / ml) could only be detected reliably in some of the samples of the 64 µg group with the highest level of ca 8 pg/ml. A more or less dose proportionality in the urinary excretion data was observed with only 1% of the dose excreted in 24 hours at the highest dose level. The limit of quantitation in urine was 11 pg/ml.

Pharmacokinetics after inhalation

The pharmacokinetics of tiotropium was estimated after repeated inhalation of 70.4 and 141 µg per day for 7 consecutive days in a three-way crossover study including a placebo-arm. However, tiotropium plasma concentrations were often below the limit of quantitation at later sampling points, thus these were replaced by ½ LoQ (limit of quantitation) in order to generate an AUC value by the linear trapezoid rule.

Pharmacokinetic data after repeated inhalation of tiotropium corrected for carry-over effects

	70.4 µg dose		**141 µg dose**	
	Day 1	Day 7	Day 1	Day 7
AUC_{0-2h} (pg.h/ml)	25 (64)	44 (18)	74 (58)	87 (28)
C_{5min} (pg/ml)	34 (63)	64 (49)	108 (74)	199 (57)
Ae_{0-4h} (% dose)	1.33 (54)	4.03 (34)	1.78 (62)	4.22 (34)
Ae_{0-12h} (% dose)	2.67 (36)	7.72 (39)	3.56 (53)	7.77 (28)

(Ae = amount excreted in urine)

In subjects receiving placebo in the second or third period, the elimination half-life was calculated. A half-life of 4 –5 days was found (n=5). In another study, the excretion in urine was determined after repeated administration for 14 consecutive days.

Renal excretion expressed as % dose (variation coefficient) during repeated inhalation of different doses of tiotropium			
	Dose 9 µg	Dose 18 µg	Dose 35 µg
Ae_{0-4h} Day 1	1.34 (35)	1.61 (65)	1.31 (50)
Ae_{0-4h} Day 7	2.56 (25)	3.66 (76)	4.38 (40)
Ae_{0-4h} Day 13	2.49 (40)	5.60 (50)	4.69 (28)
Ae_{0-4h} Day 14	3.13 (50)	3.63 (39)	4.28 (25)
Ae_{0-24h} Day 14	10.5 (26)	12.1 (20)	14.7 (14)

From the cumulative data it is clear that steady state was reached at day 7 as the total amount excreted did not increase anymore in day 13 or 14 compared to day 7 in all three dosing groups. At steady state, the percentage of the dose excreted increased with the dose by 40%.The elimination half-life was calculated from the urinary excretion data measured after the last administered dose on day 14. For this calculation the amount excreted in urine from 0-4h at each day were used. For the three doses investigated, a half-life of 5.8 to 7.7 days was calculated.

After multiple inhalation, accumulation of tiotropium by a factor of about 2 – 3 during the two weeks treatment could be observed. The bioavailability based on the excretion in the dosing interval in steady state seems to be about 20 –25%.

Pharmacokinetic variables after repeated inhalation once daily of different doses of tiotropium (geometric mean and % CV) by the Respimat device				
		Dose 8 µg	Dose 16 µg	Dose 32 µg
Day 1	C_{5min} (pg/ml)	4.23 (38)	12.5 (29)	22.1 (60)
	$AUC_{0-20\ min}$ (pg.h/ml)			4.78 (51)
	Ae_{0-4h} (% of dose)	1.49 (76)	2.99 (104)	2.24 (91)
	Ae_{0-8h} (% of dose	2.69 (50)	4.54 (97)	3.81 (71)
	Ae_{0-24h} (% of dose)	5.66 (36)	8.41 (61)	6.45 (55)
Day 7	$C_{pre\ dose}$ (pg/ml)	4.05 (78)	7.81 (28)	11.7 (51)
	C_{5min} (pg/ml)	9.51 (47)	23.2 (24)	44.2 (63)
	$AUC_{0-20\ min}$ (pg.h/ml)	3.74 (62)	6.10 (22)	10.4 (59)
	Ae_{0-4h} (% of dose)	4.54 (44)	7.62 (60)	6.82 (64)
	Ae_{0-8h} (% of dose	7.21 (36)	15.2 (33)	15.8 (32)
	Ae_{0-24h} (% of dose)		29.1 (28)	29.4 (29)
Day 14	$C_{pre\ dose}$ (pg/ml)	4.75 (69)	17.9 (35)	26.7 (56)
	C_{5min} (pg/ml)	11.0 (68)	33.3 (33)	56.5 (50)
	$AUC_{0-20\ min}$ (pg.h/ml)	3.64 (63)	10.6 (18)	14.4 (54)
	Ae_{0-4h} (% of dose)	5.41 (38)	7.69 (48)	7.40 (57)
	Ae_{0-8h} (% of dose	9.17 (31)	12.5 (51)	10.3 (53)
	Ae_{0-24h} (% of dose)	20.1 (26)	24.5 (34)	21.3 (53)

Distribution

No distribution data in humans were submitted. After intravenous dosing a very fast distribution phase was observed. The plasma levels decreased to 10% of the

maximum concentration within 15 min after stopping of the infusion. After inhalation, distribution is lower than after intravenous administration. Binding of tiotropium to a variety of binding sites in lung tissue, including muscarinic receptors, may cause this difference. After intravenous administration, the renal elimination in the first hours is considerably higher than after inhalation.

