IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/026/001
Case No: 2061417

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Spiriva 18 microgram inhalation powder, hard capsule

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/06/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Spiriva 18 microgram inhalation powder, hard capsule.

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: Lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule.
Product imported from the UK
Light green hard capsules with the product code TI 01 and company logo printed on the capsule.

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

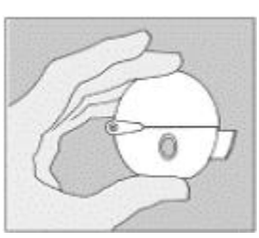
The recommended dosage of tiotropium bromide is inhalation of the contents of one capsule once daily with the HandiHaler device at the same time of day.

The recommended dose should not be exceeded.

Tiotropium bromide capsules must not be swallowed.

Tiotropium bromide should only be inhaled with the HandiHaler device.

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

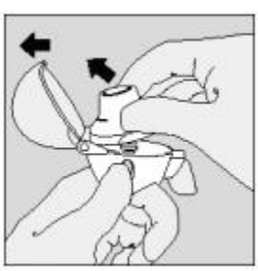
2 Mouthpiece

3 Base

4 Piercing button

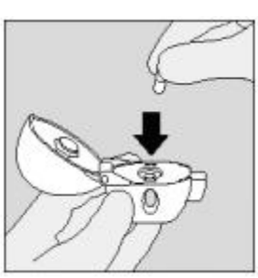
5 Centre chamber

1. To release the dust cap press the piercing button completely in and let go.

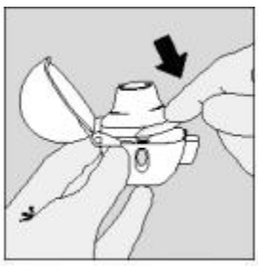


2. Open the dust cap completely by pulling it upwards.

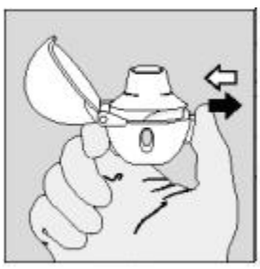
Then open the mouthpiece by pulling it upwards.



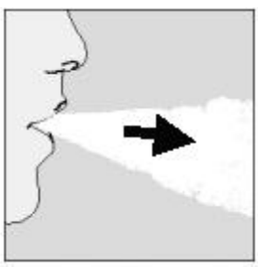
3. Remove a Spiriva capsule from the blister (only immediately before use) and place it in the centre chamber (5), as illustrated. It does not matter which way the capsule is placed in the chamber.



4. Close the mouthpiece firmly until you hear a click, leaving the dust cap open.

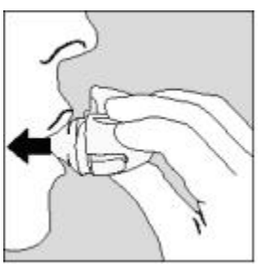


5. Hold the HandiHaler device with the mouthpiece upwards and press the piercing button completely in only once, and release. This makes holes in the capsule and allows the medication to be released when you breathe in.



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.

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 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.

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 4.4 Special warnings and special precautions for use and 5.2 Pharmacokinetic properties.

Hepatically impaired patients can use tiotropium bromide at the recommended dose (see 5.2 Pharmacokinetic properties).
Paediatric patients: Safety and effectiveness of tiotropium bromide inhalation powder in paediatric patients have not been established and therefore it should not be used in patients under 18 years of age.

4.3 Contraindications

Tiotropium bromide inhalation powder is contraindicated in patients with a hypersensitivity to tiotropium bromide, atropine or its derivatives, e.g. ipratropium or oxitropium or to the excipient lactose monohydrate which contains milk protein.

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 4.8 undesirable effects).

Inhaled medicines may cause inhalation-induced bronchospasm.

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 5.2 Pharmacokinetic properties).

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 Overdose).

Spiriva capsules contain 5.5 mg lactose monohydrate.

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.

