SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
BRONTIO 18 mcg Capsules with Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Each capsule with inhalation powder contains 0.022 milligrams tiotropium bromide equivalent to 0.018 milligrams tiotropium.
Excipient(s) with known effect:

Lactose monohydrate (from bovine milk)	9.893 mg
Lactose monohydrate (Lactohale 300) (from cow's milk)	0.085 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Light green, opaque, No.3 HPMC capsules with a white or off-white homogenous powder mixture.

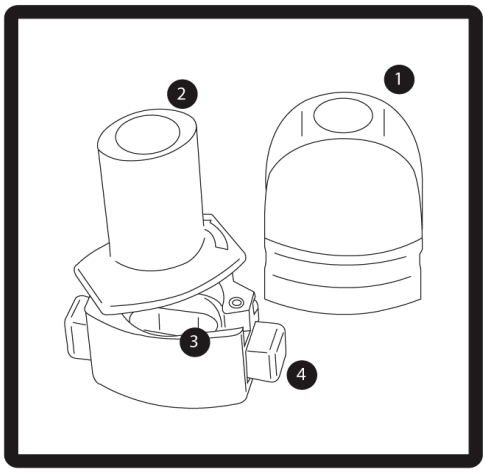
4. CLINICAL PARTICULARS
4.1 Therapeutic indications
When used regularly in moderate and severe COPD cases, BRONTIO reduces the frequency of attacks, improves symptoms and quality of life, but does not change the long-term decline in FEV_1.

4.2 Posology and method of administration
This medicine should only be used by inhalation.

Adults:
Posology/frequency and duration of administration
The recommended dosage of BRONTIO is inhalation of the contents of 1 capsule once daily.
The recommended dose should not be exceeded.

Method of administration
Inhalation should be done at the same time every day, using the inhaler device.
The capsules are not for oral administration.
BRONTIO capsules must not be swallowed.
To ensure proper use of this medicine, the patient must be trained by the doctor or other healthcare professional on how to use this inhaler.

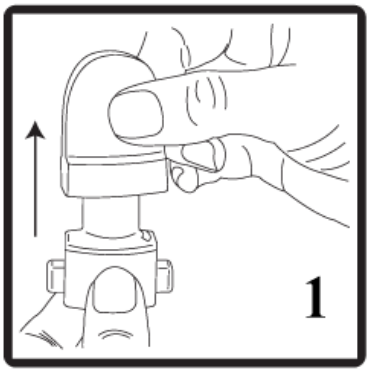
Parts of Inhaler

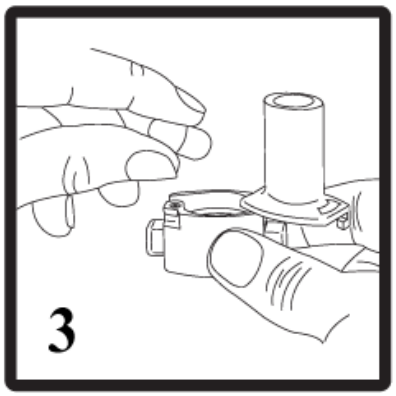
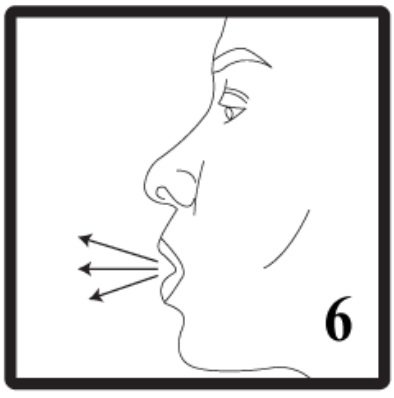


1. Cover
2. Mouthpiece
3. Capsule chamber
4. Piercing side buttons

Use of inhaler

Follow your doctor's instructions carefully while using BRONTIO.
The inhaler device is a special configured device for the inhalation of BRONTIO capsules.
It should not be used for any other medicine or purpose.

