

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Spiridow DPI Capsule 18 microgram

2. Qualitative and quantitative composition

Each capsule contains 22.5 micrograms of Tiotropium bromide monohydrate equivalent to 18 mcg Tiotropium.

The delivered dose (the dose that leaves the mouthpiece of the dry powder inhaler device) is approximately 10.4 microgram tiotropium.

Excipient with known effect:

This product contains lactose (as monohydrate).

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Inhalation powder, hard capsule.

Hard capsules with a green colour cap and transparent body (size No. 3) containing white to off white powder.

4. Clinical particulars

4.1 Therapeutic indications

Spiridow 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 dosage of tiotropium bromide is inhalation of the contents of one capsule once daily with the Inhaler device at the same time of day.

The recommended dose should not be exceeded.

Spiridow capsules are only for inhalation and not for oral intake.

Spiridow capsules must not be swallowed.

Spiridow capsules should only be inhaled with the Inhaler device.

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 stated under section 4.1.

Cystic fibrosis

The safety and efficacy of Spiridow 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 for handling and use

Remember to carefully follow your doctor's instructions for using the inhaler device. Do not swallow Spiridow capsules. Follow the stepwise instruction for use:

1. Pull off inhaler cap and hold the base of the inhaler firmly and tilt the mouthpiece to open the inhaler.
2. Separate 1 of the blisters from the blister card by tearing along the perforation. Take 1 blister and peel away the protective backing to expose the capsule.
3. With dry hands, remove 1 capsule from the blister and place the capsule into the capsule chamber.
4. Close the inhaler fully. You should hear a 'click' as it fully closes.
5. Hold the inhaler upright with the mouthpiece pointing up. Press both piercing buttons together firmly at the same time. You should hear a 'click' as the capsule is being pierced. Release the piercing buttons fully.
6. Before placing the mouthpiece in your mouth, breathe out fully. Do not blow into the mouthpiece.
7. Hold the inhaler. Make sure that the piercing buttons are to the left and right of the inhaler (not up and down). Place the mouthpiece in your mouth and close your lips firmly around the mouthpiece. Breathe in rapidly but steadily, as deeply as you can. Do not press the piercing buttons.
8. As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. If you do not hear a whirring noise, the capsule may be stuck in the capsule chamber. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the piercing buttons to loosen the capsule.
9. Continue to hold your breath for at least 5 to 10 seconds or as long as comfortably possible while removing the inhaler from your mouth, then breathe out.
10. Open the inhaler to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhaler and again place into your mouth to breath.
11. After you have finished taking your dose of Spiridow dry powder inhaler, open the mouthpiece again, remove the empty capsule by tipping it out of the capsule chamber, and throwing it away. Close the inhaler and replace the cap.

Do not leave the used capsules in the dry powder inhaler

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; 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 \leq 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).

Spiridow capsules contain lactose monohydrate. 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.

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 Spiridow during pregnancy.

Breastfeeding

It is unknown whether tiotropium bromide is excreted in human breast milk. Despite studies in rodents which have demonstrated that excretion of tiotropium bromide in breast milk occurs only in small amounts, use of Spiridow 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 Spiridow should be made taking into account the benefit of breast-feeding to the child and the benefit of Spiridow 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 Spiridow.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
<u>Metabolism and nutrition disorders</u>	
Dehydration	Not known
<u>Nervous system disorders</u>	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Insomnia	Rare
<u>Eye disorders</u>	
Vision blurred	Uncommon
Glaucoma	Rare
Intraocular pressure increased	Rare
<u>Cardiac disorders</u>	
Atrial fibrillation	Uncommon
Supraventricular tachycardia	Rare
Tachycardia	Rare
Palpitations	Rare
<u>Respiratory, thoracic and mediastinal disorders</u>	
Pharyngitis	Uncommon
Dysphonia	Uncommon
Cough	Uncommon
Bronchospasm	Rare
Epistaxis	Rare
Laryngitis	Rare
Sinusitis	Rare
<u>Gastrointestinal disorders</u>	
Dry Mouth	Common
Gastroesophageal 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
<u>Skin and subcutaneous tissue disorders, immune system disorders</u>	
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
<u>Musculoskeletal and connective tissue disorders</u>	
Joint swelling	Not known
<u>Renal and urinary disorders</u>	
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 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 Pharmacy and Poisons Board website (<https://pv.pharmacyboardkenya.org>).

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

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, M₁ to M₅. In the airways, tiotropium bromide competitively and reversibly antagonises the M₃ 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 M₃ 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 M₂-receptors is faster than from M₃, which in functional in vitro studies, elicited (kinetically controlled) receptor subtype selectivity of M₃ over M₂. The high potency and slow receptor dissociation found its clinical correlate in significant and long-acting bronchodilation in patients with COPD.

Cardiac electrophysiology

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

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 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.

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. Systemic exposure following the inhalation of tiotropium via the Inhaler 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.

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.

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 (Respitose SV003 & Lactohale 200)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage:

Store below 30°C

Do not freeze.

6.5 Nature and contents of container

Spiridow is supplied in the following dosage form, strength and pack size: Capsules (powder for inhalation) 18mcg 30's

6.6 Special precautions for disposal and other handling:

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Martin Dow Limited

Plot No. 37, Sector 19,

Korangi Industrial Area, Karachi-74900, Pakistan.

Manufacturing site address:

Martin Dow Limited

Plot No. 37, Sector 19,

Korangi Industrial Area, Karachi-74900, Pakistan.

8. Marketing authorization number

CTD9606

9. Date of first registration

06/03/2023

10. Date of revision of the text:

15/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable