SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Product Name: ATRUS ARVOHALER 18 mcg Inhalation Powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each inhalation dose contains 21.7 microgram Tiotropium bromide anhydrous equivalent to 18 microgram Tiotropium.
Excipient with known effect.
Each inhalation dose contains 5.283 milligram of Lactose (as monohydrate)

3. PHARMACEUTICAL FORM

Inhalation powder
A plastic inhaled with a turquoise cap and mouthpiece, white body and actuation button, dose counter of the remaining number of doses, and 30 dose Al/A1 blister strip filled with white homogenous powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology:

The medicinal product is intended for inhalation use only.
The recommended dose of ATRUS Arvohaler is the inhalation of one inhalation dose once daily.
Inhalation should be at the same time of day each day.
The recommended dose should not be exceeded.
Tiotropium bromide powder is only for inhalation and not for oral intake and must be not swallowed.

Special populations:

Geriatric patients can use Tiotropium bromide at the recommended dose.

Renally impaired patients can use Tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min) see section 4.4 and section 5.2.

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

Paediatric population:
COPD
There is no relevant use in the paediatric population (below 18 years) in the indication state under section 4.1

Cystic fibrosis
The safety and efficacy of Atrus Arvohaler 18 microgram in children and adolescents has not been established. No data are available.

Method of administration:
To ensure proper administration of the medicinal product the patient should be trained how to use the inhaler by the physician or by other healthcare professionals.

Instructions on how to use ATRUS ARVOHALER
Atrus Arvohaler is a device that allows you to inhale a measured dose of powder into your lungs.

As explained in the detailed instructions below, the device is prepared for use by opening the cover and pressing the actuation button on the side. The mouthpiece is placed in the mouth. To ensure a full inhalation, the mouthpiece should be placed on the mouth without leaving a gap. Then, the dose is inhaled. After the inhalation, the cover is securely closed. The actuation button automatically returns to its first position when the cover is closed. The actuation button is locked when the cover is closed.

An unused Arvohaler contains 30 doses of medicine in powder form placed separately in thedevice.

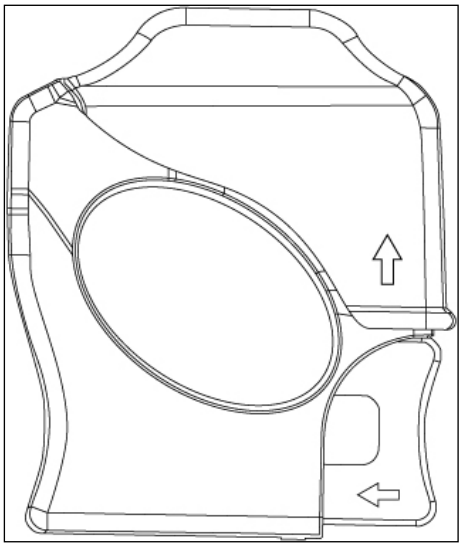
The dose indicator under Arvohaler shows how many doses are left. The doses between 10 and 0 are in red to warn you when the device is low on medicine.

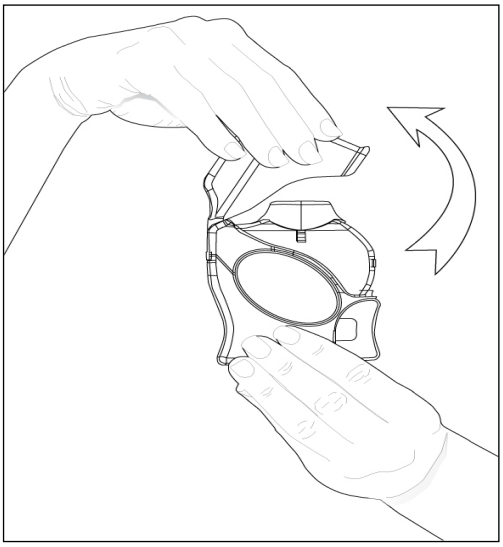
In the 30-dose packaging form, a red strip appears after "0", which shows that the blister is out of medicine. The red strip indicates that there is no medicine inside the inhaler.

The following four steps show how to use the Arvohaler device to take your medicine:
1. Open the cover
2. Press the actuation button
3. Inhale
4. Close the cover

1. Open the cover

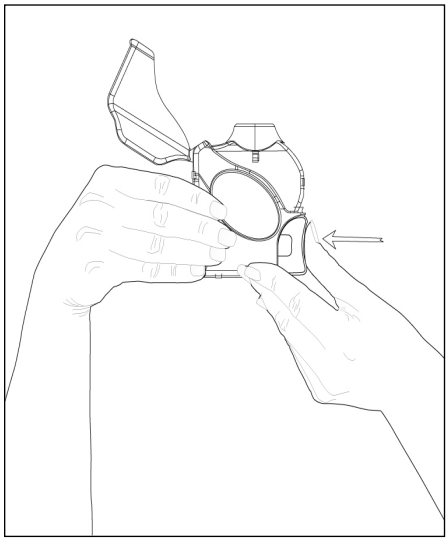
To open Arvohaler, hold the device in one hand and use your other than to open the cover in the direction indicated by the arrow. Do not force to push the actuation button when the cover is closed.

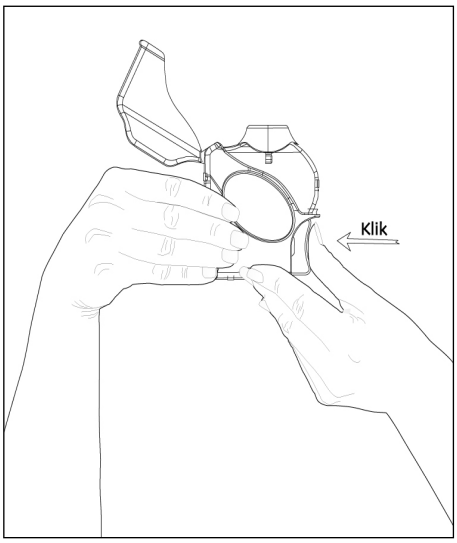




2. Press the actuation button

Hold the Arvohaler with the mouthpiece turned in your direction. Press the actuation button until you hear a click. Arvohaler is ready to use.