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

4.6 Pregnancy and lactation

For tiotropium bromide, no documented clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity associated with maternal toxicity (see section 5.3, Preclinical Safety Data). The potential risk for humans is unknown. Spiriva should therefore only be used during pregnancy when clearly indicated.

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

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

a) General Description

Many of the listed undesirable effects can be assigned to the anticholinergic properties of Spiriva. In controlled clinical studies, the most commonly observed undesirable effect was dry mouth which occurred in approximately 3% of patients.

b) Table of Undesirable Effects

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 by study investigators) observed in the tiotropium group (5,437 patients) from 19 pooled placebo-controlled clinical trials with treatment periods ranging from four weeks to one year.

MedDRA Preferred Term	**Frequency[1]**
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Taste disorders	Uncommon
Eye disorders	
Vision blurred	Rare
Intraocular pressure increased	Rare
Glaucoma	Not known*
Cardiac disorders	
Tachycardia	Rare
Palpitations	Rare
Supraventricular tachycardia	Not known*
Atrial fibrillation	Not known*

Respiratory, thoracic and mediastinal disorders	
Bronchospasm	Uncommon
Cough	Uncommon
Pharyngitis and other application site irritation	Uncommon
Dysphonia	Uncommon
Epistaxis	Rare
Sinusitis	Not known*
Gastrointestinal Disorders	
Dry Mouth	Common
Oral candidiasis	Uncommon
Nausea	Uncommon
Gastrooesophageal reflux disease	Rare
Constipation	Rare
Dental caries	Not known*
Dysphagia	Not known*
Intestinal obstruction, including ileus paralytic	Not known*

Skin and subcutaneous tissue disorders, Immune system disorders:	
Rash	Rare
Urticaria	Rare
Pruritus	Rare
Other Hypersensitivity (including immediate reactions)	Rare
Angioneurotic oedema	Not known*
Renal and Urinary Disorders	
Dysuria	Rare
Urinary retention	Rare
Urinary tract infection	Rare

[1]very common > 1/10; common > 1/100, < 1/10; uncommon > 1/1,000, < 1/100, rare > 1/10,000, < 1/1,000 according to frequency convention

*no events attributed to tiotropium by study investigators in 5,437 tiotropium treated patients; however, events are considered adverse drug reactions associated with tiotropium

c) Information Characterising Individual Serious and/or Frequently Occurring Undesirable Effects
The most common anticholinergic undesirable effect reported by COPD patients was dry mouth. Dry mouth was mild in the majority of cases. In general, dry mouth had an onset between 3 and 5 weeks. Dry mouth commonly resolved while patients continued to receive tiotropium bromide. Dry mouth led to discontinuation from the one-year studies by 3 of 906 patients (0.3% of the treated patients).
Serious undesirable effects consistent with anticholinergic effects include constipation and intestinal obstruction including ileus paralytic as well as urinary retention although none was attributed to tiotropium in the tiotropium group of 5,437 patients pooled from controlled clinical trials.

d) Pharmacological Class - Undesirable effects
Several organ systems and functions are under control of the parasympathetic nervous system and thus can be affected by anticholinergic agents. Possible adverse events attributable to systemic anticholinergic effects include dry mouth, dry throat, increased heart rate, blurred vision, increased intraocular pressure, glaucoma, urinary difficulty, urinary retention, and constipation. Urinary retention was usually observed in elderly men with predisposing factors, (e.g. prostatic hyperplasia).

In common with all inhaled medications, tiotropium may cause inhalation-induced bronchospasm. Local upper airway irritant phenomena have also been observed in patients receiving tiotropium bromide.
An increased incidence of dry mouth and constipation may occur with increasing age.

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: Anticholinergics
ATC code: R03B B04

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. 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.

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

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 dyspnea, exacerbations and health-related quality of life.

In the aforementioned studies, 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.

The following health outcome effect was demonstrated in the long term (6-month and one-year) trials:

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

The impact of improvements in dyspnea on exercise tolerance was investigated in two randomised, double-blind, placebo-controlled trials in 433 patients with moderate to severe COPD. 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: 640 seconds with Spiriva vs. 535 seconds with placebo, compared with a pre-treatment baseline of 492 seconds) and 28.3% (Trial B: 741 seconds with Spiriva vs. 577 seconds with placebo, compared with a pre-treatment baseline of 537 seconds).