Metabolism and excretion
No clinical metabolism studies were submitted. In animal it was shown that tiotropium is metabolised only to a small extent. A small part might be metabolised in the human liver (may be up to 20%). In vitro metabolism studies indicated a slow cytochrome P450 oxidation, probably CYP 2D6 and 3A4. Tiotropium up to 1 µmol/l does not inhibit cytochrome P450. The total amount of unchanged tiotropium in urine after intravenous administration was estimated on 74% of the dose. This indicates that renal excretion is the main route of elimination and the hepatic elimination is only of minor importance.

Interactions
Clinically relevant pharmacokinetic interactions with tiotropium are unlikely in view of the site of action and of the metabolic pathway.

Pharmacokinetics in special patient groups.

COPD patients
The pharmacokinetics were estimated in patients with evidence of normal renal function, history of smoking, and diagnosis of moderate to severe COPD. Two groups were included in the study: 'young' patients (n=12, 5 male 7 female, aged 45 – 58 years) and older patients (n=13, 9 male 4 female, aged 69 – 80 years). All patients received tiotropium 18 µg once daily for 14 days by inhalation. Half-lives were calculated from the urinary excretion rates. Tiotropium plasma concentrations were moderately higher (20%) in the elderly COPD patients and were associated with a corresponding lower amount of tiotropium excreted unchanged in the urine. These differences are considered not to be clinically significant. Renal clearance was significantly lower in elderly patients. Steady state is reached within 7 (to 14) days.

Patients with renal insufficiency
The pharmacokinetics after a single dose in patients with mild and moderate renal impairment was compared with normal subjects. Maximum concentrations and AUC increased with decreasing renal function and amount excreted in urine in the first 4 hours decreased more pronounced than at later time points. As an overall result the renal clearance of unchanged tiotropium decreased proportional with the creatinine clearance.

Clinical efficacy and safety

Studies comparing tiotropium with either placebo or ipratropium

Study design and methodology
The methodology of four pivotal studies, comparing tiotropium with placebo/ipratropium is summarised in the next tables.

Description of the pivotal studies			
Study No.	**Description of the studies**	**Number of patients**	**Country**
205.114/ 205.117	Efficacy/safety one-year study in COPD. Double blind, randomised, placebo-controlled, parallel group, tiotropium DPI 18 µg once a day.	470	USA
205.115/ 205.128	Efficacy/safety one-year study in COPD. Double blind, randomised, placebo-controlled, parallel group, tiotropium DPI 18 µg once a day.	451	USA

Description of the pivotal studies			
Study No.	**Description of the studies**	**Number of patients**	**Country**
205.122A 205.126A	Efficacy/safety one-year study in COPD Tiotropium DPI 18 µg once a day in comparison with ipratropium MDI 40 µg four times a day. Double blind, randomised, parallel group.	288	NL
205.122B 205.126B	Efficacy/safety one-year study in COPD: tiotropium DPI 18 µg once a day in comparison with ipratropium MDI 40 µg four times a day. Double blind, randomised, parallel group.	247	NL/BE

In- and exclusion criteria, efficacy variables and measurement		
	Placebo controlled studies (205,114/117, 205,115/128)	**Ipratropium controlled studies** (205,122/126A,205, 122B/126B)
Inclusion criteria	FEV_1 ≤65% of pred, FEV_1 /FVC≤70%, >40 years, >10 cig. pack years smoking	FEV_1 ≤65% of pred, FEV_1 /FVC≤70%, >40 years, >10 cig. pack years smoking
Exclusion criteria	Asthma, allergic rhinitis, atopy, blood eosinophils >600/mm3	Asthma, allergic rhinitis, atopy, blood eosinophils >320-400/mm^3
Pulmonary function test (FEV_1, FVC)	At 1 hour prior to and just prior to drug administration and at 30, 60, 120 and 180 minutes post dosing	At 1 hour prior to and just prior to drug administration, at 30, 60, 120, 180, 240, 300, 360* min. post dosing *only done in first 3 months
Pulm. function test (FEV_1, FVC) Quality of life instruments (SGRQ and SF36) Mahler Dyspnea indices (BDI/TDI)	At baseline, after 1, 7, 13, 25, 37 and 49 weeks (QOL was not assessed on day 7)	At baseline, after 1, 7, 13, 26, 39 and 52 weeks
PEFR by the patient	Twice daily	Twice daily
COPD symptom score Physician's global evaluation	Every 3 weeks Every 3 weeks	- -

Energy-fatigue questionnaire	At 1, 4, 10, 19, 31 and 43 weeks	-
Salbutamol rescue medication	Number of doses daily (each dose is one or two puffs)	Number of inhalations daily (each inhalation is one puff)
Primary efficacy variable	Trough FEV_1 (response)	Trough FEV_1 (response)
In- and exclusion criteria, efficacy variables and measurement		
	Placebo controlled studies	**Ipratropium controlled studies**
Secondary efficacy variable	Peak FEV_1 response, average FEV_1 response, FVC, PEFR, Mahler dyspnea indices, energy fatigue questionnaire symptom scores, rescue medication, SGRQ, SF-36, prop. of patients with exacerbation, with hospitalisation, time to first exacerbation, physician's evaluation	Peak FEV_1 response, average FEV_1 response, FVC, PEFR, Mahler dyspnea indices, rescue medication, energy fatigue questionnaire symptom scores, SGRQ, SF-36, proportion of patients with an exacerbation with a hospitalisation, time to first exacerbation