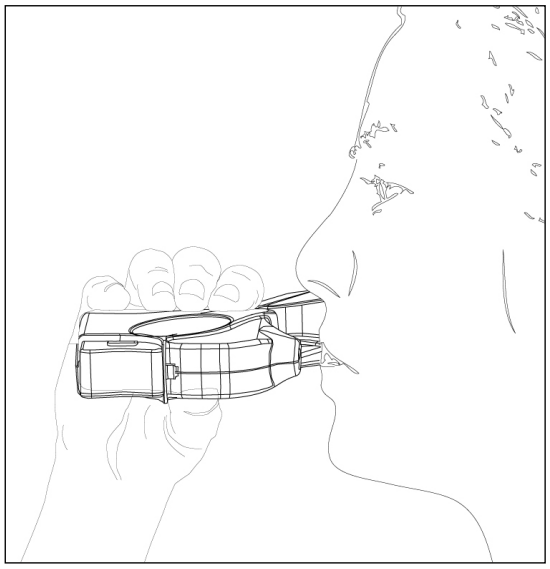


3. Inhale

Read this section carefully before inhaling the medicine.

- Hold Arvohaler away from your mouth and exhale as much as you can.
  Remember - never exhale into Arvohaler.
- Place the mouthpiece in your mouth without leaving a gap. Breathe in steadily and deeply. Breathe in through Arvohaler, not through your nose.
- Remove Arvohaler from your mouth when the inhalation is complete.

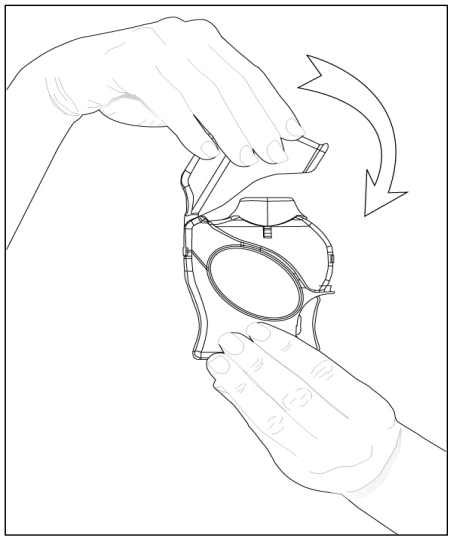
- Hold your breath for 10 seconds or for as long as is comfortable. Then, you can continue to breathe normally.

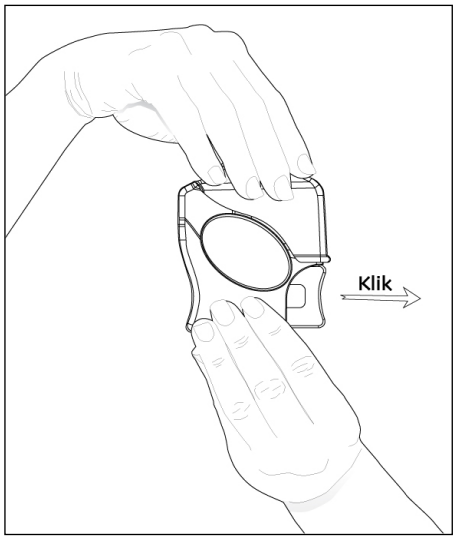


4. Close the cover

To close the Arvohaler, hold the device in one hand and use your other hand to securely close the cover.

You will hear a click when you close the cover of Arvohaler and the actuation button will automatically return to its original position. The actuation button is locked when the cover is closed.





If your doctor recommended you take two inhalation doses, close the cover of Arvohaler after the first inhalation and repeat the steps described above from 1 to 4.

REMEMBER!

The dose must be inhaled after pressing the actuation button and preparing the dose. If you don't inhale, the medicine left in the device will break the mechanism and cause problems in the following doses.

Keep Arvohaler away from water and humid environments.

Keep the cover closed when you are not using the device.
Never exhale into Arvohaler.
Press the actuation button only when you are ready to take the medicine and the cover is open.
Do not force to push the actuation button when the cover is closed.
Do not take higher doses than the doses your doctor recommended.
Keep Arvohaler out of sight and reach of children and inside its package.

4.3. Contraindications
Hypersensitivity to the active substance or to the excipient listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.

4.4 Special warnings and precautions for use

Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.

Immediate hypersensitivity reactions may occur after administration of Tiotropium bromide inhalation powder.

Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. (see section 4.8).

Inhaled medicines may cause inhalation-induced bronchospasm.

Tiotropium should be used with caution in patients with recent myocardial infarction <6 months; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; trials and these conditions may be affected by the anticholinergic mechanism of action.

As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤50 ml/min) Tiotropium bromide should be used only if the expected benefit outweighs the potential risk. There is no ling term experience in patients with severe renal impairment (see section 5.2).

Patient should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using Tiotropium bromide and consult a specialist immediately.

Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental carries.
Tiotropium bromide should not be used more frequently than once daily (see section 4.9).

Atrus Arvohaler contain 5.283 lactose monohydrate. This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose monohydrate may contain small amounts of milk proteins which may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

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

Use of LABA or ICS was not found to alter the exposure to Tiotropium.

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Atrus arvohaler during pregnancy.

Breast-feeding

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 Atrus arvohaler 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 Atrus arvohaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Atrus arvohaler therapy to the woman.

Fertility

Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness, blurred vision, or headache may influence the ability to drive and use machinery.

4.8. Undesirable effects

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Atrus arvohaler

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 with treatment periods ranging from four weeks to four 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)

System Organ Class / MedDRA Preferred Term	Frequency
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare
Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare

Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

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 ileus paralytic as well as urinary retention.

Other special 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 HPVC form at https://hpvcth.fda.moph.go.th/hpvc-form-9/ or search for AE online reporting (Health Product Vigilance Center: HPVC) in google chrome.

4.9. Overdose
High doses of tiotropium bromide may lead to anticholinergic signs and symptoms.
However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7days dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics

ATC code: R03B B04

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 antagonises the M_3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. 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_3 over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.

Clinical efficacy and safety

The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both, salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnoea, 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, FEV1 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 PEFR (peak expiratory flow rate) 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 randomised, 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. Clinical trials (up to 12 months)

Dyspnoea, Exercise tolerance

Tiotropium bromide significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index.). This improvement was maintained throughout the treatment period.

