SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Spiridow DPI Capsule 18 microgram

2. Qualitative and quantitative composition

Each capsule contains
Tiotropium bromide monohydrate Eq. to Tiotropium……18 mcg

3. Pharmaceutical form

Hard capsule (inhalation 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

The medicinal product is intended for oral inhalation only.

Recommended Dosage

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. 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 inhaler device.

Dose for Special populations

Geriatric patients and hepatically impaired 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 see specific population section.

Paediatric population

COPD

There is no relevant use in the paediatric population (below 18 years) in this indication.

Cystic fibrosis

The safety and efficacy of this medicine in children and adolescents is not known.

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.

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; hospitalization 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 colored images in association with red eyes from conjunctival congestion and corneal edema. 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

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 Tiotropium bromide 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 Tiotropium bromide 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 Tiotropium bromide should be made taking into account the benefit of breast-feeding to the child and the benefit of Tiotropium bromide 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 Tiotropium bromide.

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
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
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 are known to be 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 email productsafety@martindow.com.

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

Mechanism of action
Tiotropium bromide is a long-acting, specific, muscarinic receptor antagonist, in clinical medicine often called an anticholinergic. By binding to the muscarinic receptors in the bronchial smooth musculature, tiotropium bromide inhibits the cholinergic (bronchoconstrictive) effects of acetylcholine, released from parasympathetic nerve endings. It has similar affinity to the subtypes of muscarinic receptors, M_1 to M_5. In the airways, tiotropium bromide competitively and reversibly antagonizes the M_3 receptors, resulting in relaxation. 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
Cardiac electrophysiology
Electrophysiology: In a dedicated QT study involving 53 healthy volunteers, Tiotropium bromide 18 mcg and 54 mcg (i.e. three times the therapeutic dose) over 12 days did not significantly prolong QT intervals of the ECG.

5.2 Pharmacokinetic properties

Absorption:

Following dry powder inhalation, the absolute bioavailability is known to be 19.5% which suggests that the fraction reaching the lung is highly bioavailable. At steady state, peak tiotropium plasma levels in COPD patients are known to be 12.9 pg/ml and decrease rapidly in a multi-compartmental manner. Steady state trough plasma concentrations are known to be 1.71 pg/ml.

Distribution:

Tiotropium has a plasma protein binding of 72% and is known to have 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

Metabolism:

The extent of biotransformation is small because intravenously administered tiotropium is mainly known to be excreted unchanged (74%) in urine. The ester tiotropium bromide is nonenzymatically cleaved to the alcohol (N-methylscopine) and acid compound (dithienylglycolic acid) that are inactive on muscarinic receptors. The drug is known to be metabolized by cytochrome P450 (CYP) dependent oxidation and subsequent glutathione conjugation to a variety of Phase II-metabolites. It is known that 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. Total clearance is known to be 880 ml/min after an intravenous dose. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation to steady-state, urinary excretion is known to be 7% (1.3 µg) of the unchanged drug over 24 hours, the remainder is 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, pharmacokinetic steady state is known to reach by day 7 with no accumulation thereafter.

Specific Populations

Hepatic Impairment:

Liver insufficiency is not expected to have any relevant influence on tiotropium pharmacokinetics.

Renal Impairment

Following once daily inhaled administrations of tiotropium to steady-state in individuals with COPD ,mild renal impairment (CLCR 50-80 ml/min) is known to result in slightly higher AUC0-6,ss (between 1.8-30% higher) and similar Cmax, ss values compared to individuals with normal renal function(CLCR >80 ml/min). In individuals having COPD with moderate to severe renal impairment (CLCR <50 ml/min), the intravenous administration of Tiotropium Bromide is known to result in doubling of the total exposure (82% higher AUC0-4h and 52% higher Cmax) compared to individuals with normal renal function, which is known to be confirmed by plasma concentrations after dry powder inhalation.

Geriatric

Advancing age is known to be associated with a decrease of Tiotropium Bromide renal clearance (365 mL/min in individuals with COPD < 65 years to 271 mL/min in individuals with COPD ≥ 65 years). This is not known to result in a corresponding increase in AUC0-6,ss or Cmax,ss values.

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 are known to be observed. Other relevant effects noted in repeated dose toxicity studies are known to be 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/fetal development, parturition or postnatal development could only be demonstrated at maternally toxic dose levels. Tiotropium bromide was not teratogenic in rats or rabbits. In a general reproduction and fertility study in rats, there was no indication of any adverse effect on fertility or mating performance of either treated parents or their offspring at any dosage.

The respiratory (irritation) and urogenital (prostatitis) changes and reproductive toxicity are known to be 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

2 years

6.4 Special precautions for storage

Do not store above 25°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.

Instructions for handling and use

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

7. Marketing authorizations holder

Martin Dow Limited
Plot No. 37, Sector 19,
Korangi Industrial Area, Karachi-74900, Pakistan.

8. Marketing authorization number(s)

Spiridow DPI Capsule 18mcg: 107868

9. Date of first authorization/renewal of the authorizations

28th April 2021