	1. Pull off the cap.
	2. Hold the base of the device firmly and turn the mouthpiece in the arrow direction to open.

	3. Take one capsule out of the blister strip just before use. Place this capsule into the capsule-shaped chamber at the base of the device.
	4. Close capsule chamber by turning the mouthpiece.
	5. Hold the device in the upright position with the mouthpiece facing upward and simultaneously press the side buttons ONLY ONCE. Leave the buttons after the capsule is pierced. Please note: The capsule might splinter at this step and small capsule fragments might get into your mouth or throat during inhalation. However, the capsule is edible and therefore not harmful. Removing the capsule from its pack right before use and pressing the buttons only once will minimize the splintering risk of the capsule (see step 3).
	6. Breathe out fully.

	7. Place the mouthpiece in your mouth and tilt your head slightly backwards. Close your lips firmly around the mouthpiece and inhale as quickly and deeply as you can. While the powder disperses, you will hear a "whirr" sound because the capsule spins around in the space above the chamber. If you do not hear this whirring noise, the capsule may be stuck in the chamber. In this case, open the capsule chamber and loosen the capsule by moving it in its chamber. DO NOT PRESS the buttons more than once to release the capsule if it is jammed.
8. After hearing the "whirr" sound, hold your breath for as long as possible without discomfort while removing the device from your mouth. Then continue breathing normally. Open the device and check if there is any powder left inside the capsule. If there is, then repeat steps 6, 7 and 8.	
9. After use, discard the empty capsule and close the mouthpiece.	

Cleaning of device:
Wipe the mouthpiece and capsule chamber with a DRY and clean cloth to remove any remaining powder particles. A clean and soft brush can also be used for this purpose.
The capsules should not be exposed to high temperatures.
BRONTIO capsules contain a small amount of powder and therefore they are only partially filled.

Additional information on special populations
Renal impairment
Renally impaired patients can use BRONTIO at the recommended dose. In patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min), the use of BRONTIO should be monitored closely (see sections 4.4 "Special warning and precautions for use" and 5.2 "Pharmacokinetic properties").

Hepatic impairment
Hepatically impaired patients can use BRONTIO at the recommended dose (see section 5.2).

Pediatric population
BRONTIO cannot be used in patients under the age of 18 in case of COPD.
The safety and efficacy of BRONTIO for cystic fibrosis in children and adolescents have not been established. No data are available.

Geriatric population
Elderly patients can use BRONTIO at the recommended dose.

4.3 Contraindications
BRONTIO is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives e.g. ipratropium or oxitropium, or to other components of this medicine (see section 2 and section 6.1 "List of excipients").

4.4 Special warnings and precautions for use
BRONTIO, as a once-daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. as rescue therapy.

Immediate hypersensitivity reactions may occur after administration of BRONTIO.

As with other anticholinergic medications, BRONTIO should be used with caution as it may worsen narrow-angle glaucoma, and may cause urinary difficulties in patients with prostatic hyperplasia or bladder-neck obstruction (see section 4.8).

Inhaled medicines may cause inhalation-induced bronchospasm.

Caution should be exercised in patients with a recent (<6 months) myocardial infarction; in cases of any unstable or life threatening cardiac arrhythmia also requiring intervention or whose treatment has been changed within the last 1 year; or in cases of hospitalization due to heart failure (NYHA Class III or IV) within the last 1 year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action.

Since plasma concentrations increase due to decreased renal function, in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min), BRONTIO should be used only if the expected benefit outweighs the potential risk. There is no long-term experience in patients with severe renal impairment (see section 5.2).

Patients should be instructed on how to use BRONTIO correctly. Patients should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in development or worsening of narrow-angle glaucoma manifested by the acute symptoms such as eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema. Should any combination of these symptoms develop, patients should stop using the medication and consult a specialist immediately. Miotic eye drops are considered not to provide effective treatment.

Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries.

BRONTIO should not be used more frequently than once daily (see section 4.9).

BRONTIO capsules should only be used with the monodose inhaler device.

