1.3.1.1. Professional Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

IPRABUT 0,5 mg ipratropium bromide and 2,5 mg salbutamol sulphate per 2,5 ml solution for nebulisation.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2,5 ml unit of IPRABUT contains 0,5 mg of ipratropium bromide and 2,5 mg of salbutamol (as sulphate).

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for nebulisation

IPRABUT is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

IPRABUT is indicated for the management of reversible bronchospasm associated with obstructive pulmonary disease.

4.2. Posology and method of administration

Posology

The recommended dose is:

Adults, including elderly patients and children over 12 years of age:

Treatment of acute attacks:

1 (One) Unit dose vial is sufficient for prompt symptom relief in many cases.

In severe cases if an attack has not been relieved by one-unit dose vial, two-unit dose vials may be required. In these cases, patients should consult their doctor or the nearest hospital immediately.

Maintenance treatment:

1 (One) Unit dose vial three or four times daily.

Do not exceed the recommended dose.

Paediatric population

There is no experience in the use of IPRABUT in children under 12 years of age.

Method of administration

IPRABUT solution for nebulisation may be administered from a suitable nebuliser or an intermittent positive pressure ventilator.

IPRABUT should not be taken orally or administered parenterally.

- Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.
- It is strongly recommended not to mix IPRABUT solution for inhalation with other medicines in the same nebuliser reservoir.
- If dilution is necessary, this should be carried out using ONLY sterile sodium chloride 0,9 % solution as instructed by a medical practitioner.

For instructions on further handling or manipulation/dilution of IPRABUT before administration see section 6.6.

4.3. Contraindications

IPRABUT is contraindicated in:

- Patients with hypersensitivity to salbutamol (as sulphate), ipratropium bromide, atropine or its derivatives or to any excipients in IPRABUT listed in section 6.1.
- Patients with hypertrophic obstructive cardiomyopathy or tachydysrhythmia.
- Children under 12 years of age.

4.4. Special warnings and precautions for use

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of IPRABUT, as demonstrated by less frequent cases of urticaria, angio-oedema, rash, bronchospasm and oropharyngeal oedema.

Paradoxical bronchospasm

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. IPRABUT should be discontinued immediately, the patient should be assessed, and alternative therapy instituted if necessary.

Ocular complications

Ocular complications (i.e. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) may occur when aerosolised ipratropium bromide either alone or in conjunction with a beta$_2$-agonist, has escaped into the eyes.

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 must be instructed in the correct use of IPRABUT (see section 4.2). Care must be taken not to expose the eyes to the solution or mist of IPRABUT. It is recommended that the nebulised solution be 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.

Conditions at risk

In the following conditions IPRABUT should only be used after careful risk/benefit assessment, especially when doses higher than recommended are used: insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Cardiovascular effects

There is some evidence from post-marketing data and published literature of occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying heart disease (ischaemic heart disease, tachydysrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease.

Dyspnoea

The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea.

Hypokalaemia

Potentially serious hypokalaemia may result from beta$_2$-agonist therapy. Particular caution is advised in severe airway obstruction as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving digoxin, see section 4.5). It is recommended that serum potassium levels are monitored in such situations.

Porphyria

Safety in porphyria has not been established.

Gastrointestinal motility disturbances

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

Lactic acidosis

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see section 4.8 and 4.9).

Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Interference with laboratory tests or other diagnostic measures

The use of IPRABUT may lead to positive results with regards to salbutamol in tests for non-clinical substance abuse, e.g. in the context of athletic performance enhancement (doping).

Higher than recommended dose

If higher than recommended doses of IPRABUT are required to control symptoms, the patient's therapy plan should be reviewed by a medical practitioner.

The maximum dose should not be exceeded (see section 4.2).

Paediatric population

The safety and efficacy of IPRABUT in children less than 12 years has not been established (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

- Concurrent administration of xanthine derivatives (e.g. theophylline) as well as other beta-adrenergics and anticholinergics may increase the side effects.
- Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction. (see section 4.4).
- A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.
- Salbutamol, as contained in IPRABUT, should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.

- Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.
- Anticholinergic effects of other medicines may be enhanced.
- Digoxin may increase the hypokalaemic effect of ß2 agonists and lead to an increased disposition to dysrhythmias in patients treated with digoxin (see section 4.4).

4.6. Fertility, pregnancy and lactation

The safety of IPRABUT in pregnancy and lactation has not been established.

Pregnancy

The safety of IPRABUT in pregnancy has not been established. There is inadequate published evidence of safety in the early stages of human pregnancy but there has been evidence of some harmful effects on the foetus at very high dose levels.

Breastfeeding

The safety of IPRABUT during breastfeeding has not been established.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

IPRABUT has a moderate influence on the ability to drive and use machines.

Since adverse reactions such as dizziness, accommodation disorder, mydriasis and blurred vision have been reported in patients receiving IPRABUT, patients should not drive, use

machinery or perform any tasks that require concentration, until they are certain that IPRABUT does not adversely affect their ability to do so (see section 4.4 and section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

- Many of the listed undesirable effects can be assigned to the anticholinergic and beta$_2$ – sympathomimetic properties of IPRABUT. As with all inhalation therapy IPRABUT may show symptoms of local irritation.
- The most frequent side effects reported during clinical trials of salbutamol (as a sulphate) and ipratropium bromide were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhoea and vomiting), nausea and dizziness.

b) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown (cannot be estimated from the available data)
Immune system disorders		Anaphylactic reaction[1], hypersensitivity[1], angioedema[2] of the tongue, lips and face[1]	Angioedema
Metabolism and nutrition disorders		Hypokalaemia[2#], hyperglycaemia (with large doses)	Lactic acidosis[2] (see section 4.4)
Psychiatric disorders		Nervousness, mental disorder, agitation, restlessness, anxiety, sleep disturbances	Hyperactivity[2]
Nervous system disorders		Dizziness[1], headache[1,2], tremor[2]	
Eye disorders		Accommodation disorder[1], corneal oedema[1], angle closure glaucoma*, eye pain[1]*, increased intraocular pressure[1]*, mydriasis[1]*,	

		blurred vision[1], conjunctival hyperaemia[1], halo vision[1]	
Vascular disorders		Hypotension and collapse[2], increased systolic blood pressure	Peripheral vasodilation[2]
Cardiac disorders		Palpitations[1,2], tachycardia[2], atrial fibrillation[1,2], dysrhythmia, myocardial ischaemia[2],	Extrasystoles[2]
		supraventricular tachycardia[1,2],	
		decreased diastolic blood pressure	
Respiratory, thoracic and mediastinal disorders		Cough[1], dysphonia, throat irritation[1], bronchospasm[1,2], paradoxical bronchospasm[$1,2], dry throat[1], laryngospasm[1], pharyngeal oedema[1]	
Gastrointestinal disorders	Dry mouth[1,]	Nausea[1],	Mouth and throat irritation[2]
		gastrointestinal motility disorder e.g. diarrhoea[1], constipation[1], vomiting[1], mouth oedema, stomatitis[1], dyspepsia, abdominal pain	
Skin and subcutaneous tissue disorders		Skin reactions, hyperhidrosis, rash[1], urticaria[1,2], pruritus[1], sweating	
Musculoskeletal and connective tissue disorders		Muscle spasms[2], muscular weakness, myalgia	
Renal and urinary disorders		Urinary retention[^1]	
General disorders and administrative site conditions		Asthenia	

1) *Side effects experienced with ipratropium bromide*

2) *Side effects experienced with salbutamol*

c) Description of selected adverse reactions

* Ocular complications with symptoms mentioned above may occur when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta$_2$-agonist, has escaped into the eyes.

[$]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. IPRABUT should be discontinued immediately, the patient should be assessed, and alternative therapy instituted if necessary (see section 4.4).