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 hospitalised due to a COPD exacerbation (p=0.056). The number of hospitalisations due to COPD was reduced by 30% (0.25 to 0.18 events per patient year of exposure).
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). While the SGRQ subdomains "activity" and "impact on daily life" were not improved significantly, the improvement on total score resulted from a marked improvement in the SGRQ subdomain disease related "symptoms".

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. It is expected from the chemical structure of the compound (quaternary ammonium compound) and from *in-vitro* experiments that tiotropium bromide is poorly absorbed from the gastrointestinal tract (10-15%). Oral solutions of tiotropium bromide have an absolute bioavailability of 2-3%. Maximum tiotropium bromide plasma concentrations were observed five minutes after inhalation. Food is not expected to influence the absorption of this quaternary ammonium compound.

Distribution: The drug is bound by 72% to plasma proteins and shows a volume of distribution of 32 L/kg. At steady state, tiotropium bromide plasma levels in COPD patients at peak were 17 – 19 pg/ml when measured 5 minutes after dry powder inhalation of a 18 microgram dose and decreased rapidly in a multi-compartmental manner. Steady state trough plasma concentrations were 3-4 pg/ml. 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 terminal elimination half-life of tiotropium bromide is between 5 and 6 days following inhalation. Total clearance was 880 ml/min after an intravenous dose in young healthy volunteers with an interindividual variability of 22%. Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After dry powder inhalation urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in gut that is eliminated via the faeces. The renal clearance of tiotropium bromide exceeds the creatinine clearance, indicating secretion into the urine. After chronic once daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2-3 weeks with no accumulation thereafter.

Linearity / Nonlinearity: Tiotropium bromide demonstrates linear pharmacokinetics in the therapeutic range after both intravenous administration and dry powder inhalation.

c) Characteristics in Patients

Geriatric Patients: As expected for all predominantly renally excreted drugs, advanced age was associated with a decrease of tiotropium bromide renal clearance (326 mL/min in COPD patients < 58 years to 163 mL/min in COPD patients > 70 years) which may be explained by decreased renal function. Tiotropium bromide excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients), however plasma concentrations did not change significantly with advancing age within COPD patients if compared to inter- and intraindividual variability (43% increase in AUC_{0-4h} after dry powder inhalation.

Renally Impaired Patients: In common with all other drugs that undergo predominantly renal excretion, renal impairment was associated with increased plasma drug concentrations and reduced renal drug clearance after both intravenous infusion and dry powder inhalations. Mild renal impairment (CL_{CR} 50-80 ml/min) which is often seen in elderly patients increased tiotropium bromide plasma concentrations slightly (39% increase in AUC_{0-4h} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CL_{CR} < 50 ml/min) the intravenous administration of tiotropium bromide resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4h}), 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 bromide pharmacokinetics. Tiotropium bromide is predominantly cleared by renal elimination (74% in young healthy volunteers) and simple non-enzymatic ester cleavage to pharmacologically inactive products.

Paediatric Patients: See 4.2 Posology and Method of Administration

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. 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 (which contains milk protein)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

After first opening of the blister: 9 days

Discard the HandiHaler device 12 months after first use.

6.4 Special precautions for storage

Do not store above 25°C

Do not freeze.

6.5 Nature and contents of container

Aluminium / PVC / Aluminium blister strips containing 10 capsules.

The HandiHaler is a single dose inhalation device made from plastic materials (ABS) and stainless steel.

Package sizes and devices supplied:

• Cardboard box containing 30 capsules (3 blister strips)

• Cardboard box containing HandiHaler device and 30 capsules (3 blister strips)

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
4 Altona Road
Lisburn
BT27 5QB
Northern Ireland

8 Parallel Product Authorisation Number

PPA 1473/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th June 2009

10 DATE OF REVISION OF THE TEXT