The impact of improvements in dyspnoea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with Tiotropium Bromide 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 Bromide 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 Bromide 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 Tiotropium Bromide 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 randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of Tiotropium Bromide 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

Table1: Summary of Exacerbation endpoints

Endpoint	Tiotropium Bromide 18 microgram N=3,707	Salmeterol 50 microgram (HFA pMDI) N=3,669	Ratio (95% CI)	p-value
Time (day) to first exacerbation †	187	145	0.83 (0.77-0.90)	<0.001
Time to first severe (hospitalised) 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 (hospitalised) 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) centre and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre 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 analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.
Compared with salmeterol, Tiotropium Bromide 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 Bromide also increased the time to the first severe (hospitalised) 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, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving Tiotropium Bromide), the improvement in FEV1 resulting from Tiotropium Bromide, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Tiotropium Bromide group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV1 compared to placebo was similar between Tiotropium Bromide 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).

Paediatric population

The European Medicines Agency has waived the obligation to submit results of studies with Tiotropium Bromide in all subsets of the paediatric population in COPD and cystic fibrosis (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties
a) General Introduction
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.

b) General Characteristics of the Active Substance after Administration of the Medicinal Product
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. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation.

At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-compartmental 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 nonenzymatically 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 metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites.
In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 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 µg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. 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.

c) Characteristics in Patients

Geriatric Patients: 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.

Renally Impaired Patients: 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.

Hepatically Impaired Patients: 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.

d) Pharmacokinetic / Pharmacodynamic Relationship(s)
There is no direct relationship between pharmacokinetics and pharmacodynamics.

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 in animals reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy 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/foetal 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 five-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

6.2. Incompatibilities
Not applicable.

6.3. Shelf Life
24 months

6.4. Special precautions for storage
Should be stored under 30°C at room temperature.
Do not Freeze
Keep away from children.

6.5. Nature and contents of container
A plastic inhaled with a turquoise cap and mouthpiece, white body and actuation button, dose counter of the remaining number of doses, and 30 dose Al/A1 blister strip filled with white homogenous powder and a carton box packaging

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Manufacturer:

ARVEN İLAÇ SAN. VE TİC. A.Ş

Balabandere Caddesi, İlaç Sanayi Sk. No:14, 34460 İstinye-Sarıyer/İstanbul / TURKEY

Tel: 0 (288) 263 44 07

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Healol Pharmaceuticals Co.,Ltd

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Tel: (66-2)381-6901-3

8. Marketing authorisation number(s)
Reg. No.:.....

9. Date of first authorisation/renewal of the authorisation

.....

10. Date of revision of the text

.....

SPC

Checklist for Summary of product characteristics (SmPC)

E-identifier No. e6500150 Product Name Atrus Arvohaler 18 mcg Inhalation Powder Active Substance Tiotropium Bromide

Strength 18 mcg/actuation Dosage Form Inhalation Powder Co-PTL คุณพรนรี

MAH Healol Pharmaceuticals Co. Ltd Contact Person ชุติพันธ์ หนูสุก E-mail: chutipan.nus@gmail.com

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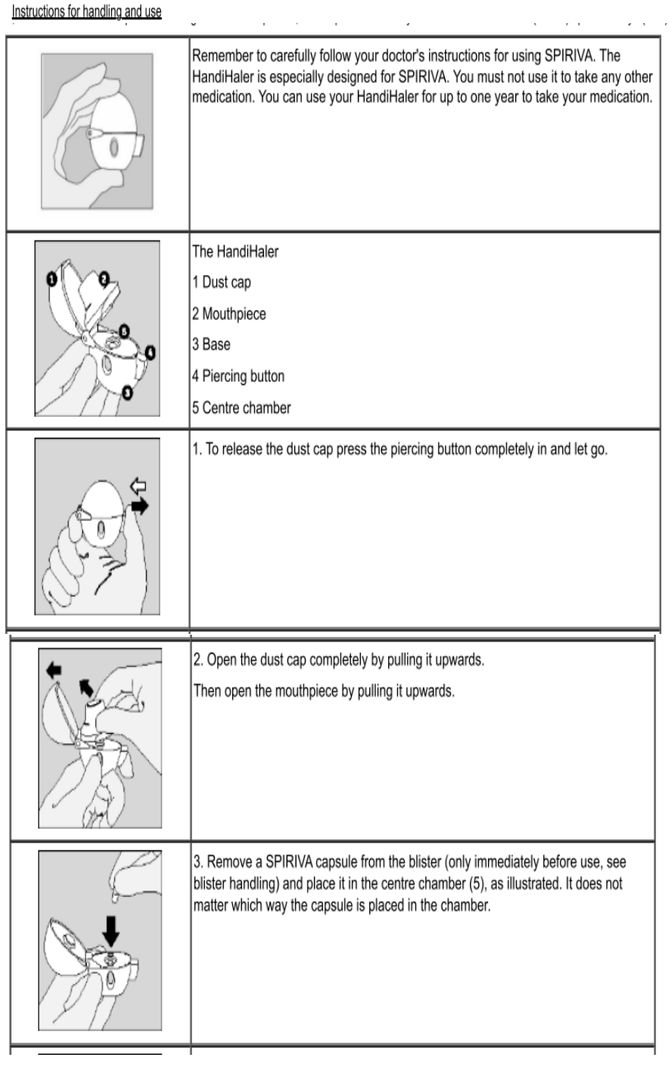
Instruction **ผู้รับอนุญาต (MAH) :** 1. ผู้รับอนุญาตตรวจสอบเอกสารกำกับยา (SmPC) ว่ามีหัวข้อตามที่กำหนดหรือไม่ โดยทำเครื่องหมาย (√) หรือ (X) ในช่อง MAH SmPC หากไม่ปรากฏหัวข้อดังกล่าว (เปรียบเทียบกับเอกสารกำกับยาอ้างอิง) ให้ระบุ n/a

