Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ipragard Inhaler CFC-Free 20 micrograms per metered dose, pressurised inhalation, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose (ex-valve) contains 20 micrograms of ipratropium bromide (as the monohydrate). This is equivalent to a delivered dose (ex-actuator) of 18 micrograms ipratropium bromide (as the monohydrate).

Each metered dose (ex-valve) contains 8.4 mg of ethanol
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Pressurised inhalation, solution
Each container is filled with clear, colourless liquid, free from suspended particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ipragard Inhaler CFC-Free is indicated for the regular treatment of reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD) and chronic asthma.

4.2 Posology and method of administration

Posology

For inhalation use.

Children and adolescents:

This pressurised metered dose inhaler is not to be used in children, 12 years of age and younger or adolescents 13 to 17 years of age.

Adults (including the elderly) with asthma or COPD:

- 1 or 2 puffs to be inhaled three or four times daily.
- However, in early treatment some patients may need up to 4 puffs at a time to obtain maximum benefit.

The recommended dose should not be exceeded.

If therapy does not produce a significant improvement, if the patient's symptoms are getting worse or if a reduced response to treatment becomes apparent, medical advice must be sought. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Method of administration

The correct administration of ipratropium bromide from the inhaler is essential for successful therapy. It is imperative that patient’s inhaler technique should be checked to ensure optimum drug delivery of ipratropium bromide to the lungs from time to time.

It is advised to read the Patient Information Leaflet **carefully before using this inhaler and to take note regarding how to use the inhaler, how to inhale from the inhaler correctly and how to clean the inhaler.**

The canister should be pressed twice to release two metered doses into the air before the inhaler is used for the first time, or when the inhaler has not been used for 3 days or more, to ensure that the inhaler is working properly and that it is ready for use.

On each occasion on which the inhaler is used the following instructions should be followed:

1. Stand or sit upright while using the Ipragard Inhaler
2. Remove the mouthpiece cover.
3. Check inside and outside the mouthpiece of the inhaler to make sure that it is clean and free from dust and dirt and any loose objects before inhaling.
4. Hold the inhaler upright between the thumb(s) on the base of the mouthpiece and a forefinger(s)/index finger(s) on the top of the inhaler (the arrow on the base of the container should be pointing upwards), breathe out for as long as is comfortable, and as slowly and deeply as possible.
5. Immediately after breathing out place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it
6. Breathe in slowly and deeply, through the mouth and immediately after starting to breathe in press down firmly on the top of the inhaler to release one actuation (puff) and continue to breathe in steadily and deeply.
7. Hold the breath, remove the inhaler from the mouth and take away the finger from top of the inhaler. Continue to hold the breath for as long as is comfortable, for 10 seconds if possible.
8. Breathe out slowly Do not breathe out into the inhaler.
9. If a second inhalation is required you should wait at least one minute and then repeat steps 4 to 8.
10. Replace the mouthpiece cover after use.

IMPORTANT

- Do not inhale too quickly, start breathing in as slowly and steadily as possible just before pressing the inhaler
- Do not rush through the entire procedure
- Elderly patients and patients with weak hands may use the inhaler with both hands
- Practice inhalation technique in front of a mirror; if a mist is seen following inhalation, either from the inhaler itself or from the sides of the mouth, the inhalation procedure should be repeated

Cleaning
It is important to clean your inhaler regularly. Otherwise it may not work properly.

- Remove the canister and green mouthpiece cover.
- Wash and clean the white mouthpiece in warm soapy water.
- Rinse in warm water and allow to air dry without using any heating system.
- Make sure the small hole in the mouthpiece is washed through thoroughly.

Once the white mouthpiece is dry, replace the canister and the cap

DO NOT PUT THE METAL CANISTER INTO WATER

Please read the Patient Information Leaflet for appropriate instructions for use/inhalation

This pressurised metered dose inhaler is NOT to be used with any spacing device. If a spacing device is required the patient will have to have their anticholinergic treatment changed to an alternative product that can be used with a spacing device.

The canister is not transparent. It is therefore not possible to see when it is empty. The inhaler will deliver 200 actuations. When these have all been used (usually after 3 - 4 weeks of regular use) the inhaler may still appear to contain a small amount of fluid. However the inhaler should be replaced in order to ensure that each metered dose contains the correct amount of medicine.

If the Inhaler has been exposed to low temperatures, the patient should take the metal canister out of the plastic case and warm it in their hands for a minimum of two minutes.

WARNING:

The plastic mouthpiece has been specially designed for use with Ipragard Inhaler CFC-Free to ensure that each metered dose contains the correct amount of medicine. The mouthpiece must never be used with any other metered dose inhaler nor must Ipragard Inhaler CFC-Free be used with any mouthpiece other than the one supplied with the product.

The mouthpiece should always be kept clean (as per the cleaning procedure mentioned above).