Definitions and abbreviations used in the description of the clinical studies	
FEV_1	Forced expiratory volume in one second
Trough FEV1	Mean of the two FEV1 readings at the end of the dosing interval, 23 to 24 hours post drug administration
Trough FEV1 response	Change from baseline in trough FEV1
Peak FEV1 response	Maximum value post treatment administration minus baseline
Average FEV1 response	Change from baseline in average value over the first 3 hours
FVC	Forced vital capacity
Mahler Dyspnea Indices	BDI and TDI (see text)
BDI	Baseline Dyspnea Index; three components, score 0-4; focal score is the sum of the components (0-12)

TDI	Transitional Dyspnea Index; change in score compared to baseline; three components, score –3 to +3; focal score is the sum of the components (–9 to +9) (one unit difference is meaningful)
SGRQ	St. George's Respiratory Questionnaire; disease specific QoL; 4 components, score 0-100 (4 units difference is meaningful)
Definitions and abbreviations used in the description of the clinical studies	
SF-36	Short-Form-36; non specific QoL; 8 components, score 0-100
Exacerbation	Complex of respiratory events reported as adverse events with a duration of 3 or more days
DPI	Dry powder inhaler
MDI	Metered dose inhaler
QoL	Quality of life
PEFR	Peak expiratory flow rate

The main purpose of the studies was to evaluate the short and long term efficacy and safety of tiotropium in COPD patients. The design of the pivotal studies is in accordance with the Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD of the CPMP (CPMP/EWP/562/98). The study duration is long enough and the amount of participants is large. Two placebo-controlled and two active comparator studies are performed (double dummy). The studied dose of 18 µg once daily via the HandiHaler is in agreement with the current application. The comparator ipratropium 40 µg four times a day is an obvious and rational choice since ipratropium is widely used as short-acting anti-cholinergic bronchodilator in COPD patients. The chosen selection criteria provide the participation of "true" COPD patients, and the exclusion of asthma patients.

The chosen efficacy variables; lung function, quality of life, symptoms and exacerbation parameters cover the goals of treatment for COPD patients and are therefore all clinically relevant outcome parameters. The choice of the primary efficacy variable, trough FEV_1, is not common. However, it is unpractical to perform lung function over 24 hours and wakening patients for lung function measurements may influence the results. Therefore 24-hour FEV_1 measurements are not first choice in large long-term trials. In smaller studies, 6,12, and 24-hour measurements were performed to assure the long lasting bronchodilatory effect. Hence, it is reasonable to choose trough FEV_1 as one of the primary efficacy parameters for a long-acting bronchodilator in large long-term studies.

The other -secondary- lung function efficacy variables provide information about the maximal bronchodilatory effect and the duration of action. Health related quality of life was assessed by the SGRQ and by the questionnaire Multiple Outcomes Survey Short Form-36. Both questionnaires are widely used in the international literature. The SGRQ is an established, validated, reproducible COPD specific instrument and is cited in the CPMP points to consider document and international COPD treatment guidelines* The questionnaire scores responses on many questions divided over 3 domains; symptoms, activity and impacts. Furthermore, a total score is calculated. The score ranges form 0 to 100; the higher the score, the worse the quality of life. Based on the literature, the threshold for clinical significance is 4 units, in total score as well as in impact score. . The SF-36 is a well-established non-disease specific questionnaire to assess quality of life in eight domains. The score ranges from 0-100, the higher the score, the better the quality of life.

"Symptoms" are studied with several tools: the Mahler dyspnea index**, the symptom score, the night-time awakenings, the salbutamol rescue use, the energy fatigue questionnaire and with the physician's global evaluation. The BDI describes the grade of breathing difficulty at baseline by scoring three components; functional impairment, magnitude of task and magnitude of effort The score varies for each component from 0 to 4. The focal score is the sum of the components (0 to 12). The TDI is an evaluative instrument that describes the changes in scores compared to baseline. The changes vary from minus 3 to plus 3, hence the TDI focal score varies from minus 9 to plus 9. One unit difference is supposed to be clinically meaningful. An interviewer determines the score based on the answers of the patient. The validity, reliability, and responsiveness of the Mahler dyspnea index have been shown satisfactory.

The frequency and severity of exacerbations is considered more and more of importance in the treatment of COPD patients. In all studies, a clear and acceptable definition of "exacerbation" is determined beforehand. The incidence of exacerbations is of course dependent on the exposure time, and therefore the company calculated the number of exacerbations and the number of hospitalisations (days) expressed in exposure units.

The statistical model was analysis of covariance with terms for treatment, centre, and treatment-by-centre interaction. The intent-to-treat principle is used in the efficacy analysis. Since both placebo-controlled and both comparator-controlled studies used the same design, the two are analysed as combined studies. The null hypothesis was that there is no difference between placebo/ipratropium and tiotropium in mean trough FEV_1 response after 13 weeks. The alternative hypothesis was that the mean trough FEV_1 response is greater with tiotropium than with placebo/ipratropium. The sample sizes were chosen to expose adequate numbers of patients to tiotropium for one year for safety evaluation (at least 300 patients over six months and 200 patients over one year). Of course, sample sizes addressed efficacy considerations too. The magnitude of a clinically meaningful improvement in trough FEV_1 for COPD patients is difficult to determine. Therefore,

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- European Respiratory Society guideline- ERS 1995
- American Thoracic Society guideline -ATS 1995

** The Mahler dyspnea index is a described extensively in "Clinical measurement of dyspnea" (volume 137, page 271).

in the protocols calculations were provided to ensure that a range of possible values that could be considered clinically meaningful could be detected with at least 90% power. Based on previous studies of up to four-week duration the standard deviation at three months was expected to be 170 ml. This supported an improvement in trough FEV_1 as little as 56 ml at 5% level of significance and 90% power.

