IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA0465/173/002
Case No: 2054664

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Atrovent UDVs 500microgram/2ml Nebuliser Solution

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 **20/10/2008** until **08/01/2011**.

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

Atrovent® UDVs® 500 micrograms/2ml Nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose unit contains 0.025% w/v ipratropium bromide (monohydrate) i.e. 500 micrograms in 2 ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Nebuliser Solution.
Product imported from the UK:
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ATROVENT 250 UDVs, 1 ml and ATROVENT UDVs, 2 ml are indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease and, when used concomitantly with inhaled $beta_2$-agonists, for treatment of acute and chronic asthma and acute bronchospasm associated with chronic obstructive pulmonary disease.

4.2 Posology and method of administration

The dosage should be adapted to the individual needs of the patient. Unless otherwise prescribed the following doses are recommended:

Adults (including the elderly) and children over 12 years of age:

500 micrograms 3 to 4 times daily.
For treatment of acute bronchospasm, 500 micrograms.
Repeated doses can be administered until the patient is stable. The time interval between the doses may be determined by the physician.
It is advisable not to exceed the recommended daily dose during either acute or maintenance treatment. Daily doses exceeding 2 mg in adults and children over 12 years of age should only be given under medical supervision.

Children under 12 years of age:

250 micrograms up to a total daily dose of 1mg.
The time interval between doses may be determined by the physician.

For acute bronchospasm, repeated doses may be administered until the patient is stable. The time interval between doses may be determined by the physician.

It is advisable not to exceed the recommended daily dose. Daily doses exceeding 1mg in this age group should be given under medical supervision.

There is limited information for children under 6 years of age, therefore the recommended dose should only be given under medical supervision.

ATROVENT UDVs can be administered combined with an inhaled $beta_2$-agonist.

The dose of nebuliser solution may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used; if dilution is necessary use only sterile sodium chloride 0.9% solution.

If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought. In the case of acute or rapidly worsening dyspnoea (difficulty in breathing) a doctor should be consulted immediately.

ATROVENT UDVs can be administered using a range of commercially available nebulising devices.

ATROVENT UDVs and disodium cromoglycate inhalation solutions that contain the preservative benzalkonium chloride should not be administered simultaneously in the same nebuliser as precipitation may occur.

Administration

The unit dose vials are intended only for inhalation with suitable nebulising devices and should not be taken orally or administered parenterally.

1. Get your nebuliser ready by following the manufacturer's instructions and the advice of your doctor.

2. Carefully separate a new dose unit from the strip. NEVER use one which has been opened already.

3. Open by simply twisting off the top, always taking care to hold it in an upright position.

4. Unless otherwise instructed by your doctor, squeeze all the contents into the nebuliser chamber. If dilution is necessary this should be carried out using ONLY sterile sodium chloride 0.9% solution and as instructed by your doctor.

5. Use your nebuliser as directed by your doctor.

6. After you have finished, throw away any leftover solution. Follow the manufacturer's instructions for cleaning your nebuliser. It is important that your nebuliser is kept clean.

4.3 Contraindications

Known hypersensitivity to atropine or its derivatives, or to any other component of the product.

4.4 Special warnings and precautions for use

Caution is advocated in the use of anticholinergic agents in patients with narrow-angle glaucoma, or with prostatic hyperplasia or bladder-outflow obstruction.

As patients with cystic fibrosis may be prone to gastro-intestinal motility disturbances, ATROVENT, as with other anticholinergics, should be used with caution in these patients.

Immediate hypersensitivity reactions following the use of ATROVENT have been demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic $beta_2$-agonist, has come into contact with the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival and corneal congestion 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 must be instructed in the correct administration of ATROVENT UDVs. Care must be taken not to allow the solution or mist to enter the eyes. It is recommended that the nebulised solution is administered via a mouthpiece. If this is not available and a nebuliser mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

4.5 Interaction with other medicinal products and other forms of interaction

There is evidence that the administration of ATROVENT with beta-adrenergic drugs and xanthine preparations may intensify the bronchodilator effect of ATROVENT.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma (see Special Warnings and Special Precautions for Use) may be increased when nebulised ipratropium bromide and $beta_2$-agonists are administered simultaneously.