Each BRONTIO capsule contains 9.978 mg lactose monohydrate. Patients with rare heredity problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption must not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Although no regular drug interaction studies have been conducted, inhalation powder of tiotropium bromide has been used concomitantly with other medications commonly used in the treatment of COPD without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids.

Long-acting beta agonists or inhaled corticosteroids have not been found to alter tiotropium exposure.

The co-administration of tiotropium with other anticholinergic-containing drugs has not been studied and is therefore not recommended.

Additional information on special populations

No specific data available.

Pediatric population
No specific data available.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category is "C".

Women of childbearing potential / Contraception
Women of childbearing potential should use medically effective forms of birth control methods during treatment.

Pregnancy
There are no data based on adequate and well-controlled studies regarding its use in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see section 5.3). BRONTIO should not be used during pregnancy unless the potential benefits outweigh the potential risk to the fetus.

Animal studies are insufficient regarding effects on pregnancy /and-or/ embryonal/fetal development /and-or/ parturition /and-or/ postnatal development. The potential risk for humans is unknown.

Breastfeeding
It is unknown whether tiotropium bromide is excreted in human breast milk. Despite studies in rodents which have demonstrated that excretion of tiotropium bromide in breast milk occurs only in small amounts, use of BRONTIO is not recommended during breast-feeding. Tiotropium bromide is a long-acting compound. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with BRONTIO should be made taking into account the benefit of breast-feeding to the child and the benefit of BRONTIO therapy to the woman.

Fertility
No clinical data on fertility are available for tiotropium. In a non-clinical study with tiotropium, no adverse reactions with respect to fertility were observed (see section 5.3). Reproductive studies in rats or rabbits showed that harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels.

4.7. Effects on ability to drive and use machines
No studies regarding the effects on the ability to drive and operate machinery have been performed. Occurrence of dizziness, blurred vision, or headache may affect the ability to drive and use machines.

4.8. Undesirable effects
Summary of the safety profile
Many of the listed undesirable effects can be attributed to the anticholinergic properties of tiotropium.

Tabulated summary of adverse reactions
The frequencies assigned to the undesirable effects listed below are based on crude incidence rates of

adverse drug reactions (i.e. events attributed to tiotropium) observed in the tiotropium group (9,647 patients) from 28 pooled placebo-controlled clinical trials covering the treatment periods ranging from 4 weeks to 4 years.

Frequency is defined using the following convention:
Very common : (≥1/10)
Common : (≥1/100 to <1/10)
Uncommon : (≥1/1,000 to <1/100)
Rare : (≥1/10,000 to <1/1,000)
Very rare : (<1/10,000)
Not known : cannot be estimated from the available data.

Metabolism and nutrition disorders
Not known: Dehydration

Nervous system disorders
Uncommon: Dizziness, headache, taste disorders
Rare: Insomnia

Eye disorders
Uncommon: Vision blurred
Rare: Glaucoma, intraocular pressure increased

Cardiac disorders
Uncommon: Atrial fibrillation
Rare: Supraventricular tachycardia, tachycardia, palpitations

Respiratory, thoracic and mediastinal disorders
Uncommon: Pharyngitis, dysphonia, cough
Rare: Bronchospasm, epistaxis, laryngitis, sinusitis

Gastrointestinal disorders
Common: Dry mouth
Uncommon: Gastroesophageal reflux disease, constipation, oropharyngeal candidiasis
Rare: Intestinal obstruction (including ileus paralytic), gingivitis, glossitis, dysphagia, stomatitis, nausea
Not known: Dental caries

Skin and subcutaneous tissue disorders
Uncommon: Rash
Rare: Urticaria, pruritus, angioedema
Not known: Skin infection and skin ulcer, dry skin

Immune system disorders
Rare: Hypersensitivity (including immediate reactions)
Not known: Anaphylactic reaction

Musculoskeletal and connective tissue disorders
Not known: Joint swelling

Renal and urinary disorders
Uncommon: Urinary retention, dysuria
Rare: Urinary tract infection

Description of selected adverse reactions
In controlled clinical studies, the commonly observed undesirable effects were anticholinergic undesirable effects such as dry mouth which occurred in approximately 4% of patients.
In 28 clinical trials, dry mouth led to discontinuation in 18 of 9,647 tiotropium treated patients (0.2%).
Serious undesirable effects consistent with anticholinergic effects include glaucoma, constipation and intestinal obstruction including paralytic ileus as well as urinary retention.