Efficacy

Baseline characteristics
All baseline patient characteristics such as age (±65 years) and sex were similar in the two placebo-controlled studies as well as in the two comparator studies. In total 906 patients were treated with tiotropium, 179 with ipratropium and 371 with placebo. The mean FEV_1 of the participants was 1.0 and 1.2 litre in the placebo-controlled and in the comparator studies respectively, which means that mainly patients with severe COPD participated. The patients in the placebo trials had more cigarette pack years (63 years) than those in the ipratropium trials (34 years). The results for the two placebo-controlled studies as well as for the two comparator trials were consistent and therefore results can be pooled.

Lung function
All lung function data over one year show that tiotropium therapy results in a statistically significant long term bronchodilator efficacy in comparison to placebo as well as to ipratropium. The primary efficacy variable, mean trough FEV_1 response, with tiotropium is 0.11 and 0.12 litre in the placebo and comparator trials respectively. The peak response with tiotropium is 0.26 and 0.31 litre in the placebo and comparator studies respectively. This response is not only statistically significant but also clinically relevant. A small improvement of 110-260-310 ml in FEV_1 implicates a much larger improvement in airway resistance in patients with a low baseline FEV_1. The mean trough FEV_1reached a steady state after one-week tiotropium treatment and remained the same during the following year. The secondary efficacy lung function variables confirm the results of the primary efficacy variable. The results after 13 weeks are similar to those after one-year study.

Efficacy results over 1 year of the four pivotal studies				
	Placebo 205.114/117 and 205.115/128	**Tiotropium** 205.114/117 and 205.115/128	**Ipratropium** 205.122/126A and 205.122B/126B	**Tiotropium** 205.122/126A and 205.122B/126B
Lung function				
Trough FEV1 response (l)(SE)	-0.04 (0.01)	0.11 (0.01)*	-0.03 (0.01)	0.12 (0.01)*
Average FEV1 response (l)(SE)	-0.02 (0.01)	0.19 (0.01)*	0.13 (0.01)	0.23 (0.01)*
Peak FEV1 response (l)(SE)	0.04 (0.01)	0.26 (0.01)*	0.21 (0.01)	0.31 (0.01)*

Trough FVC response (l)(SE)	-0.04 (0.02)	0.26 (0.02)*	0.11 (0.04)	0.32 (0.03)*
Trough FEV1 (l)	1.0 to 1.0	1.0 to 1.1*	1.2 to 1.2	1.2 to 1.3*
Peak FEV1 (l)	1.0 to 1.1	1.0 to 1.3*	1.2 to 1.4	1.2 to 1.5*
PEFR morning (l/min)	193 to 206	192 to 227*	252 to 257	263 to 273*

Efficacy results over 1 year of the four pivotal studies				
	Placebo 205.114/117 and 205.115/128	**Tiotropium** 205.114/117 and 205.115/128	**Ipratropium** 205.122/126A and 205.122B/126B	**Tiotropium** 205.122/126A and 205.122B/126B
Symptoms				
TDI focal score (SE)	-0.09 (0.15)	1.06 (0.12)*	-0.44 (0.23)	0.46 (0.16)*
BDI focal score	6.2 to 6.1	6.0 to 7.1*	7.4 to 7.0	7.1 to 7.6*
Percentage of patients with a TDI focal score ≥ 1	29	46*	18	31*
Mean number of rescue salbutamol weekly	3.6 to 4.1	3.6 to 3.2*	2.7 to 2.6	2.7 to 2.2
Energy fatigue quest, severity of condition: fatigue level: energy level:	 2.9 to 3.0 3.3 to 3.3 3.0 to 3.0	 2.9 to 3.1 3.3 to 3.4* 3.0 to 2.9*	 3.5 to 3.3 3.4 to 3.4 2.7 to 2.7	 3.5 to 3.6* 3.4 to 3.5 2.7 to 2.6
Symptom score wheezing	0.8 to 0.9	0.8 to 0.8*		
Symptom score Shortness of breath	1.5 to 1.7	1.5 to 1.5*		
Mean number of awakenings per night (13 weeks)	0.5 to 0.4	0.5 to 0.3*		
Physician's global evaluation	4.5 to 4.6	4.5 to 5.0*		
Mean COPD symptom scores	0.82 to 0.94	0.82 to 0.79*		
Withdrawals (%)	27.8*	18.7	21.2	15.2
Efficacy results over 1 year of the four pivotal studies ***Quality of life***				
	Placebo	**Tiotropium**	**Ipratropium**	**Tiotropium**