4.6 Pregnancy and lactation

The safety of ATROVENT during human pregnancy has not been established. The benefits of using ATROVENT 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.

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

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The most frequent non-respiratory adverse reactions reported in clinical trials with ATROVENT were headache, nausea (with or without vomiting) and dryness of the mouth.
The following side effects have been observed with ATROVENT: tachycardia, palpitations, supraventricular tachycardia and atrial fibrillation in patients known to be susceptible, visual accommodation disturbances, gastro-intestinal motility disturbances and urinary retention. These side effects have been rare and reversible. The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

Ocular side effects have been reported (see: Special Warnings and Special Precautions for Use).

As with other inhaled bronchodilator therapy, cough, local irritation and inhalation induced bronchoconstriction may occur.

Allergic-type reactions such as skin rash, angioedema of the tongue, lips and face, urticaria, laryngospasm and anaphylactic reactions have been reported.

4.9 Overdose

No symptoms specific to overdosage have been encountered. In view of the wide therapeutic window and topical administration of ATROVENT, 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

ATROVENT is a quaternary ammonium compound with anticholinergic (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 cyclic guanosine monophosphate (cyclic GMP) caused by interaction of acetylcholine with the muscarinic receptor on bronchial smooth muscle.

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

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

In controlled 90 day studies in patients with bronchospasm associated with chronic obstructive pulmonary disease (e.g. chronic bronchitis and emphysema) significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ increases of 15% or more) occurred within 15 minutes, reached a peak in 1-2 hours, and persisted in the majority of patients up to 6 hours.

The bronchodilator effect of ATROVENT in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children over 6 years of age. In most of these studies ATROVENT was administered in combination with an inhaled $beta_2$-agonist.

Although the data are limited, ATROVENT has been shown to have a therapeutic effect in the treatment of bronchospasm associated with viral bronchiolitis and bronchopulmonary dysplasia in infants and very small children.

5.2 Pharmacokinetic properties

The therapeutic effect of ATROVENT is produced by a local action in the airways. Therefore time courses of bronchodilation and systemic pharmacokinetics do not run in parallel.

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

Due to the negligible gastro-intestinal absorption of ipratropium bromide the bioavailability of the swallowed dose portion accounts for only approximately 2% of the dose. This fraction of the dose does not make a relevant contribution to the plasma concentrations of the active ingredient. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes) and has a nearly complete systemic availability.

From data of renal excretion (0-24 hours) the total systemic bioavailability (pulmonary and gastro-intestinal portions) of inhaled doses of ipratropium bromide was estimated to be in the range of 7 to 28%. It is assumed that this is also a valid range for the inhalation from the solution for inhalation preparation.

Kinetic parameters describing the distribution of ipratropium bromide were calculated from plasma concentrations after i.v. administration.

A rapid biphasic decline in plasma concentrations is observed. The volume of distribution (Vz) is 338 L (≅4.6 L/kg). The drug is minimally (less then 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the ammonium structure of the molecule.

The half -life of the terminal elimination phase is about 1.6 hours.

The mean total clearance of the drug is determined to be 2.3 L/min. The major portion of approximately 60% of the systemic available dose is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

A portion of approximately 40% of the systemic available dose is cleared via urinary excretion corresponding to an experimental renal clearance of 0.9 L/min. (After oral dosing less than 1% of the dose is renally excreted, indicating an insignificant absorption of ipratropium bromide from the gastro-intestinal tract.)

In excretion balance studies after intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all metabolites) is excreted via the biliary-faecal route. The dominant excretion of drug-related radioactivity occurs via the kidneys.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
1N Hydrochloric Acid
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

As the product contains a preservative, a fresh vial should be used for each dose and the vial should be opened immediately before administration.
Any solution left in the vial should be discarded.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

Low-density polyethylene (LDPE) single dose units formed in strips of 10. Each single dose unit contains 2ml of solution. Pack sizes of 60 .

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 222,
Western Industrial Estate,
Naas Road,
Dublin 12.

8 MARKETING AUTHORISATION NUMBER

PPA 465/173/2