Information regarding special populations
Geriatric population
An increase in anticholinergic effects may occur with increasing age.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
High doses of tiotropium may lead to anticholinergic signs and symptoms.

However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg tiotropium in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7-day dosing of up to 170 mcg tiotropium bromide in healthy volunteers. In a multiple-dose study in COPD patients with a maximum daily dose of 43 mcg tiotropium bromide for 4 weeks, no significant undesirable effects have been observed.

Bilateral conjunctivitis in addition to dry mouth was seen in healthy volunteers following repeated once daily inhalation of 141 mcg tiotropium, which resolved while still under treatment. In a multiple-dose study in COPD patients with a maximum daily dose of 36 mcg tiotropium for 4 weeks, the only observed adverse effect attributable to tiotropium was dry mouth.

Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics, tiotropium.
ATC code: R03BB04

Mechanism of action
Tiotropium bromide is a long-acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of

acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly antagonizes the M_3 receptors, resulting in relaxation. Competitive and reversible antagonism has been demonstrated at receptors of human and animal origin and in isolated organ preparations. In preclinical *in vitro* and *in vivo* studies, the bronchoprotective effects were dose-dependent and lasted longer than 24 hours. The long duration is probably due to the very slow dissociation from the M_3 receptor, exhibiting a significantly longer dissociation half-life than ipratropium. As an N-quaternary anticholinergic, tiotropium bromide is topically (broncho-) selective when administered by inhalation, demonstrating an acceptable therapeutic range before systemic anticholinergic effects may occur.

Pharmacodynamic effects
The bronchodilation is primarily a local effect (on the airways), not a systemic one. Dissociation from M_2-receptors is faster than from M_3, which in functional *in vitro* studies, elicited (kinetically controlled) receptor subtype selectivity of M_3over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.

Cardiac electrophysiology
Electrophysiology: In a dedicated QT study involving 53 healthy volunteers, Tiotropium 18 mcg and 54 mcg (i.e. 3 times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

Clinical efficacy and safety
The clinical development program included four 1-year and two 6-month randomized, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year program consisted of 2 placebo-controlled trials and 2 trials with an active control (ipratropium). The two 6-month trials were both, salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnea, exacerbations and health-related quality of life.

Lung function
Tiotropium bromide, administered once daily, provided significant improvement in lung function (forced expiratory volume in one second, FEV_1 and forced vital capacity, FVC) within 30 minutes following the first dose which was maintained for 24 hours. Pharmacodynamic steady state was reached within one week with the majority of bronchodilation observed by the third day. Tiotropium bromide significantly improved morning and evening peak expiratory flow rate (PEFR) as measured by patient's daily recordings. The bronchodilator effects of tiotropium bromide were maintained throughout the one-year period of administration with no evidence of tolerance.

A randomized, placebo-controlled clinical study in 105 COPD patients demonstrated that bronchodilation was maintained throughout the 24 hour dosing interval in comparison to placebo regardless of whether the drug was administered in the morning or in the evening.

Long-term clinical trials (6 months and 1 year)
Dyspnea, exercise tolerance
Tiotropium bromide significantly improved dyspnea (as evaluated using the Transition Dyspnea Index.). This improvement was maintained throughout the treatment period.

The impact of improvements in dyspnea on exercise tolerance was investigated in two randomized,

double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with tiotropium significantly improved symptom-limited exercise endurance time during cycle ergometry at 75% of maximal work capacity by 19.7% (Trial A) and 28.3% (Trial B) compared with placebo.