	205.114/117 and 205.115/128	205.114/117 and 205.115/128	205.122/126A and 205.122B/126B	205.122/126A and 205.122B/126B
SGRQ symptoms	59 to 58	59 to 55*	53 to 51	53 to 47
SGRQ activities	64 to 64	64 to 60*	58 to 56	58 to 55
SGRQ impacts score	33 to 34	33 to 30*	35 to 35	35 to 31*
Efficacy results over 1 year of the four pivotal studies ***Quality of life***				
	Placebo	**Tiotropium**	**Ipratropium**	**Tiotropium**
SGRQ total score	47 to 47	47 to 44*	45 to 44	45 to 41*
% of patients with change ≥4 in SGRQ total score	30	49*	35	52*
SF-36 physical sum.	35 to 33	35 to 36*	39 to 38	39 to 40*

Exacerbations				
% of patients with hospitalizations	9	6*	12	7*
% of patients with oral steroid courses	25	16*	28	22
% of patients with exacerbations	42	36*	46	35*

**p=0.05.*
SGRQ; the lower the score, the better QoL, SF-36; the higher the score, the better QoL

Symptoms
The results of the Mahler's dyspnea scores over the whole year show a statistically significant beneficial effect of tiotropium compared to placebo. This is valid for the focal score as well as for the three different components: functional impairment, magnitude of task and magnitude of effort. The difference in focal score varies trough the year from 0.81 to 1.14 between tiotropium and placebo. Seventeen percent more patients experienced meaningful benefits in dyspnea score (TDI) with tiotropium compared to placebo. This beneficial efficacy on dyspnea score of tiotropium is supported by the results of the COPD symptom scores, the energy fatigue score, the number of rescue medication, the number of nocturnal awakenings and the physician's global evaluation. Although the results are rather small, they are considered clinically relevant. For patients with a chronic disease such as COPD any benefit with respect to symptoms is important in daily life. The results of tiotropium on symptoms compared to ipratropium follow the results

compared to placebo, yet the differences are smaller. Tiotropium is at least as good, or on several points even better than ipratropium with respect to symptoms.

Quality of life
The results of the disease specific SGRQ clearly shows a beneficial efficacy of tiotropium in quality of life compared to placebo as well as compared to ipratropium. Quality of life is considered an important parameter for treatment in patients with COPD. With tiotropium 19 and 17%, more patients experienced a clinically meaningful improvement in quality of life than with placebo and ipratropium respectively. It is noted that in the placebo-group, only in the first 3 months, an improvement in SGRQ score is seen as well. The physical data of the SF-36 questionnaire support the beneficial efficacy of tiotropium on quality of life in general.

Exacerbations
Fewer patients experienced exacerbations and hospitalisations with tiotropium than with placebo or ipratropium. After normalisation for the extent of exposure, the number of exacerbations per 100 patient years was 76 in the tiotropium group and 95 in the placebo group ($p<0.05$). The number of exacerbation days was not different in the one-year placebo controlled trials but reduced with tiotropium in the one-year ipratropium controlled trials. Kaplan-Meier curves have shown that the propensity for an exacerbation or hospitalisation is reduced with tiotropium. Tiotropium delays the occurrence of an exacerbation.

Efficacy in subgroups
Many drug-demographic interactions were evaluated; age, gender, race, duration of disease, previous ipratropium use and smoking history. Analysis was performed for trough, average and peak FEV_1, and additionally for health related quality of life and dyspnea index. Tiotropium was equally effective in subgroups based on these several demographic parameters. For smoking habits, the differences appear large, yet the variability is also large and consequently the differences are not statistically significant. Furthermore, subgroup analysis was performed with respect to the severity of disease. Tiotropium appears to be more effective in COPD patients with FEV_1<50% of the predicted value than in patients with an FEV1 value> 50% predicted likely a result of patients with lower lung function being more symptomatic.

Safety
Safety data are available from the four large pivotal studies, from the two salmeterol-compared studies, from the supportive additional studies and the pharmacodynamic studies. Safety was monitored through adverse event reporting, vital signs, physical examinations, laboratory testing (blood and urine sampling) and electrocardiograms. One phase III trial (205.123) included 24-hour Holter monitoring. The primary safety evaluation is based on the four pivotal studies.

Adverse events
The expected anticholinergic events are; dry mouth, tachycardia, urinary retention, constipation, and glaucoma. Drug- related adverse events occurred in 19% of the patients in the tiotropium group compared to 9% in the placebo group. In the active controlled trials, 21% of the patients in the tiotropium group reported drug-related adverse events in comparison with 12 % of the patients in the ipratropium group. The adverse event occurring statistically significantly more often in the tiotropium

group was “dry mouth/throat”. This adverse event was an expected anti-cholinergic effect. However, the events of dry mouth are more frequently reported during tiotropium therapy than during ipratropium therapy. The same pattern was noted for the complaint “constipation” for tiotropium vs. placebo in the one-year trials but not in the one-year ipratropium-controlled trials. The absolute number of patients with constipation is less than the number with dry mouth problems. Urinary retention occurred in only four elderly patients with tiotropium therapy and none with placebo or ipratropium treatment. Glaucoma was reported in three patients in the tiotropium group compared with one in the placebo group and none in the ipratropium group, however there was no imbalance in glaucoma reports Patients with a prior history of glaucoma were excluded. No effect of tiotropium on heart rate or rhythm was seen except for a slight increase in tachycardia in the placebo-controlled trials. Furthermore, there appeared to be an increased incidence in pharyngitis, sinusitis and moniliasis. This may be related to the drying of the mucous membranes. Another explanation may be that due to the bronchodilating effect of tiotropium more respiratory infections are reported as upper airway rather than lower airway problems

No paradoxical bronchospasm was observed in any of the patients. No differences were seen in laboratory values, electrocardiograms, vital signs, or physical examination.
Less patients in the tiotropium group discontinued the study due to adverse events than in the placebo and ipratropium group.