4.3 Contraindications

Ipratropium bromide should not be used by patients with known hypersensitivity to atropine or its derivatives, or to ipratropium bromide or to any other component of the product.

4.4 Special warnings and precautions for use

If treatment with ipratropium bromide does not produce significant improvement, if the patient's symptoms are getting worse or if a reduced response to treatment becomes apparent, medical advice must be sought. In the case of acute or rapidly deteriorating dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

Increasing use of any as required short-acting β_2 adrenoceptor agonist bronchodilators to relieve asthma symptoms, lack of relief from as required short-acting β_2 adrenoceptor agonist bronchodilators, short-acting bronchodilators becoming ineffective and/or increasing symptoms indicate deterioration of asthma control and patients should be reviewed by a doctor

It should be noted that an exacerbation of the clinical symptoms of asthma may be due to an acute respiratory tract bacterial infection and treatment may require appropriate antibiotics, an increase in the dose of any inhaled corticosteroids and/or a short course of oral conrticosteroids. A rapid acting, short acting inhaled β_2 adrenoceptor agonist should always be available as rescue medication.

Hypersensitivity reactions following the use of ipratropium bromide have been seen and have presented as urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Caution is advocated in the use of anticholinergic agents in patients predisposed to or with narrow-angle glaucoma, or with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-outflow obstruction).

As patients with cystic fibrosis may be prone to gastrointestinal motility disturbances, ipratropium bromide, as with other anticholinergics, should be used with caution in these patients.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with a β_2 adrenoceptor agonist, has come into contact with the eyes. Thus patients must be instructed in the correct administration of Ipragard Inhaler CFC-Free and warned against the accidental release of the contents of the inhaler into the eye. Since ipratropium bromide is inhaled via a mouthpiece and with manual control, the risk of the mist entering the eyes is limited. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals

and patients who may be susceptible to glaucoma should be warned specifically on the need for ocular protection.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develop, treatment with miotic drops should be initiated and specialist advice sought immediately.

Patients should be informed when starting treatment that the onset of action of ipratropium bromide is slower than that of inhaled sympathomimetic bronchodilators.

As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid –acting inhaled bronchodilator and should be treated straightaway. Ipragard Inhaler CFC-Free should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

This medicinal product contains a small amount of ethanol (8.4 mg in one single dose).

Ipratropium bromide has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in these patient populations

4.5 Interaction with other medicinal products and other forms of interaction

There is evidence that the administration of ipratropium bromide with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect.

4.6 Fertility, pregnancy and lactation

There is no experience of the use of this product in pregnancy and lactation in humans. It should not be used in pregnancy or lactation unless the expected benefits to the mother are thought to outweigh any potential risks to the fetus or neonate.

Pregnancy

The safety of ipratropium bromide during human pregnancy has not been established. The benefits of using ipratropium bromide during a confirmed or suspected pregnancy must be weighed against the possible hazards to the unborn child. Preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

Breastfeeding

It is not known whether ipratropium bromide is excreted into breast milk. It is unlikely that ipratropium bromide would reach the infant to an important extent, however caution should be exercised when ipratropium bromide is administered to nursing mothers.

Studies of HFA-134a administered to pregnant and lactating rats and rabbits have not revealed any special hazard.

Fertility

The effect of ipratropium bromide on fertility has not been studied, no fertility data are available. . Therefore in case of planned pregnancy the product should be used with caution after consultation with doctor.

4.7 Effects on ability to drive and use machines

Ipratropium bromide has a moderate influence on the ability to drive or use machines.

No studies on the effects on the ability to drive and use machines have been performed, however patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis, blurred

vision, visual halos and/or coloured images, red eyes, eye pain or discomfort during treatment with ipratropium bromide. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery and should contact their doctor straightaway.
If the eyes are affected in any way at all do not drive or operate machinery. Contact your doctor.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic properties of ipratropium bromide. As with all inhalation therapy ipratropium bromide may show symptoms of local irritation.

The most frequent side effects known from clinical trials were headache, throat irritation, cough, dry mouth, gastro-intestinal motility disorders (including constipation, diarrhoea and vomiting), nausea, and dizziness.