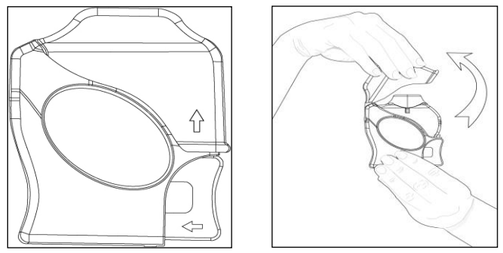
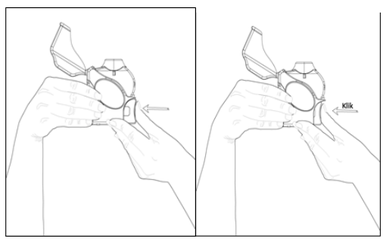
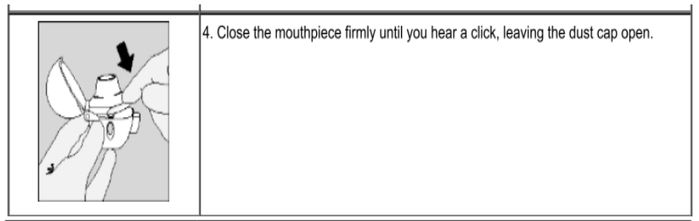
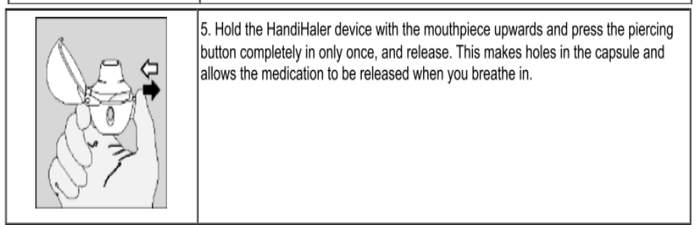
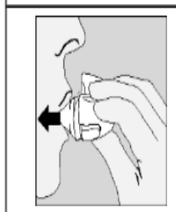
2. ผู้รับอนุญาตตรวจสอบข้อความในเอกสารกำกับยา (SmPC) ว่ามีเนื้อหาตรงกับเอกสารกำกับยาฉบับอ้างอิงหรือไม่ (เอกสารกำกับยาฉบับอ้างอิงระบุแหล่งที่มาของเอกสารพร้อมระบุ Revision Date) โดยทำเครื่องหมาย (√) หรือ (X) ในช่องดังกล่าว

3. เอกสารกำกับยา (SmPC) ของผู้รับอนุญาตถ้ามีหัวข้อหรือเนื้อหาไม่ตรงกับเอกสารกำกับยาอ้างอิง โปรดระบุเหตุผลและเอกสารอ้างอิงประกอบ

เจ้าหน้าที่ (Co-PTL) : ตรวจสอบข้อมูลในช่อง MAH ที่ผู้รับอนุญาตแสดงรายละเอียดว่ามีความสอดคล้องหรือไม่ โดยระบุ “สอดคล้อง” หรือ “ไม่สอดคล้อง” หากไม่ปรากฏหัวข้อ ดังกล่าว (เปรียบเทียบกับเอกสารกำกับยาอ้างอิง) ให้ระบุ n/a และผลพิจารณาหากพบว่า “ไม่สอดคล้อง” หรือมีข้อแก้ไขเพิ่มเติม โปรดระบุคำอธิบาย

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	เอกสารกำกับยาไม่มีหัวข้อและ/หรือเนื้อหาตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	ผลการประเมิน	คำอธิบายผลการประเมิน “ไม่สอดคล้อง” และ/หรือมีข้อแก้ไขเพิ่มเติม
1.NAME OF THE MEDICINAL PRODUCT					
Name	NAME OF THE MEDICINAL PRODUCT **Product Name:** ATRUS ARVOHALER 18 mcg Inhalation Powder	**1. Name of the medicinal product** SPIRIVA® 18 microgram, inhalation powder, hard capsule	เป็นไปตามบริบทของยา		
Strength	18 mcg	18 microgram			
Pharmaceutical form*	Inhalation Powder	inhalation powder			
2 QUALITATIVE AND QUANTITATIVE COMPOSITION	Each inhalation dose contains 21.7 microgram Tiotropium bromide anhydrous equivalent to 18 microgram Tiotropium. Excipient with known effect. Each inhalation dose contains 5.283 milligram of Lactose (as monohydrate)	**2. Qualitative and quantitative composition** Each capsule contains 22.5 microgram tiotropium bromide monohydrate equivalent to 18 microgram tiotropium. The delivered dose (the dose that leaves the mouthpiece of the HandiHaler® device) is 10 microgram tiotropium. Excipient with known effect: Each capsule contains 5.5 milligram of lactose (as monohydrate). For the full list of excipients, see section 6.1.			
3 PHARMACEUTICAL FORM*	Inhalation powder A plastic inhaled with a turquoise cap and mouthpiece, white body and actuation button, dose counter of the remaining number of doses, and 30 dose Al/A1 blister strip filled with white homogenous powder.	**3. Pharmaceutical form** Inhalation powder, hard capsule. Light green hard capsules containing the inhalation powder with the product code TI 01 and company logo printed on the capsule.			
4. CLINICAL PARTICULARS					
4.1 Therapeutic indications	4.1. Therapeutic indications Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD)	**4.1 Therapeutic indications** Tiotropium is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).			
4.2 Posology and method of administration					
Posology	**Posology:** The medicinal product is intended for inhalation use only. The recommended dose of ATRUS Arvohaler is the inhalation of one inhalation dose once daily. Inhalation should be at the same time of day each day. The recommended dose should not be exceeded. Tiotropium bromide powder is only for inhalation and not for oral intake and must be not swallowed.	Posology The medicinal product is intended for inhalation use only. The recommended dosage of tiotropium bromide is inhalation of the contents of one capsule once daily with the HandiHaler device at the same time of day. The recommended dose should not be exceeded. Tiotropium bromide capsules are only for inhalation and not for oral intake. Tiotropium bromide capsules must not be swallowed. Tiotropium bromide should only be inhaled with the HandiHaler device.			
Special populations	**Special populations:** Geriatric patients can use Tiotropium bromide at the recommended dose. Renally impaired patients can use Tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min) see section 4.4 and section 5.2. Hepatically impaired patients can use Tiotropium bromide at the recommended dose. (see section 5.2)	Special populations Geriatric patients can use tiotropium bromide at the recommended dose. Renally impaired patients can use tiotropium bromide at the recommended dose. For patients with moderate to severe impairment (creatinine clearance ≤ 50 ml/min) see section 4.4 and section 5.2. Hepatically impaired patients can use tiotropium bromide at the recommended dose (see section 5.2).			

