Optra-S®

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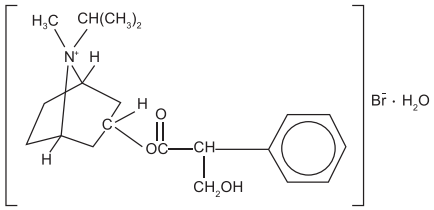
(Ipratropium Bromide + Salbutamol)

Nebuliser Solution 0.5mg + 2.5mg/2.5mL

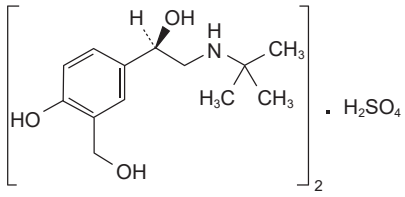
DESCRIPTION
Optra-S Nebuliser Solution contains Ipratropium Bromide & Salbutamol belongs to class of anticholinergic bronchodilator.

Ipratropium Bromide
Ipratropium Bromide is a synthetic quaternary ammonium compound, chemically related to atropine. It is chemically described as (1R,3r,5S,8r)-3-[[(2RS)-3-Hydroxy-2-phenylpropanoyl] oxy]-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane Bromide monohydrate. Its molecular formula is $C_{20}H_{30}BrNO_3 \cdot H_2O$ and the structural formula is:



Ipratromium Bromide Monohydrate

Salbutamol Sulphate
The chemical name of Salbutamol Sulphate is Bis[(1RS)-2-[(1,1-dimethylethyl)amino]-]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol]sulphate. Its molecular formula is $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ and the structural formula is:



Salbutamol Sulphate

QUANTITATIVE & QUALITATIVE COMPOSITION
Optra-S (Ipratropium Bromide + Salbutamol) Nebuliser Solution 0.5mg + 2.5mg/2.5mL is available for administration as:

Each 2.5mL Unit Dose Vial (UDV) contains:
Ipratropium Bromide Monohydrate equivalent to Ipratropium Bromide…0.5mg
Salbutamol Sulphate equivalent to Salbutamol…2.5mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Ipratropium Bromide + Salbutamol Nebuliser Solution provides the simultaneous delivery of Ipratropium Bromide and Salbutamol Sulphate allowing effects on both muscarinic and beta-2 adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

Ipratropium Bromide
Ipratropium Bromide has anticholinergic (parasympatholytic) properties. It inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics inhibit the increase in intracellular Ca^{2+} that is caused by the action of acetylcholine on the muscarinic receptors in bronchial smooth muscle. Ca^{2+} release is mediated through a "second messenger" system which consists of IP3 (inositol triphosphate) and DAG (diacylglycerol).

Salbutamol
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.

Pharmacokinetics
Ipratropium Bromide
Absorption
Cumulative renal excretion (0 to 24 hours) of Ipratropium (the parent substance) is estimated at 46% after an intravenously administered dose, less than 1% of an oral dose and around 3% to 13% of an inhaled dose. Based on these data, the total systemic bioavailability of oral and inhaled doses of Ipratropium Bromide are estimated at 2% and 7% to 28% respectively.

Distribution
The apparent volume of distribution at steady-state (Vdss) is approximately 176L (≈ 2.4L/kg). The active substance is minimally (less than 20%) bound to plasma proteins.

Metabolism
After intravenous administration, around 60% of the dose is metabolised, the largest part through probable oxidation in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have been regarded as ineffective. After administration via inhalation 87%-89% of a dose is metabolized, the major portion probably in liver by oxidation.

Elimination
The half-life in the terminal elimination phase is around 1.6 hours. Ipratropium has a total clearance of 2.3L/min and a renal clearance of 0.9L/min. The half-life for elimination of drug related radioactivity following inhalation is 3.2 hours.

Salbutamol
Absorption
Salbutamol is rapidly and completely absorbed following inhalation or oral administration and has an oral bioavailability of approximately 50%. Mean peak plasma salbutamol concentrations of 492pg/mL occur within three hours after inhalation of Ipratropium Bromide + Salbutamol nebuliser solution.

Distribution
The apparent volume of distribution (Vz) is approximately 156L (≈ 2.5L/kg). Only 8% of the active substance is bound to plasma proteins.

