APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

PROPRIETARY NAME (and dosage form):

Atrovent® 20 HFA
metered dose inhaler

COMPOSITION:
Each 50 µL metered dose (puff) contains 0,021 mg ipratropium bromide monohydrate corresponding to 0,020 mg ipratropium bromide anhydrous.

Excipients:
Propellant: 1,1,1,2 – tetrafluoroethane (HFA [hydrofluoroalkane] 134a).
Other excipients: citric acid anhydrous, water purified, ethanol anhydrous (15 % *m/m*), nitrogen (inert gas).

CATEGORY AND CLASS:
A 10.2.1 Bronchodilators-Inhalants

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. 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).

Pharmacokinetic properties:
Absorption:
The therapeutic effect of ipratropium 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 and inhalation technique. The major part of the dose is swallowed and passes through the gastrointestinal tract.

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

Cumulative renal excretion (0 - 24 hrs) of the 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 relevantly contribute to systemic exposure.

Distribution:
Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (Vdss) is approximately 176 L (≈ 2,4 L/kg). Ipratropium is minimally (less than 20 %) bound to plasma proteins. The quaternary amine ipratropium does not cross the blood brain barrier.

Biotransformation:
After intravenous administration approximately 60 % of a dose is metabolised, the major portion probably in the liver by oxidation.
The known metabolites, which are formed by hydrolysis, dehydration or elimination of the hydroxy-methyl group in the tropic acid moiety, show very little or no affinity for the muscarinic receptor and have to be regarded as ineffective.

Elimination:
The half-life of the terminal elimination phase is approximately 1,6 hours.

Ipratropium has a total clearance of 2,3 L/min and a renal clearance of 0,9 L/min.

In an excretion balance study cumulative renal excretion (6 days) of medicine-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 medicine-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of medicine-related radioactivity (parent compound and metabolites) is 3,6 hours.

INDICATIONS:
To relieve the reversible bronchospasm in chronic obstructive pulmonary disease, in patients with:
- chronic bronchitis
- bronchial asthma
- emphysema

CONTRAINDICATIONS:

ATROVENT 20 HFA metered dose inhaler is contraindicated in patients known to be hypersensitive to atropine-like substances (such as the active substance ipratropium bromide) or to any other component of ATROVENT 20 HFA.
Safety in children has not been proven.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity:
Immediate hypersensitivity reactions may occur after administration of ATROVENT 20 HFA metered dose inhaler, as demonstrated by urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

Paradoxical bronchospasm:
ATROVENT 20 HFA may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ATROVENT 20 HFA should be discontinued immediately and substituted with an alternative therapy.

Ocular complications:
ATROVENT 20 HFA should be used with caution in patients predisposed to narrow-angle glaucoma.
There have been reports of ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when ATROVENT 20 HFA either alone or in combination with an adrenergic β_2 agonist, has come in contact with the eyes. Thus patients must be instructed in the correct administration of ATROVENT 20 HFA metered dose inhaler.
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.
Care must be taken not to allow the spray to enter the eyes.

Renal and urinary effects:
ATROVENT 20 HFA should be used with caution in patients with pre-existing urinary outflow tract obstruction (e.g. prostatic hyperplasia or bladder-neck obstruction).

Gastrointestinal motility disturbances:
Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

The plastic mouthpiece has been specially designed for use with ATROVENT 20 HFA metered dose inhaler to ensure that the right amount of medicine is always obtained with each dose sprayed. The mouthpiece must never be used with any other metered dose inhaler nor must the ATROVENT 20 HFA metered dose inhaler be used with any mouthpiece other than the one supplied with ATROVENT 20 HFA.
The canister is under pressure and should on no account be opened by force or exposed to temperatures exceeding 50 °C.

Effects on ability to drive and use machines:
No studies of 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 and blurred vision during treatment with ATROVENT 20 HFA. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above-mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

INTERACTIONS:
The chronic co-administration of ATROVENT 20 HFA metered dose inhaler with other anticholinergic medicines has not been studied. Therefore, the chronic co-administration of ATROVENT 20 HFA with other anticholinergic medicines is not recommended.

Beta-adrenergics and xanthine preparations may intensify the bronchodilatory effect.

HUMAN REPRODUCTION:
Pregnancy:
Safety in pregnancy has not been established.

Lactation:
Safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:
Dosage and administration:
The dosage should be adapted to the individual requirements of the patient.
If therapy does not produce a significant improvement or if the patient's condition gets worse, medical advice must be sought.

The following doses are recommended for adults:

Maintenance treatment:
2 metered doses (puffs) four times daily.
Since a requirement for increasing the doses suggests that additional therapeutic modalities may be needed, a total daily dose of 12 puffs should not be exceeded.

Instructions for use:
The correct administration is essential for successful therapy.
Before first time use: The valve should be depressed twice before the inhaler is used.