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other (ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ).....Revision Date.....
Paediatric population	**Paediatric population:** *COPD* There is no relevant use in the paediatric population (below 18 years) in the indication state under section 4.1 *Cystic fibrosis* The safety and efficacy of Atrus Arvohaler 18 microgram in children and adolescents has not been established. No data are available.	Paediatric population *COPD* There is no relevant use in the paediatric population (below 18 years) in the indication stated under section 4.1. *Cystic fibrosis* The safety and efficacy of Spiriva 18 microgram in children and adolescents has not been established. No data are available.			
Method of administration	**Method of administration:** **Method of administration:** To ensure proper administration of the medicinal product the patient should be trained how to use the inhaler by the physician or by other healthcare professionals. **Instructions on how to use ATRUS ARVOHALER** Atrus Arvohaler is a device that allows you to inhale a measured dose of powder into your lungs. As explained in the detailed instructions below, the device is prepared for use by opening the cover and pressing the actuation button on the side. The mouthpiece is placed in the mouth. To ensure a full inhalation, the mouthpiece should be placed on the mouth without leaving a gap. Then, the dose is inhaled. After the inhalation, the cover is securely closed. The actuation button automatically returns to its first position when the cover is closed. The actuation button is locked when the cover is closed. An unused Arvohaler contains 30 doses of medicine in powderform placed separately in the device. The dose indicator under Arvohaler shows how many doses are left. The doses between 10 and 0 are in red to warn you when the device is low on medicine. In the 30-dose packaging form, a red strip appears after "0", which shows that the blister is out of medicine. The red strip indicates that there is no medicine inside the inhaler. The following four steps show how to use the Arvohaler device to take your medicine: 1. Open the cover 2. Press the actuation button 3. Inhale 4. Close the cover	Method of administration To ensure proper administration of the medicinal product the patient should be trained how to use the inhaler by the physician or by other healthcare professionals. Instructions for handling and use  Remember to carefully follow your doctor's instructions for using SPIRIVA. The HandiHaler is especially designed for SPIRIVA. You must not use it to take any other medication. You can use your HandiHaler for up to one year to take your medication. The HandiHaler 1 Dust cap 2 Mouthpiece 3 Base 4 Piercing button 5 Centre chamber 1. To release the dust cap press the piercing button completely in and let go. 2. Open the dust cap completely by pulling it upwards. Then open the mouthpiece by pulling it upwards. 3. Remove a SPIRIVA capsule from the blister (only immediately before use, see blister handling) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.	-ในส่วนของ Instructions on how to useนั้น เนื่องจากลักษณะdeviceมีวิธีใช้ที่ต่างกัน จึงไม่สามารถแก้ไขให้เหมือนกับยาต้นแบบได้		

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other (ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ).....Revision Date...
Method of administration	**1. Open the cover** To open Arvohaler, hold the device in one hand and use your other than to open the cover in the direction indicated by the arrow. Do not force to push the actuation button when the cover is closed.  2. Press the actuation button Hold the Arvohaler with the mouthpiece turned in your direction. Press the actuation button until you hear a click. Arvohaler is ready to use.  3. Inhale Read this section carefully before inhaling the medicine. - Hold Arvohaler away from your mouth and exhale as much as you can. Remember - never exhale into Arvohaler. - Place the mouthpiece in your mouth without leaving a gap. Breathe in steadily and deeply. Breathe in through Arvohaler, not through your nose. - Remove Arvohaler from your mouth when the inhalation is complete. - Hold your breath for 10 seconds or for as long as is comfortable. Then, you can continue to breathe normally.	 4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.  5. Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in only once, and release. This makes holes in the capsule and allows the medication to be released when you breathe in.  6. Breathe out completely. Important: Please avoid breathing into the mouthpiece at any time.  7. Raise the HandiHaler to your mouth and close your lips tightly around the mouthpiece. Keep your head in an upright position and breathe in slowly and deeply but at a rate sufficient to hear or feel the capsule vibrate. Breathe in until your lungs are full; then hold your breath as long as comfortable and at the same time take the HandiHaler out of your mouth. Resume normal breathing. Repeat steps 6 and 7 once, in order to empty the capsule completely.  8. Open the mouthpiece again. Tip out the used capsule and dispose. Close the mouthpiece and dust cap for storage of your HandiHaler device.			

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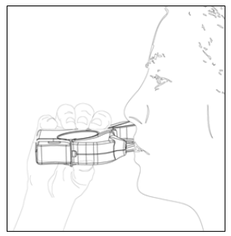
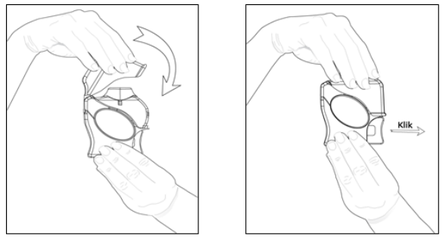
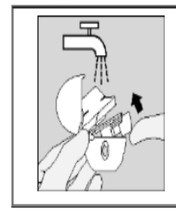
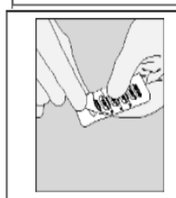
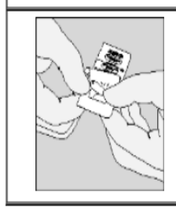
Method of administration	 **4. Close the cover** To close the Arvohaler, hold the device in one hand and use your other hand to securely close the cover. You will hear a click when you close the cover of Arvohaler and the actuation button will automatically return to its original position. The actuation button is locked when the cover is closed.  If your doctor recommended you take two inhalation doses, close the cover of Arvohaler after the first inhalation and repeat the steps described above from 1 to 4. **REMEMBER!** The dose must be inhaled after pressing the actuation button and preparing the dose. If you don't inhale, the medicine left in the device will break the mechanism and cause problems in the following doses. Keep Arvohaler away from water and humid environments. Keep the cover closed when you are not using the device. Never exhale into Arvohaler. Press the actuation button only when you are ready to take the medicine and the cover is open. Do not force to push the actuation button when the cover is closed. Do not take higher doses than the doses your doctor recommended. Keep Arvohaler out of sight and reach of children and inside its package.	Cleaning your HandiHaler  Clean the HandiHaler once a month. Open the dust cap and mouthpiece. Then open the base by lifting the piercing button. Rinse the complete inhaler with warm water to remove any powder. Dry the HandiHaler thoroughly by tipping excess of water out on a paper towel and air-dry afterwards, leaving the dust cap, mouthpiece and base open. It takes 24 hours to air dry, so clean it right after you have used it and it will be ready for your next dose. If needed, the outside of the mouthpiece may be cleaned with a moist but not wet tissue. Blister handling  A. Separate the blister strips by tearing along the perforation.  B. Peel back foil (only immediately before use) using the tab until one capsule is fully visible. In case a second capsule is exposed to air inadvertently this capsule has to be discarded.  C. Remove capsule. SPIRIVA® capsules contain only a small amount of powder so that the capsule is only partially filled.			