Metabolism
Salbutamol is metabolised via conjugation to salbutamol 4'-O-sulphate. The R(-)- enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer. The majority of the dose was excreted as parent substance (64.2%), and 12% was excreted as sulphate conjugate. After oral administration urinary excretion of unchanged active substance and sulphate conjugate were 31.8% and 48.2% of the dose, respectively.

Elimination
Following a single inhalation, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the urine within 24 hours. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480mL/min and a mean renal clearance of 291mL/min.

Special Populations
Children
This medicine is not recommended in children below 12 years of age because it has not been studied in this age group.

Patients with hepatic or renal impairment
Ipratropium Bromide + Salbutamol has not been studied in patients with hepatic or renal insufficiency and must therefore be administered with caution in these patient groups.

THERAPEUTIC INDICATIONS
Optra-S (Ipratropium Bromide + Salbutamol) Nebuliser Solution is indicated for the symptomatic treatment of bronchospasm in adults and adolescents over 12 years of age with chronic obstructive pulmonary disease who require treatment with both Ipratropium Bromide and Salbutamol.

DOSAGE AND ADMINISTRATION
The recommended dose is:
Adults (including elderly patients and children over 12 years)
1 single unit dose vial three or four times daily.

Important Administration Instructions
Ipratropium Bromide + Salbutamol are intended for the inhalation only and may be administered from a suitable nebuliser or an intermittent positive pressure ventilator. The single dose units must not be taken orally or administered parenterally.
Treatment should be initiated and administered under medical supervision, e.g., in hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician.
The treatment with the nebuliser solution unit dose vials should always be started with the lowest recommended dose (1 unit dose vial). In very severe cases two unit dose vials may be required for symptom relief. Administration should be stopped when sufficient symptom relief is achieved.

ADVERSE REACTIONS
Uncommon: Nervousness, dizziness, headache, tremor, palpitations, tachycardia, cough, dysphonia, throat irritation, dry mouth, nausea, skin reaction and blood pressure systolic increased.

Not Known: Lactic acidosis

Rare: Anaphylactic reaction, hypersensitivity, angioedema of the tongue, lips and face, hypokalemia, mental disorder, accommodation disorder, corneal edema, glaucoma, eye pain, intraocular pressure increased, mydriasis, vision blurred, conjunctival hyperaemia, halo vision, arrhythmia, atrial fibrillation, myocardial ischemia, supraventricular tachycardia, bronchospasm, paradoxical bronchospasm, dry throat, laryngospasm, pharyngeal edema, gastrointestinal motility disorder, diarrhea, constipation, vomiting, edema mouth, stomatitis, hyperhidrosis, rash, urticaria, pruritus, muscle spasms, muscular weakness, myalgia, urinary retention, asthenia and blood pressure diastolic decreased.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Ipratropium Bromide + Salbutamol is contraindicated in:
- Patients with hypersensitivity to the active substance(s) or to any of the excipients of the product.

- Patients with hypersensitivety to atropine or it's derivatives.
- Patients with hypertrophic obstructive cardiomyopathy.
- Patients with tachyarrhythmia.

PRECAUTIONS

Dyspnoea

Patients must be advised to contact a doctor or the nearest hospital immediately in the event of acute or rapidly worsening dyspnoea (breathing difficulties), or if a reduced response to treatment becomes apparent. This could be a sign of a worsening of the patient's chronic obstructive pulmonary disease, and other therapy may be required.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration of Ipratropium Bromide + Salbutamol Nebuliser Solution, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and oropharyngeal edema.

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. Ipratropium Bromide + Salbutamol should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.

Eye Problems

Eye problems (i.e. mydriasis, blurring of vision, increased intraocular pressure, narrow-angle glaucoma and eye pain) have been reported when an Ipratropium Bromide aerosol alone or in combination with a $beta_2$ agonist has come into contact with the eyes.
If any combination of these symptoms develops the patient must seek doctor advice immediately.

Systemic Effects

In conditions like 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 Ipratropium Bromide + Salbutamol should only be used after careful risk/benefit assessment.

Lactic Acidosis

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting $beta_2$ agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease. 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 $beta_2$ agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Cardiovascular Effects

Cardiovascular effects may be seen with sympathomimetic medicinal products including Ipratropium Bromide + Salbutamol. Patients with underlying severe heart disease (e.g. ischemic heart disease, arrhythmia or severe heart failure), who are receiving Salbutamol for respiratory disease, must be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention must be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalemia

Potentially serious hypokalemia 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 hypokalemia on cardiac rhythm (especially in patients receiving digoxin). It is recommended that serum potassium levels are monitored in such situations.