Frequencies

Very common $\geq$ 1/10

Common $\geq$ 1/100 < 1/10

Uncommon $\geq$ 1/1,000 < 1/100

Rare $\geq$ 1/10,000 < 1/1,000

Very rare < 1/10,000

Immune system disorder

Hypersensitivity (1)	Uncommon
Anaphylactic reaction	Uncommon
Angioedema of tongue, lips & face	Uncommon

Nervous system disorders

Headache	Common
Dizziness	Common

Eye disorders

Blurred vision	Uncommon
Mydriasis (2)	Uncommon
Intraocular pressure increased (2)	Uncommon
Glaucoma (2)	Uncommon
Eye pain (2)	Uncommon

Halo vision	Uncommon
Conjunctival hyperaemia	Uncommon
Corneal oedema	Uncommon
Accommodation disorder	Rare
Cardiac Disorders	
Palpitations	Uncommon
Supraventricular tachycardia	Uncommon
Atrial fibrillation	Rare
Heart rate increased	Rare
Respiratory, Thoracic and Mediastinal Disorders	
Throat irritation	Common
Cough	Common
Bronchospasm	Uncommon
Paradoxical bronchospasm(3)	Uncommon
Laryngospasm	Uncommon
Pharyngeal oedema	Uncommon
Dry throat	Uncommon
Gastro-intestinal Disorders	
Dry mouth	Common
Nausea	Common
Gastro-intestinal motility disorder e.g. Diarrhoea	Common Uncommon
Constipation	Uncommon
Vomiting	Uncommon
Stomatitis	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Uncommon
Pruritus	Uncommon
Urticaria	Rare

Renal and Urinary Disorders

Urinary retention (4) Uncommon

(1) Hypersensitivity reactions following the use of ipratropium bromide have been seen and have presented as urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis. If severe allergic reactions occur, ipratropium bromide should be discontinued immediately, do not use your Ipragard Inhaler CFC-Free again, talk to your doctor or pharmacist immediately.

(2) Ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an β_2 adrenoceptor agonist, has come into contact with the eyes - see section 4.4.

(3) As with other inhalation therapy paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid –acting inhaled bronchodilator and should be treated straightaway. Ipratropium bromide should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

(4) The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

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 IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of ipratropium bromide, no serious anticholinergic symptoms are to be expected. As with other anticholinergics, dry mouth, visual accommodation disturbances and tachycardia would be the expected symptoms and signs of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC Code): R03B B01

Ipratropium bromide is a quaternary ammonium compound with anti-cholinergic (parasympatholytic) properties.In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca++ which is caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle. Ca++ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol).

The bronchodilation following inhalation of ipratropium bromide is induced by local drug concentrations sufficient for anticholinergic efficacy at the bronchial smooth muscle and not by systemic drug concentrations.

In clinical trials using metered dose inhalers in patients with reversible bronchospasm associated with asthma or chronic obstructive pulmonary disease significant improvements in pulmonary function (FEV, increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted for approximately 4 hours.

Preclinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance or gas exchange.

5.2 Pharmacokinetic properties

Absorption

The therapeutic effect of ipratropium bromide is produced by a local action in the airways. Time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.

Following inhalation, 10 to 30% of a dose is generally deposited in the lungs, depending on the formulation, device and inhalation technique. The major part of the dose is swallowed and passes through the gastro-intestinal tract.

The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).

Cumulative renal excretion (0-24 hrs) of parent compound is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3 to 13% of an inhaled dose. Based on these data the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively.

Taking this into account, swallowed dose portions of ipratropium bromide do not contribute significantly to systemic exposure.

Distribution

The drug is minimally (less than 20%) bound to plasma proteins. The quarternary amine of the ipratropium ion does not cross the blood-brain barrier.

Biotransformation

Ipratropium has a mean total clearance of 2.3 L / min and a renal clearance of 0.9 L / min. After intravenous administration approximately 60% of the dose is metabolised, mainly by conjugation (40%), whereas after inhalation about 77% of the systemically available dose is metabolised by ester hydrolysis (41%) and conjugation (36%).

Elimination

After inhalation of ipratropium bromide
either with HFA 134a or CFC propellant, cumulative renal excretion over 24 hours was approximately 12% and l0%, respectively.

In an excretion balance study cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.2 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1, 1, 1, 2- tetrafluoroethane (HFA 134a)
Ethanol anhydrous
Purified water
Citric acid anhydrous.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25°C. Protect from direct sunlight, heat and frost.

The canister contains a pressurised liquid. Do not expose to temperatures higher than 50°C. Do not pierce the canister.

If the Inhaler has been exposed to low temperatures, the patient should take the metal canister out of the plastic case and warm it in their hands for a minimum of two minutes.

6.5 Nature and contents of container

An Inhaler comprises of 19 ml pressurised pure aluminium anodized canister (containing 12.8 ml of solution) sealed with a 50 µl metering valve made up of a thermoplastic and a plastic actuator made up of polypropylene having a white mouthpiece fitted with a green mouthpiece cover. Each canister contains 200 metered actuations of 20 micrograms of ipratropium bromide.
Ipragrad Inhaler CFC-Free contains a propellant, HFA134a, and does not contain any chlorofluorocarbons (CFCs).

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Cipla (EU) Limited .
Hillbrow House,
Hillbrow Road,
Esher, Surrey,
KT10 9NW,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1809/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th March 2014

10 DATE OF REVISION OF THE TEXT