Health-related quality of life

In a 9-month, randomized, double-blind, placebo-controlled clinical trial of 492 patients, tiotropium improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with tiotropium which achieved a meaningful improvement in the SGRQ total score (i.e. >4 units) was 10.9% higher compared with placebo (59.1% in the SPIRIVA groups vs. 48.2% in the placebo group (p=0.029). The mean difference between the groups was 4.19 units (p=0.001; confidence interval: 1.69-6.68). The improvements of the subdomains of the SGRQ-score were 8.19 units for "symptoms", 3.91 units for "activity" and 3.61 units for "impact on daily life". The improvements of all of these separate subdomains were statistically significant.

COPD exacerbations

In a randomized, double-blind, placebo controlled trial of 1,829 patients with moderate to very severe COPD, tiotropium bromide statistically significantly reduced the proportion of patients who experienced exacerbations of COPD (32.2% to 27.8%) and statistically significantly reduced the number of exacerbations by 19% (1.05 to 0.85 events per patient year of exposure). In addition, 7.0% of patients in the tiotropium bromide group and 9.5% of patients in the placebo group were hospitalized due to a COPD exacerbation (p=0.056). The number of hospitalizations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).

A one-year randomized, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of tiotropium once daily with that of 50 microgram of salmeterol HFA pMDI twice daily on the incidence of moderate and severe exacerbations in 7,376 patients with COPD and a history of exacerbations in the preceding year.

Table 1: Summary of exacerbation endpoints

Endpoint	**Tiotropium 18 mcg N = 3,707**	**Salmeterol 50 mcg N = 3,669**	**Ratio (95% CI)**	**p-value**
Time [days] to first exacerbation†	187	145	0.83 (0.77 - 0.90)	<0.001
Time to first severe (hospitalized) exacerbation§	-	-	0.72 (0.61 - 0.85)	<0.001
Patients with ≥1 exacerbation, n (%)*	1,277 (34.4)	1,414 (38.5)	0.90 (0.85 - 0.95)	<0.001
Patients with ≥1 severe (hospitalized) exacerbation, n (%)*	262 (7.1)	336 (9.2)	0.77 (0.66 - 0.89)	<0.001

† Time [days] refers to 1st quartile of patients. Time to event analysis was done using Cox's proportional hazards regression model with (pooled) center and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) center and treatment as covariate; ratio refers to hazard ratio. Time [days] for the 1st quartile of patients cannot be calculated, because proportion of patients with severe exacerbation is too low.
* Number of patients with event were analyzed using Cochran-Mantel-Haenszel test stratified by pooled center; ratio refers to risk ratio.

Compared with salmeterol, Tiotropium increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001).

Tiotropium also increased the time to the first severe (hospitalized) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

Long-term clinical trials (more than 1 year, up to 4 years)
In a 4-year, randomized, double-blind, placebo-controlled clinical trial of 5,993 randomized patients (3.006 receiving placebo and 2,987 receiving Tiotropium), the improvement in FEV_1 resulting from Tiotropium, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥45 months of treatment in the Tiotropium group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV_1 compared to placebo was similar between Tiotropium and placebo. During treatment, there was a 16% reduction in the risk of death. The incidence rate of death was 4.79 per 100 patient years in the placebo group vs. 4.10 per 100 patient years in the tiotropium group (hazard ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97). Treatment with tiotropium reduced the risk of respiratory failure (as recorded through adverse event reporting) by 19% (2.09 vs. 1.68 cases per 100 patient years, relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 0.999).

5.2 Pharmacokinetic properties
General Characteristics
Tiotropium bromide is a non-chiral quaternary ammonium compound and is sparingly soluble in water. Tiotropium bromide is administered by dry powder inhalation. Generally with the inhaled route of administration, the majority of the delivered dose is deposited in the gastro-intestinal tract, and to a lesser extent in the intended organ of the lung. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption:
Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium) that tiotropium is poorly absorbed from the gastro-intestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-chamberal manner. Steady state trough plasma concentrations were 1.71 pg/ml.