Adverse events (% of patients)				
	Tiotropium vs placebo		Tiotropium vs ipratropium	
	Placebo	**Tiotropium**	**Ipratropium**	**Tiotropium**
Dry mouth	3	16	6	12
Epistaxis	2	4	1	1
Pharyngitis	7	9	3	7
Rhinitis	5	6	2	3
Sinusitis	9	11	2	3
Dysphonia	0	2	1	1
Upper airway infection	37	41	35	43
Moniliasis	2	4	2	3
Constipation	1	3	1	1
Urinary tract infection	5	7	2	4
Adverse events leading to discontinuation	14	10	12	10

Deaths
Adverse events leading to death occurred in 26 out of the 1456 participants. None of the deaths was considered drug-related

Salmeterol-compared studies

Study design and methodology

The main purpose of the two studies was to confirm the short and long term efficacy and safety of tiotropium in COPD patients and to compare the efficacy with the long-acting bronchodilator salmeterol. The methodology of the studies is very similar to the pivotal studies with placebo and or ipratropium comparison. The comparator salmeterol 50 µg twice a day via the metered dose inhaler is an obvious and rational choice since salmeterol is another long-acting bronchodilator, which is already registered for COPD patients. In the statistics, the ITT principle is used in the analysis. The null hypothesis was rejected when there appeared no difference between placebo, tiotropium and salmeterol. If the null hypothesis was rejected, then the three individual alternative hypotheses were tested. The standard deviation of the trough FEV_1 was 0.2 litre based on prior studies. Nine hundred patients in the two studies should detect a 56 ml difference in mean FEV_1 trough response between salmeterol and tiotropium at a 5% significance level with a power of at least 80%.

Description of the studies and baseline characteristics

Study No.	**Description of the studies**	**Number of patients**	**Base-line FEV_1)**
205.130/	Efficacy/safety 6-months study in COPD. Double-blind, double-dummy, randomised, placebo-controlled, parallel group, tiotropium DPI 18 µg once a day, salmeterol 50 µg MDI twice a day	Tiotropium-arm: 209 Salmeterol-arm: 213 Placebo-arm: 201	Tiotropium-arm: 1.1 Salmeterol-arm: 1.1 Placebo-arm: 1.1
205.137/	Efficacy/safety 6-months study in COPD. Double-blind, double-dummy, randomised, placebo-controlled, parallel group, tiotropium DPI 18 µg once a day, salmeterol 50 µg MDI twice a day	Tiotropium-arm: 193 Salmeterol-arm: 192 Placebo-arm: 199	Tiotropium-arm: 1.1 Salmeterol-arm: 1.0 Placebo-arm: 1.1

Efficacy

All baseline patient characteristics such as age, sex, and lung function were similar in the two studies. The long-term efficacy results are summarised in the next table.

Efficacy results over six months of the two-salmeterol studies

	Placebo 205.130	**Tiotropium** 205.130	**Salme-terol** 205.130	**Placebo** 205.137	**Tiotropium** 205.137	**Salme-terol** 205.137
Lung function						
Trough FEV1 response (l)(SE)	-0.03 (0.02)	0.11(0.01)*#	0.05 (0.01)*	-0.03 (0.02)	0.07 (0.02)*	0.05 (0.02)*
Average FEV1 response (l)(SE) 0-3	0.01 (0.02)	0.19 (0.02)*#	0.15 (0.02)*	0.01 (0.02)	0.22(0.02)*#	0.14 (0.02)*

hour						
Average FEV1 response (l)(SE) 0-12 hour	-0.02 (0.02)	0.20 (0.02)*#	0.12 (0.02)*			
Peak FEV1 response (l)(SE) 0-3 hours	0.08 (0.02)	0.27 (0.02)*#	0.21 (0.02)*	0.08 (0.02)	0.30 (0.02)*#	0.21 (0.02)*
Trough FVC response (l)(SE)	-0.02 (0.03)	0.23 (0.03)*#	0.12 (0.03)*	-0.03 (0.03)	0.15 (0.03)*	0.10 (0.03)*
PEFR morning (l/min)	224 to 234	228 to 261*	226 to 255*	254 to 255	252 to 272*	245 to 278*

Symptoms						
	Placebo 205.130	**Tiotropium** 205.130	**Salme-terol** 205.130	**Placebo** 205.137	**Tiotropium** 205.137	**Salme-terol** 205.137
TDI focal score (SE)	-0.63 (0.31)	0.39 (0.28)*#	-0.39 0.28)*	-0.42 (0.29)	0.80 (0.28)*	0.85 (0.29)*
Patients with TDI focal score ≥ 1 (%)	26	42*	35	33	45*	48*
Mean number of rescue salbutamol weekly	3.2 to 4.5	3.3 to 3.0*	4.0 to 3.0*	2.7 to 3.4	3.2 to 3.3	3.1 to 2.9
Symptom score wheezing	0.9 to 1.0	0.9 to 0.8*	0.9 to 0.8*	0.8 to 0.8	0.8 to 0.8	0.8 to 0.8
Symptom score shortness of breath	1.4 to 1.5	1.5 to 1.2*#	1.5 to 1.3*	1.5 to 1.4	1.6 to 1.4	1.5 to 1.3
Physician's global evaluation	4.6 to 4.4	4.5 to 5.0*	4.5 to 4.8*	4.6 to 4.6	4.4 to 4.7	4.4 to 4.7