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4.3 Contraindications	4.3. Contraindications Hypersensitivity to the active substance or to the excipient listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.	4.3 Contraindications Hypersensitivity to the active substance or to the excipient listed in section 6.1 or to atropine or its derivatives, e.g. ipratropium or oxitropium.			
4.4 Special warnings and precautions for use	4.4 Special warnings and precautions for use Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. Immediate hypersensitivity reactions may occur after administration of Tiotropium bromide inhalation powder. Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. (see section 4.8). Inhaled medicines may cause inhalation-induced bronchospasm. Tiotropium should be used with caution in patients with recent myocardial infarction <6 months; any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; trials and these conditions may be affected by the anticholinergic mechanism of action. As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤50 ml/min) Tiotropium bromide should be used only if the expected benefit outweighs the potential risk. There is no ling term experience in patients with severe renal impairment (see section 5.2). Patient should be cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using Tiotropium bromide and consult a specialist immediately. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental carries. Tiotropium bromide should not be used more frequently than once daily (see section 4.9). Atrus Arvohaler contain 5.283 lactose monohydrate. This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose monohydrate may contain small amounts of milk proteins which may cause allergic reactions.	4.4 Special warnings and precautions for use Tiotropium bromide, as a once daily maintenance bronchodilator, should not be used for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. Immediate hypersensitivity reactions may occur after administration of tiotropium bromide inhalation powder. Consistent with its anticholinergic activity, tiotropium bromide should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. (see section 4.8). Inhaled medicines may cause inhalation-induced bronchospasm. Tiotropium should be used with caution in patients with recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year. These patients were excluded from the clinical trials and these conditions may be affected by the anticholinergic mechanism of action. As plasma concentration increases with decreased renal function in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) tiotropium bromide 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 cautioned to avoid getting the drug powder into their eyes. They should be advised that this may result in precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema. Should any combination of these eye symptoms develop, patients should stop using tiotropium bromide and consult a specialist immediately. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries. Tiotropium bromide should not be used more frequently than once daily (see section 4.9). SPIRIVA capsules contain 5.5 mg lactose monohydrate. This amount does not normally cause problems in lactose intolerant patients. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The excipient lactose monohydrate may contain small amounts of milk proteins which may cause allergic reactions.			

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	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ).....Revision Date...
4.5 Interaction with other medicinal products and other forms of interaction	**4.5. Interaction with other medicinal products and other forms of interaction** Although no formal drug interaction studies have been performed, Tiotropium bromide inhalation powder has been used concomitantly with other drugs without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD. Use of LABA or ICS was not found to alter the exposure to Tiotropium. The co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied and is therefore not recommended.	**4.5 Interaction with other medicinal products and other forms of interaction** Although no formal drug interaction studies have been performed, tiotropium bromide inhalation powder has been used concomitantly with other drugs without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, commonly used in the treatment of COPD. Use of LABA or ICS was not found to alter the exposure to tiotropium. The co-administration of tiotropium bromide with other anticholinergic-containing drugs has not been studied and is therefore not recommended.			
Additional information on special populations (i.e. Paediatric population) **(IF APPLICABLE)**					
4.6 Fertility, pregnancy and lactation					
Women of childbearing potential / Contraception in males and females	Fertility Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see section 5.3).	Fertility Clinical data on fertility are not available for tiotropium. A non-clinical study performed with tiotropium showed no indication of any adverse effect on fertility (see section 5.3).			
Pregnancy	Pregnancy There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Atrus arvohaler during pregnancy.	Pregnancy There is a very limited amount of data from the use of tiotropium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see 5.3). As a precautionary measure, it is preferable to avoid the use of Spiriva during pregnancy.			
Fertility	Breast-feeding 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 Atrus arvohaler 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 Atrus arvohaler should be made taking into account the benefit of breast-feeding to the child and the benefit of Atrus arvohaler therapy to the woman.	Breast-feeding 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 Spiriva 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 Spiriva should be made taking into account the benefit of breast-feeding to the child and the benefit of Spiriva therapy to the woman.			
4.7 Effects on ability to drive and use machines	**4.7. Effects on ability to drive and use machines** No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness, blurred vision, or headache may influence the ability to drive and use machinery.	**4.7 Effects on ability to drive and use machines** No studies on the effects on the ability to drive and use machines have been performed. The occurrence of dizziness, blurred vision, or headache may influence the ability to drive and use machinery.			

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ).....Revision Date...
4.8 Undesirable effects	**4.8. Undesirable effects** Summary of the safety profile Many of the listed undesirable effects can be assigned to the anticholinergic properties of Atrus arvohaler 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 with treatment periods ranging from four weeks to four 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)	**4.8 Undesirable effects** Summary of the safety profile Many of the listed undesirable effects can be assigned to the anticholinergic properties of SPIRIVA. 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 with treatment periods ranging from four weeks to four 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)			

System Organ Class / MedDRA Preferred Term	Frequency
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
Cardiac disorders	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare

System Organ Class / MedDRA Preferred Term	Frequency
Metabolism and nutrition disorders	
Dehydration	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
Eye disorders	
Vision blurred	Uncommon
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Cardiac disorders	
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Tachycardia	Rare
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Respiratory, thoracic and mediastinal disorders	
Pharyngitis	Uncommon
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Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
Gastrointestinal disorders	
Dry Mouth	Common
Gastrooesophageal reflux disease	Uncommon
Constipation	Uncommon
Oropharyngeal candidiasis	Uncommon
Intestinal obstruction, including ileus paralytic	Rare

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☑ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ).....Revision Date...
4.8 Undesirable effects					

Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare
Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

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 ileus paralytic as well as urinary retention.

Other special 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 HPVC form at https://hpvcth.fda.moph.go.th/hpvc-form-9/ or search for AE online reporting (Health Product Vigilance Center: HPVC) in google chrome.