Before each use the following rules should be observed:
1. Remove protective cap from the mouthpiece.
2. Breathe out deeply.

3. Hold the metered dose inhaler as shown in Fig. 1. Place the mouthpiece into the mouth, closing the lips around the mouthpiece. The arrow and the base of the canister should be pointing upwards.



Fig. 1

4. Breathe in as deeply as possible and press the base of the canister firmly at the same time - this releases one metered dose. Hold the breath for a few seconds, then remove the mouthpiece from the mouth and breathe out. The same action should be repeated for a second inhalation.
5. Replace the protective cap after use.
6. After not using the inhaler for three days the valve has to be actuated once.

The container is not transparent. It is, therefore, not possible to see when it is empty. The inhaler will deliver 200 doses (puffs). When these have all been used, the canister may still appear to contain a small amount of fluid. The inhaler should, however, be replaced because the right amount of medication might not be obtained with each puff. The amount of doses in the canister can be checked as follows:
Shaking the canister will show if there is any remaining fluid. Alternatively remove the canister from the plastic mouthpiece and put it into a container of water. The contents of the canister can be estimated by observing its position in the water (see Fig. 2).

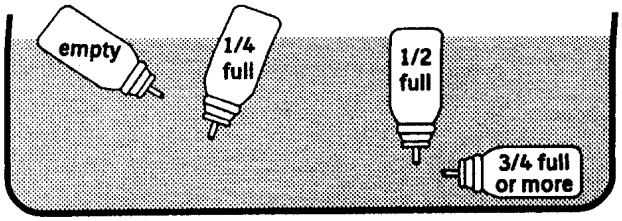


Fig. 2

SIDE EFFECTS:

Many of the listed side effects can be assigned to the anticholinergic properties of ATROVENT 20 HFA. ATROVENT 20 HFA may lead to symptoms of local irritation. Side effects were identified from data obtained in clinical trials and pharmacovigilance during post-approval use of ATROVENT.

The most frequent side effects reported in clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhoea and vomiting), nausea and dizziness.

Frequency classes:
Derived from clinical trial data: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports; not known (cannot be estimated from the available data).

Immune system disorders:
Uncommon: hypersensitivity, anaphylactic reaction

Nervous system disorders:
Common: headache, dizziness

Eye disorders:
Uncommon: blurred vision, mydriasis, increased intraocular pressure, glaucoma, eye pain, halo vision, conjunctival hyperaemia, corneal oedema
Rare: accommodation disorder

Cardiac disorders:
Uncommon: palpitations, supraventricular tachycardia
Rare: atrial fibrillation, increased heart rate

Respiratory, thoracic and mediastinal disorders:
Common: cough, throat irritation
Uncommon: bronchospasm, paradoxical bronchospasm, laryngospasm, pharyngeal oedema, dry throat

Gastrointestinal disorders:
Common: dry mouth, nausea, gastrointestinal motility disorder
Uncommon: constipation, diarrhoea, vomiting, stomatitis, mouth oedema

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus, angioedema
Rare: urticaria

Renal and urinary disorders:
Uncommon: urinary retention
The risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Post-marketing experience:

In a 5 year placebo controlled trial, hospitalisations for supraventricular tachycardia and/or atrial fibrillation occurred with an incidence rate of 0,5 % in COPD patients receiving ATROVENT inhaler (CFC-containing formulation).

In addition to the side effects reported in the controlled clinical trials, side effects have been identified during post-approval use of ATROVENT; because these side effects are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure to ATROVENT.
Allergic-type reactions such as skin rash, angioedema including that of the tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases.
Additionally, urinary retention, mydriasis, gastrointestinal distress (diarrhoea, nausea, vomiting), cough and bronchospasm including paradoxical bronchospasm, hypersensitivity reactions, increased intraocular pressure, accommodation disorder, increased heart rate, pharyngeal oedema, and gastrointestinal motility disorders have been reported during the post-marketing period with use of ATROVENT.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No symptoms specific to overdosage have been encountered. Minor systemic manifestations of anticholinergic action including dry mouth, visual accommodation disorder and increase of heart rate may occur.
Treatment is symptomatic and supportive.

IDENTIFICATION:

Clear, colourless liquid under pressure in a one-piece stainless steel canister fitted with a metering valve.

PRESENTATION:

Metered dose inhaler consisting of a stainless steel canister, sealed with a metering valve and fitted with a mouthpiece.
Each metered dose inhaler contains 200 metered doses (10 mL).

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep out of the reach of children.
Do not expose the canister to high temperatures and do not force it open.

REGISTRATION NUMBER:

37/10.2.1/0273

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Ingelheim Pharmaceuticals (Pty) Limited
407 Pine Avenue
Randburg

South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 25 November 2005
Revised: 20 March 2018.

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