Quality of life						
SGRQ symptoms	53 to 51	54 to 44*	52 to 46*	49 to 46	47 to 44	48 to 44
SGRQ activities	63 to 59	61 to 59	61 to 58	58 to 59	60 to 56*	60 to 57
SGRQ impacts score	35 to 31	33 to 29*#	33 to 31*	33 to 33	34 to 31	33 to 32
SGRQ total score	47 to 43	45 to 40*	45 to 42	43 to 43	45 to 41*	44 to 42
Patients with change ≥4 in SGRQ total score (%)	42	51*#	40	37	46	47

Exacerbations						
Events/100 patient years	149	107*	123	135	111	110
Event days/100 pat years	2500	1724*	2408	2076	1677	2015
Patients with hospitalisations (%)	6	3	5	4	4	5

Withdrawals due to exacerbation (%)	17.9	5.7	13.6	14.1	8.8	16.1
Patients with exacerbations (%)	39	32	35			

- p<0.05 to placebo, # tiotropium to salmeterol

All lung function data over six months clearly show that tiotropium as well as salmeterol therapy results in statistically significant long term bronchodilator efficacy in comparison to placebo. Most lung function variables show a statistically significant benefit of tiotropium compared to salmeterol. Many patients experienced a meaningful benefit in dyspnea score (TDI) with tiotropium and salmeterol compared to placebo. Tiotropium shows a beneficial trend compared to salmeterol. The beneficial efficacy on dyspnea score of tiotropium and salmeterol is supported by the results of the number of rescue medication, the number of withdrawals and the physician's global evaluation. Although the results are rather small, they are considered clinically relevant since any benefit with respect to symptoms is important in daily life for patients with a chronic disease such as COPD. The results of the disease specific SGRQ shows a beneficial efficacy of tiotropium in quality of life compared to placebo. In the data of salmeterol only a positive trend is seen. Quality of life is considered an important parameter for treatment in patients with COPD. With tiotropium more patients experienced a clinically meaningful improvement in quality of life than with placebo and salmeterol (change $\geq$ 4). Fewer patients experienced with tiotropium treatment exacerbations and hospitalisations than with placebo. Salmeterol shows only a positive trend.

Safety

The safety profile in the salmeterol compared studies shows similar results as in the four pivotal studies.

OVERALL CONCLUSION ON QUALITY, EFFICACY, SAFETY AND BENEFIT/RISK ASSESSMENT

Quality

The chemical-pharmaceutical documentation shows that Spiriva 18 µg can be produced with consistent and sufficient quality. The blister package allows to take one capsule at a time, so the inhalation powder in the other capsules remains protected from moist air. The shelf life is 18 month when stored below 25 ºC. The inhalation powder is administered by means of the HandiHaler, a device specially developed for Spiriva capsules.

Preclinical pharmacology and toxicology

In preclinical experiments, tiotropium acts like ipratropium as a selective and reversible muscarine receptor antagonist. Its is up to 3 times more potent (based on weight) than ipratropium and has a marked longer duration of action. Besides dry mouth, systemic anticholinergic effects do not occur at doses within the therapeutic range. In acute inhalation studies, tiotropium has a low order of toxicity. Repeated dose toxicity studies revealed anticholinergic effects that affected the gastro-intestinal and urogenital tracts, the heart and the eyes. Repeated dose toxicity studies revealed anticholinergic effects that affected the gastro-intestinal and the urinogenital tracts, the heart and eyes. Other relevant effects were mild irritation of the respiratory tract and prostatitis in rats.

In rats and rabbits, reproductive toxicity of tiotropium bromide was shown at maternally toxic dose levels. Reproductive effects were reduced ovulation, reductions in implantation rates, reduced in utero survival and litter sizes, reduced ossification of sternebrae, foetuses with 13th rib, and delays in development of sexual maturity and behavioural developmental parameters.
No genotoxic or oncogenic potential was demonstrated.

Clinical pharmacodynamics
Four dose response studies were performed in COPD patients and four additional pharmacodynamic studies. The three single dose trials provided an assessment of acute response and provided the spectrum of doses to evaluate in longer-term studies. The studies were not powered to statistically differentiate inter-dose effects. However, the efficacy and safety findings of the multiple dose ranging trial and the consistent dose ordering observed in the single dose ranging trials do provide guidance for dose selection of 18 µg for phase III trials. A dose of 9 µg appeared less effective than 18 µg, and 36 µg showed a trend in more adverse events than the dose of 18 µg.
The other pharmacodynamic studies showed that within one week lung function reached a steady state. Furthermore, there was no difference in bronchodilator effect between the time of dosing (AM or PM). The study with the HandiHaler showed that almost all COPD patients could generate a flow large enough to use the HandiHaler properly.

Clinical Pharmacokinetics
The pharmacokinetics of tiotropium appeared difficult to assess due to the low plasma concentrations. When using a sensitive analytical method plasma levels were often below the limit of quantitation. In urine higher amounts are found, so pharmacokinetic evaluation is mainly based on data from urine samples. The absolute bioavailability of tiotropium after inhalation is about 20% and after oral administration only 2-3%. Distribution after inhalation is fast and the protein binding is about 74%. The terminal half-life was estimated on 4 to 5 days. Steady state is reached between 7 and 14 days. Studies in geriatric COPD patients showed no clinically significant difference in plasma concentrations than in younger patients. Studies in patients with renal failure showed that maximum concentrations and AUC increased with decreasing renal function and amount excreted in urine in the first 4 hours decreased more pronounced than at later time points. As a overall result the renal clearance of unchanged tiotropium decreased proportional with the creatinine clearance. Therefore, a warning is enclosed in the SPC.