Gingivitis	Rare
Glossitis	Rare
Dysphagia	Rare
Stomatitis	Rare
Nausea	Rare
Dental caries	Not known
Skin and subcutaneous tissue disorders, immune system disorders	
Rash	Uncommon
Urticaria	Rare
Pruritus	Rare
Hypersensitivity (including immediate reactions)	Rare

Angioedema	Rare
Anaphylactic reaction	Not known
Skin infection, skin ulcer	Not known
Dry skin	Not known
Musculoskeletal and connective tissue disorders	
Joint swelling	Not known
Renal and urinary disorders	
Dysuria	Uncommon
Urinary retention	Uncommon
Urinary tract infection	Rare

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 %).

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Other special population

An increase in anticholinergic effects may occur with increasing age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Topic	MAH			Co-PTL	
	MAH SmPC	SmPC Reference ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....
4.9 Overdose	**4.9. Overdose** High doses of tiotropium bromide may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7days dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed.	**4.9 Overdose** High doses of tiotropium bromide may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 microgram tiotropium bromide in healthy volunteers. Additionally, no relevant adverse effects, beyond dry mouth, were observed following 7 day dosing of up to 170 microgram tiotropium bromide in healthy volunteers. In a multiple dose study in COPD patients with a maximum daily dose of 43 microgram tiotropium bromide over four weeks no significant undesirable effects have been observed. Acute intoxication by inadvertent oral ingestion of tiotropium bromide capsules is unlikely due to low oral bioavailability.			
5. PHARMACOLOGICAL PROPERTIES					
5.1 Pharmacodynamic properties	**5. PHARMACOLOGICAL PROPERTIES** **5.1. Pharmacodynamic properties** Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics	**5. Pharmacological properties** **5.1 Pharmacodynamic properties** Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants, anticholinergics			
ATC code	ATC code: R03B B04	ATC code: R03B B04			
Mechanism of action (if known)	<u>Mechanism of action</u> 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 antagonises the M_3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. 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	<u>Mechanism of action</u> 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 antagonises the M_3 receptors, resulting in relaxation. The effect was dose dependent and lasted longer than 24h. 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	<u>Pharmacodynamic effects</u> 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_3 over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.	<u>Pharmacodynamic effects</u> 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_3 over M_2. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.			

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Clinical efficacy and safety	Clinical efficacy and safety The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both, salmeterol and placebo controlled. These studies included lung function and health outcome measures of dyspnoea, 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, FEV1 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 PEFR (peak expiratory flow rate) 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 randomised, 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. Clinical trials (up to 12 months) *Dyspnoea, Exercise tolerance* Tiotropium bromide significantly improved dyspnoea (as evaluated using the Transition Dyspnoea Index.). This improvement was maintained throughout the treatment period. The impact of improvements in dyspnoea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. In these trials, six weeks of treatment with Tiotropium Bromide 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 Bromide 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 Bromide 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 Tiotropium Bromide 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.	Clinical efficacy and safety The clinical development programme included four one-year and two six-month randomised, double-blind studies in 2663 patients (1308 receiving tiotropium bromide). The one-year programme consisted of two placebo-controlled trials and two trials with an active control (ipratropium). The two six-month trials were both, salmeterol and placebo controlled. 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In these trials, six weeks of treatment with SPIRIVA 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, SPIRIVA improved health-related quality of life as determined by the St. George's Respiratory Questionnaire (SGRQ) total score. The proportion of patients treated with SPIRIVA 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”. 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	MAH SmPC	SmPC Reference ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....

Clinical efficacy and safety

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 randomised, double-blind, double-dummy, parallel-group trial compared the effect of treatment with 18 microgram of Tiotropium Bromide 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

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Endpoint	Tiotropium Bromide 18 microgram N=3,707	Salmeterol 50 microgram (HFA pMDI) N=3,669	Ratio (95% CI)	p-value
Time (day) to first exacerbation †	187	145	0.83 (0.77-0.90)	<0.001
Time to first severe (hospitalised) 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 (hospitalised) 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) centre and treatment as covariate; ratio refers to hazard ratio.
§ Time to event analysis was done using Cox's proportional hazards regression model with (pooled) centre 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 analysed using Cochran-Mantel-Haenszel test stratified by pooled centre; ratio refers to risk ratio.
Compared with salmeterol, Tiotropium Bromide 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 Bromide also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

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Compared with salmeterol, SPIRIVA 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). SPIRIVA also increased the time to the first severe (hospitalised) exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001).

Topic	MAH	Co-PTL

	MAH SmPC	SmPC Reference ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	MAH SmPC	SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....
Clinical efficacy and safety	*Long-term clinical trials (more than 1 year, up to 4 years)* In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving Tiotropium Bromide), the improvement in FEV1 resulting from Tiotropium Bromide, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Tiotropium Bromide group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV1 compared to placebo was similar between Tiotropium Bromide 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).	Long-term clinical trials (more than 1 year, up to 4 years) In a 4-year, randomised, double-blind, placebo-controlled clinical trial of 5,993 randomised patients (3.006 receiving placebo and 2,987 receiving Spiriva), the improvement in FEV1 resulting from Spiriva, compared with placebo, remained constant throughout 4 years. A higher proportion of patients completed ≥ 45 months of treatment in the Spiriva group compared with the placebo group (63.8% vs. 55.4%, p<0.001). The annualized rate of decline of FEV1 compared to placebo was similar between Spiriva 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).			
Paediatric population (ถ้ามี)	Paediatric population The European Medicines Agency has waived the obligation to submit results of studies with Tiotropium Bromide in all subsets of the paediatric population in COPD and cystic fibrosis (see section 4.2 for information on paediatric use).	Paediatric population The European Medicines Agency has waived the obligation to submit results of studies with Spiriva in all subsets of the paediatric population in COPD and cystic fibrosis (see section 4.2 for information on paediatric use).			
5.2 Pharmacokinetic properties	**5.2. Pharmacokinetic properties** a) General Introduction 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.	**5.2 Pharmacokinetic properties** a) General Introduction 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.			