Gastro-intestinal motility disturbances

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances, and therefore Ipratropium Bromide, as with other anticholinergics, must be used with caution in these patients.

Dental Caries

In the event of dry mouth, it is important to observe good oral hygiene due to the increased risk of caries.

Interference with laboratory tests or other diagnostic measures

The use of Ipratropium Bromide + Salbutamol may lead to positive results with regards to Salbutamol in tests for non-therapeutic substance abuse, e.g. in the context of athletic performance enhancement (doping).

Effects on ability to drive and use machines

Patients must be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with Ipratropium Bromide + Salbutamol. If patients experience the above-mentioned side effects, they must avoid potentially hazardous tasks such as driving or operating machines.

Pregnancy

Ipratropium Bromide + Salbutamol should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the fetus.

Nursing Mother

Ipratropium Bromide + Salbutamol should not be administered to breast-feeding mothers unless the expected benefit is thought to outweigh any possible risk to the neonate.

DRUG INTERACTIONS

- The long-term co-administration of Ipratropium Bromide + Salbutamol with other anticholinergic medicinal products has not been studied. Therefore, the long-term co-administration of Ipratropium Bromide + Salbutamol with other anticholinergic medicinal products is not recommended.
- Concurrent use of corticosteroids (e.g. prednisolone), beta-2 agonists (e.g. fenoterol), anticholinergics (e.g. tiotropium) and xanthine derivatives (e.g. theophylline or aminophylline) may enhance the effect of Ipratropium Bromide + Salbutamol on airway function and may increase the severity of side effects. Treatment with Ipratropium Bromide + Salbutamol can lead to hypokalemia. This effect may be enhanced by the concomitant treatment with xanthines, steroids and diuretics. Special consideration must be given to this when treating patients with severe airway obstruction.
- A potentially serious reduction in bronchodilatory effect may occur during concurrent administration of beta-blockers, such as propranolol.
- Beta-2 adrenergic agonists must be administered with caution to patients being treated with monoamine oxidase inhibitors (e.g. Phenelzine) or tricyclic antidepressants (e.g. Amitriptyline), since the action of beta-2 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 beta2 agonists.

OVERDOSAGE

Symptoms

Acute effects of overdosage with Ipratropium Bromide are mild and transient (such as dry mouth, visual accommodation disorders) due to its poor systematic absorption after either inhalation or oral administration.
Manifestations of overdosage with Salbutamol are the result of $beta_2$ adrenergic overstimulation, which may include tachycardia, anginal pain, hypertension, palpitations, tremor, hypokalemia, hypotension, widening of the pulse pressure, arrhythmias and flushing. Metabolic acidosis has also been observed with overdosage of Salbutamol, including lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta agonist therapy. Therefore, monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Management of overdose

Treatment with Ipratropium Bromide + Salbutamol must be discontinued. Acid base and electrolyte monitoring should be considered. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but caution must be used in administering these medicinal products to patients with a history of bronchospasm.

STORAGE

Do not store above 30°C.
Store unused vials in the foil pouch and carton in order to protect from light.
Do not freeze.

The expiration date refers to the product correctly stored at the required conditions.

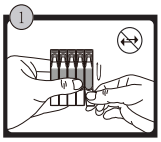
For nebulisation only, not to be injected.

HOW SUPPLIED

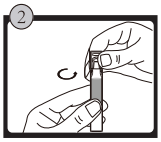
Optra-S (Ipratropium Bromide + Salbutamol) 0.5mg + 2.5mg/2.5mL Nebuliser Solution is available in pack size of 10's.

DIRECTIONS FOR USE

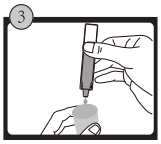
The ampoule should be opened immediately before use and any solution remaining after use should be discarded.



Detach a vial from the bottom.



Twist the top firmly to open the vial.



Pour the medicine into nebuliser.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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Jewim Pharmaceutical (Shandong) Co., Ltd.
West of Peitianman Street, Taian Hi-Tech
Industrial Development Zone,
Shandong Province, China.

Manufactured for:
Getz pharma (PVT) LIMITED
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