Clinical efficacy
The design of the pivotal studies is in accordance with the Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with COPD of the CPMP.
The study duration is long enough and the amount of participants is large. Two placebo-controlled and four active comparator studies are performed. The studied dose of 18 µg once daily via the HandiHaler is in agreement with the current application. The comparator ipratropium and salmeterol is an obvious and rational choice since ipratropium is widely used as short-acting anti-cholinergic bronchodilator in COPD patients and salmeterol is widely used as long-acting sympathicomimetic bronchodilator in COPD patients. The chosen selection criteria provide the participation of "true" COPD patients, and the exclusion of asthma patients. The chosen efficacy variables; lung function, quality of life, symptoms and exacerbation parameters cover the goals of treatment for COPD patients and are

therefore all clinically relevant outcome parameters. The instruments that are used to study the efficacy variables are valid. The statistics are performed properly.

All lung function data over one year clearly show that tiotropium therapy results in statistically significant long term bronchodilator efficacy in comparison with both placebo and ipratropium. The primary efficacy variable mean trough response with tiotropium is 0.11 and 0.12 litre in the placebo and comparator trials respectively. The peak (and average) response with tiotropium is 0.26 (average; 0.19) and 0.31 (average; 0.23) litre in the two pooled studies. These lung function results are clinically relevant since a small improvement of 110-260-310 ml in FEV1 implicates a much larger improvement in airway resistance in patients with a low baseline FEV1.

The results of the Mahler's dyspnea scores over the whole year show a statistically significant beneficial effect of tiotropium compared to placebo. This beneficial efficacy on dyspnea score of tiotropium is supported by the results of the COPD symptom scores, the energy fatigue score, the number of rescue medication, the number of nocturnal awakenings and the physician's global evaluation. The results of the disease specific SGRQ show a beneficial efficacy of tiotropium in quality of life compared to placebo.

The results of tiotropium on symptoms and quality of life compared to the results with ipratropium, follow the results compared to placebo, yet the differences are smaller. Tiotropium is at least as good, or on several points even better than ipratropium. Fewer patients experience exacerbations and hospitalizations with tiotropium treatment than with placebo or ipratropium. Fewer exacerbations occurred with tiotropium per 100 patient years. Furthermore, tiotropium delays the occurrence of an exacerbation. The results of the salmeterol-compared studies confirm that tiotropium improves lung function, symptoms, quality of life and exacerbations. Furthermore, the efficacy results of tiotropium with respect to lung function, symptoms, and quality of life are at least as good as the results of salmeterol therapy.

Clinical safety

Safety data show that during tiotropium treatment anticholinergic events occur, especially dry mouth, more often than with ipratropium therapy. In most cases, the complaints of dry mouth are temporarily. There is a small increase in incidence of pharyngitis, sinusitis, and moniliasis during tiotropium. This may be related to the drying of the mucous membranes. This higher incidence of upper airway infections is mentioned in the SPC text.

Benefit/risk assessment

The beneficial efficacy of tiotropium with respect to lung function, symptoms, quality of life, and exacerbations in patients with COPD is not only statistically significant but also clinically relevant in the treatment of COPD patients. The efficacy of tiotropium is favourable in comparison with ipratropium and as least as good as salmeterol. Anticholinergic adverse events occur more often with tiotropium than with ipratropium especially for dry mouth, which is in most cases temporarily. Furthermore, upper airway infections are reported more often. However, since the adverse events are not very serious, the safety profile is acceptable. Therefore, it is concluded that the benefit/risk assessment is positive.

PUBLISHED CLINICAL STUDIES

Vincken W, van Noord JA, Greefhorst APM, Bantje ThA, Kesten S, Korducki L and Cornelissen PJG. Improved Health Outcomes in Patients with COPD During 1 yr's Treatment With Tiotropium. Eur Respir J. 2002;19: 209-216.

Casaburi R, Mahler DA, Jones PW, Wanner A, San Pedro G, Zuwallack RL, Menjoge SS, Serby CW and Witek TJ. A Long-Term Evaluation of Once-Dai1y Inha1ed Tiotropium in Chronic Obstructive Pulmonary Disease. Eur Respir J. 2002; 19:217-224.

Casaburi R, Briggs, Jr DD, Donohue JF, Serby CW, Menjoge SS, Witek TJ, Jr. for the US tiotropium study group. The spirometric efficacy of once dai1y dosing with tiotropium in stable COPD: A 13-week multi-center trial. Chest 2000; 118:1294-1302.

Littner MR, Ilowite JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, Witek TJ, Jr. Long-acting bronchodilation with once dai1y dosing of tiotropium (SpirivaTM) in stable COPD. Am J. Respir Crit Care Med 2000; 161:1136-1142.

Van Noord JA, Bantje ThA, Eland ME, Korducki L, Cornelissen PJG. A randomised controlled comparison of tiotropium and ipratropium in the treatment of COPD. THORAX 2000; 55: 289-294.

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