Topic	MAH MAH SmPC	MAH SmPC Reference ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....	กรณีเอกสารกำกับยาไม่ตรงกับเอกสารอ้างอิง (ระบุเหตุผล)	Co-PTL MAH SmPC	Co-PTL SmPC Ref. ☐ EMA ☐ US FDA ☐ Other(ระบุ)..... Revision Date.....
5.2 Pharmacokinetic properties	b) General Characteristics of the Active Substance after Administration of the Medicinal Product *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. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-compartmental 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 nonenzymatically 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 metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites. In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 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 μg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. 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.	b) General Characteristics of the Active Substance after Administration of the Medicinal Product *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. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Maximum tiotropium plasma concentrations were observed 5-7 minutes after inhalation. At steady state, peak tiotropium plasma levels in COPD patients were 12.9 pg/ml and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 1.71 pg/ml. Systemic exposure following the inhalation of tiotropium via the HandiHaler device was similar to tiotropium inhaled via the Respimat inhaler. *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 nonenzymatically 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 metabolised by cytochrome P450 (CYP) dependent oxidation and subsequent glutathion conjugation to a variety of Phase II-metabolites. In vitro studies in liver microsomes reveal that the enzymatic pathway can be inhibited by the CYP 2D6 (and 3A4) inhibitors, quinidine, ketoconazole and gestodene. Thus CYP 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 μg) of the unchanged drug over 24 hours, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. 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.			

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5.2 Pharmacokinetic properties	c) Characteristics in Patients *Geriatric Patients*: 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. *Renally Impaired Patients*: 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. *Hepatically Impaired Patients*: 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. d) Pharmacokinetic / Pharmacodynamic Relationship(s) There is no direct relationship between pharmacokinetics and pharmacodynamics.	c) Characteristics in Patients *Geriatric Patients:* 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. *Renally Impaired Patients:* 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. *Hepatically Impaired Patients:* 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. *Paediatric Patients:* See section 4.2 d) Pharmacokinetic / Pharmacodynamic Relationship(s) There is no direct relationship between pharmacokinetics and pharmacodynamics.			

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5.3 Preclinical safety data	**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 in animals reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy 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/foetal 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 five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.	**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 in animals reduced food consumption, inhibited body weight gain, dry mouth and nose, reduced lacrimation and salivation, mydriasis and increased heart rate were observed. Other relevant effects noted in repeated dose toxicity studies were: mild irritancy 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/foetal 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 five-fold the therapeutic exposure. Studies on genotoxicity and carcinogenic potential revealed no special hazard for humans.			
6.1 List of excipients	6. PHARMACEUTICAL PARTICULARS **6.1. List of excipients** Lactose monohydrate	**6. Pharmaceutical particulars** **6.1 List of excipients** Lactose monohydrate (which may contain small amounts of milk proteins)			
6.2 Incompatibilities	**6.2. Incompatibilities** Not applicable.	**6.2 Incompatibilities** Not applicable.			
6.3 Shelf life	**6.3. Shelf Life** 24 months	**6.3 Shelf life** 2 years After first opening of the blister use within the next 9 days. Discard the HandiHaler device 12 months after first use.	เป็นไปตามบริบทของยา		

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6.4 Special precautions for storage	**6.4. Special precautions for storage** Should be stored under 30˚C at room temperature. Do not Freeze Keep away from children.	**6.4 Special precautions for storage** Do not store above 25°C Do not freeze.	เป็นไปตามบริบทของยา		
6.5 Nature and contents of container	**6.5. Nature and contents of container** A plastic inhaled with a turquoise cap and mouthpiece, white body and actuation button, dose counter of the remaining number of doses, and 30 dose Al/A1 blister strip filled with white homogenous powder and a carton box packaging	**6.5 Nature and contents of container** Aluminium / PVC / Aluminium peel-off blister containing 10 capsules. The HandiHaler is a single dose inhalation device made from acrylonitrile butadiene styrene (ABS) plastic materials and stainless steel. The capsule chamber is made from methyl-methacrylate-acrylonitrile-butadiene-styrene (MABS) or polycarbonate (PC) plastic material. Package sizes and devices supplied: • Cardboard box containing 30 capsules (3 blisters) • Cardboard box containing 60 capsules (6 blisters) • Cardboard box containing 90 capsules (9 blisters) • Cardboard box containing HandiHaler device and 10 capsules (1 blister) • Cardboard box containing HandiHaler device and 30 capsules (3 blisters) • Hospital pack: Bundle pack containing 5 cardboard boxes of 30 capsules plus HandiHaler device • Hospital pack: Bundle pack containing 5 cardboard boxes of 60 capsules The HandiHaler device is packed/available in a cardboard box. Not all pack sizes may be marketed.	เป็นไปตามบริบทของยา		
6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product	**6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product** Any unused medicinal product or waste material should be disposed of in accordance with local requirements.	**6.6 Special precautions for disposal and other handling** Any unused medicinal product or waste material should be disposed of in accordance with local requirements.			
7. MARKETING AUTHORISATION HOLDER	**7. Marketing authorisation holder** **Manufacturer:** **ARVEN İLAÇ SAN. VE TİC. A.Ş** **Balabandere Caddesi, İlaç Sanayi Sk. No:14, 34460 İstinye-Sarıyer/İstanbul / TURKEY** **Tel: 0 (288) 263 44 07** **Fax: 0 (288) 263 44 09** **Importer:** Healol Pharmaceuticals Co.,Ltd 1112 88-90, Sukhumvit Road, Phra Khanong, Khlong Toei, Bangkok 10110, Thailand Tel: (66-2)381-6901-3	**7. Marketing authorisation holder** Boehringer Ingelheim International GmbH Binger Straße 173 D-55216 Ingelheim am Rhein Germany	เป็นไปตามบริบทของยา		
8 MARKETING AUTHORISATION NUMBER(S)	**8. Marketing authorisation number(s)** Reg. No.:.....	**8. Marketing authorisation number(s)** PL 14598/0062	เป็นไปตามบริบทของยา		
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION	**9. Date of first authorisation/renewal of the authorisation**	**9. Date of first authorisation/renewal of the authorisation** 09/10/2016	เป็นไปตามบริบทของยา		

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10 DATE OF REVISION OF THE TEXT	10. Date of revision of the text	**10. Date of revision of the text** January 2019	เป็นไปตามบริบทของยา		
11 DOSIMETRY (IF APPLICABLE)	-	-			
12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)	-	-			

หมายเหตุ * pharmaceutical dosage form ให้ระบุรูปแบบตรงตาม EDQM Standard Terms

** ผลิตภัณฑ์ดังกล่าวหากมีหลายความแรงและมีการใช้ SmPC ร่วมกันสามารถทำ Checklist รวมเป็นฉบับเดียวกันได้ (จะต้องสอดคล้องกับ SmPC Reference ด้วย)