[^] The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

[#] Potentially serious hypokalaemia may result from $beta_2$ agonist therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/ and to **Aspen Pharmacare:**

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

The effects of overdosage are expected to be primarily related to salbutamol. The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, dysrhythmias and flushing.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth and visual accommodation disturbances) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Treatment

Administration of sedatives, tranquillisers and, in severe cases, intensive therapy. Beta-receptor blockers, preferably $beta_1$-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma. Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 10.2.1 Bronchodilators-inhalants

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases

ATC code: R03AL02

Mechanism of action

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties which inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Salbutamol is a $beta_2$-adrenergic agent which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

The simultaneous delivery of ipratropium bromide and salbutamol sulphate allows stimulation of both muscarinic and $beta_2$-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each medicine singly.

5.2. Pharmacokinetic properties

Combination of ipratropium bromide and salbutamol sulphate

Absorption

It has been shown that co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and that therefore the additive activity of the combination is due to the local effect on the lung following inhalation.

Ipratropium bromide

Absorption

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as determined by blood level and renal excretion studies. After inhalation, maximal responses usually develop over 30 minutes, lasting for 4 to 6 hours.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed.

The apparent volume of distribution at steady-state (V_{dss}) is approximately 176 litres (≈ 2,4 L/kg). The medicine is minimally (less than 20 %) bound to plasma proteins. Ipratropium bromide does not cross the blood brain barrier, nor the placental barrier.

Biotransformation

Ipratropium has a total clearance of 2,3 L/min and a renal clearance of 0,9 L/min. After administration via inhalation approximately 87 % to 89 % of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination

After administration via inhalation about 3,2 % of medicine related radioactivity, i.e. parent compound and metabolites, is eliminated in urine. Total radioactivity excreted via the faeces was for this route of administration. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective. The elimination half-life is about 3 to 4 hours after inhalation or intravenous administration.

Salbutamol

Absorption

Salbutamol sulphate is rapidly and completely absorbed following oral administration either by the inhaled or gastric route and has an oral bioavailability of approximately 50 %. Mean peak plasma salbutamol concentrations of 492 pg/mL occur within three hours after inhalation of IPRABUT.

Distribution

Peak plasma salbutamol concentrations are seen within three hours of administration. Kinetic parameters were calculated from plasma concentrations after intravenous administration. The apparent volume of distribution (Vz) is approximately 156 litres (≈ 2,5 L/kg). Only 8 % of the medicine is bound to plasma proteins. Intravenous salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5 % of the plasma concentrations.

Biotransformation

Following this single inhaled administration, approximately 27 % of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine.

Elimination

Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulfate. The R(-)- enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+) –enantiomer. Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64,2) and 12 % were excreted as sulphate conjugate. After oral administration urinary excretion of unchanged medicine and sulphate conjugate were 31,8 % and 48,2 % of the dose, respectively. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291 mL/min.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydrochloric acid (for pH adjustment), sodium chloride, water for injection.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 30 °C.

Always keep unopened units in the original package and PET/Al/PE pouch so they are well protected from light.

Units in an open PET/Al/PE pouch must be used within 7 days.

Do not freeze.

6.5. Nature and contents of container

IPRABUT is packed in strips of 5 unit-dose, LDPE containers. Sheets of 5 units are packed into a PET/Al/PE pouch. The pouches are packed into an outer cardboard carton.

Pack size: 30's or 60's

Not all packs and pack sizes are necessarily marketed.

Each labelled unit-dose, LDPE container contains 2,5 ml solution.

6.6. Special precautions for disposal and other handling.

Instructions for use:

1. Prepare the nebuliser for filling, according to the instructions provided by the manufacturer or your doctor.
2. Tear one-unit dose vial from the strip.
3. Open the unit dose vial by firmly twisting the top.
4. Squeeze the contents of the unit dose vial into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. After use throw away any solution left in the reservoir and clean the nebuliser, following the manufacturer's instructions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead

2191

8. REGISTRATION NUMBER

51/10.2.1/0153

9. DATE OF FIRST AUTHORISATION

28 September 2021

10. DATE OF REVISION OF TEXT

28 September 2021

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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