Distribution:
Tiotropium has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium bromide does not penetrate the blood-brain barrier to any relevant extent.

Biotransformation:
The extent of biotransformation is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. The ester tiotropium bromide is non-enzymatically cleaved to the alcohol (N-methylscopine) and acid compound

(dithienylglycolic acid) that are inactive on muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that some further drug (<20% of dose after intravenous administration) is metabolized by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites. This enzymatic pathway can be inhibited by the CYP450 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP450 2D6 and 3A4 are involved in metabolic pathway that is responsible for the elimination of a smaller part of the dose. Tiotropium bromide even in supra-therapeutic concentrations does not inhibit CYP 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A in human liver microsomes.

Elimination:
The effective half-life of tiotropium ranges between 27-45 h in COPD patients. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation by COPD patients to steady-state, urinary excretion is 7% (1.3 mcg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Linearity/Nonlinearity:
Tiotropium demonstrates linear pharmacokinetics in the therapeutic range independent of the formulation.

Characteristics in Patients
Age
Pediatric population:
See section 4.2.

Geriatric population:
As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 ml/min in COPD patients <65 years to 271 ml/min in COPD patients ≥65 years) This did not result in a corresponding increase in $AUC_{0-6,ss}$ or $C_{max,ss}$ values.

Renal impairment
Following once daily inhaled administrations of tiotropium to steady-state in COPD patients, mild renal impairment (CL_{CR} 50-80 ml/min) resulted in slightly higher $AUC_{0-6,ss}$ (between 1.8-30% higher) and similar $C_{max,ss}$ values compared to patients with normal renal function(CL_{CR} >80 ml/min).

In COPD patients with moderate to severe renal impairment (CL_{CR} <50 ml/min), the intravenous administration of tiotropium resulted in doubling of the total exposure (82% higher AUC_{0-4h}) and 52% higher C_{max}) compared to COPD patients with normal renal function, which was confirmed by plasma concentrations after dry powder inhalation.

Hepatic impairment
Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Japanese COPD patients
In cross trial comparison, mean peak tiotropium plasma concentrations 10 minutes post-dosing at steady-state were 20% to 70% higher in Japanese compared to Caucasian COPD patients following inhalation of tiotropium but there was no signal for higher mortality or cardiac risk in Japanese patients compared to Caucasian patients. Insufficient pharmacokinetic data is available for other ethnicities or races.

Pharmacokinetic/Pharmacodynamic Relationship
There is no direct relationship.

5.3 Preclinical safety data
Many effects observed in conventional studies of safety pharmacology, repeated dose toxicity, and reproductive toxicity could be explained by the anticholinergic properties of tiotropium bromide. Typically, reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed in animals. Other relevant effects noted in repeated dose toxicity studies were mild irritation of the respiratory tract in rats and mice evinced by rhinitis and epithelial changes of the nasal cavity and larynx, and prostatitis along with proteinaceous deposits and lithiasis in the bladder in rats.

Harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.

The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity were observed at local or systemic exposures more than 5-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate (from bovine milk)
Lactose monohydrate (Lactohale 300) (from cow’s milk)

No:3 HPMC capsule
Hypromellose
Brilliant blue FCF-FD&C Blue 1
Titanium dioxide
Yellow iron oxide

6.2 Incompatibilities
BRONTIO has no known incompatibilities.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C. Do not freeze the capsules.

Opened sachets should be used within 29 days.

6.5 Nature and contents of container

BRONTIO 18 mcg Capsules with Inhalation Powder are packaged in transparent PVC/PVDC-Alu foil blisters which are packed in Aluminum sachets containing 30, 60 or 90 capsules. Aluminum sachet, monodose dry powder inhaler device and a package leaflet are presented in cardboard boxes.

6.6 Special precautions for disposal and other handling

There are no particular requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2017/604

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 17.08.2017
Date of last renewal :

10. DATE OF REVISION OF THE TEXT