## 5. Product Information

## 5.1. Prescribing Information (Summary of Product Characteristics)

"Prescription only medicine"

**1. Name of the Medicinal Product:**

IPRAX-MOL (Salbutamol and Ipratropium Bromide Nebulizer Solution (Sterile) 2.5 mg & 500 mcg)

**2. Qualitative and Quantitative Composition:**

**a) Qualitative Composition**

**Product Name:** IPRAX-MOL

**Generic Name:** Salbutamol and Ipratropium Bromide Nebulizer Solution Sterile 2.5 mg & 500mcg

**Label Claim:** Each 2.5 mL contains:

Salbutamol Sulphate BP
Eq. to Salbutamol……..…2.5 mg
Ipratropium Bromide BP…....….500 mcg
In Isotonic Solution..……..q.s

**Average Fill Volume :** 2.5 mL

**3. Pharmaceutical Form**

Nebulizer Solution (Respules)

**Description:** Clear colourless solution, free from extraneous particles.

**4. Clinical Particulars**

**4.1 Therapeutic indications**

The management of bronchospasm in patients suffering from chronic obstructive pulmonary disease who require regular treatment with both ipratropium and salbutamol.

**4.2 Posology and method of administration**

**Salbutamol and Ipratropium Bromide Nebulizer Solution** is intended for 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 the 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 in UDVs should always be started with the lowest recommended dose (1 UDV). In very severe cases two unit dose vials may be required for symptom relief. Administration should be stopped when sufficient symptom relief is achieved.

The recommended dose is:

*Adults (including elderly patients and children over 12 years):*

1 single dose unit three or four times daily.

*Children under 12 years:*

There is no experience of the use of Salbutamol and Ipratropium Bromide Nebulizer Solution in children under 12 years.

Administration:

Please refer to the patient information leaflet for instructions for use with a nebuliser.
Since the single dose units contain no preservatives, it is important that the contents are used immediately after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, open or damaged single dose units should be discarded.
It is strongly recommended not to mix Salbutamol and Ipratropium Bromide Nebulizer Solution with other drugs in the same nebuliser.

**4.3 Contraindications**

Salbutamol and Ipratropium Bromide Nebulizer Solution are contraindicated in patients with hypertrophic obstructive cardio- myopathy or tachyarrhythmia.
Salbutamol and Ipratropium Bromide Nebulizer Solution also contraindicated in patients with a history of hypersensitivity to ipratropium bromide, salbutamol sulfate or to atropine or its derivatives.

**4.4 Special warnings and precautions for use**

Hypersensitivity
Immediate hypersensitivity reactions may occur after administration of Salbutamol and Ipratropium Bromide Nebulizer Solution, as demonstrated by rare cases of urticaria, angioedema, 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. Salbutamol and Ipratropium Bromide Nebulizer Solution should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.
Ocular complications
There have been rare cases of ocular complications (i.e. mydriasis, blurring of vision, narrow-angle glaucoma and eye pain) when the contents of metered aerosols containing ipratropium bromide have been sprayed inadvertently into the eye.
Patients must be instructed in the correct use of Salbutamol and Ipratropium Bromide Nebulizer Solution and warned not to allow the solution or mist to enter the eyes. This is particularly important in patients who may be predisposed to glaucoma. Such patients should be warned specifically to protect their 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.

Systemic effects
In the following conditions Salbutamol and Ipratropium Bromide Nebulizer Solution should only be used after careful risk/benefit assessment: 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
Cardiovascular effects may be seen with sympathomimetic drugs including Salbutamol and Ipratropium Bromide Nebulizer Solution. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease,

arrhythmia 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. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalaemia
Potentially serious hypokalaemia may result from beta2-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). 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.

Dyspnoea
The patient should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea. In addition, the patient should be warned to seek medical advice should a reduced response become apparent.

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. 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 Salbutamol and Ipratropium Bromide Nebulizer Solution 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).

**4.5 Interaction with other medicinal product and other forms of interaction**

The chronic co-administration of Salbutamol and Ipratropium Bromide Nebulizer Solution with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of Salbutamol and Ipratropium Bromide Nebulizer Solution with other anticholinergic drugs is not recommended.
The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of Salbutamol and Ipratropium Bromide Nebulizer Solution. The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the severity of side effects. A potentially serious reduction in effect may occur during concurrent administration of beta-blockers.
Beta2-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta2-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.

## 4.6 Fertility, Pregnancy and Lactation

Ipratropium bromide has been in general use for several years and there is no definite evidence of ill-consequence during pregnancy; animal studies have shown no hazard.

Salbutamol has been in widespread use for many years without apparent ill consequence during pregnancy. There is inadequate published evidence of safety in the early stages of human pregnancy but in animal studies there has been evidence of some harmful effects on the foetus at very high dose levels. As with all medicines, Salbutamol and Ipratropium Bromide Nebulizer Solution should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus. Similarly, Salbutamol and Ipratropium Bromide Nebulizer Solution should not be administered to breast-feeding mothers unless the expected benefit is thought to outweigh any possible risk to the neonate.

## 4.7 Effects on ability to drive and 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 and blurred vision during treatment with Salbutamol and Ipratropium Bromide Nebulizer Solution. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

## 4.8 Undesirable effects

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic and beta2 –sympathomimetic properties of Salbutamol and Ipratropium Bromide Nebulizer Solution. As with all inhalation therapy Salbutamol and Ipratropium Bromide Nebulizer Solution may show symptoms of local irritation.

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.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during use of Salbutamol and Ipratropium Bromide Nebulizer Solution in clinical trials and during the post-marketing experience.

Frequencies

| | |
|---|---|
| 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 |
| Not known | Frequency cannot be estimated from the available data |

| **MedDRA System Organ Class**<br>Adverse reactions | Frequency |
|---|---|
| **Immune system disorders** | |
| Anaphylactic reaction | Rare |
| Hypersensitivity | Rare |

| | |
|---|---|
| Angioedema of the tongue, lips and face | Rare |
| **Metabolism and nutrition disorders** | |
| Hypokalaemia | Rare |
| Lactic acidosis | Not known |
| **Psychiatric disorders** | |
| Nervousness | Uncommon |
| Mental disorder | Rare |
| **Nervous system disorders** | |
| Dizziness | Uncommon |
| Headache | Uncommon |
| Tremor | Uncommon |
| **Eye disorders** | |
| Accommodation disorder | Rare |
| Corneal oedema | Rare |
| Glaucoma (1) | Rare |
| Eye pain (1) | Rare |
| Increased intraocular pressure (1) | Rare |
| Mydriasis (1) | Rare |
| Blurred vision | Rare |
| Conjunctival hyperaemia | Rare |
| Halo vision | Rare |
| **Cardiac disorders** | |
| Palpitations | Uncommon |
| Tachycardia | Uncommon |
| Arrhythmia | Rare |
| Atrial fibrillation | Rare |
| Myocardial ischaemia | Rare |
| Supraventricular tachycardia | Rare |
| **Respiratory, thoracic and mediastinal disorders** | |
| Cough | Uncommon |
| Dysphonia | Uncommon |
| Throat irritatio | Uncommon |
| Bronchospasm | Rare |

| | |
|---|---|
| Paradoxical bronchospasm (2) | Rare |
| Dry Throat | Rare |
| Laryngospasm | Rare |
| Pharyngeal oedema | Rare |
| **Gastrointestinal disorders** | |
| Dry mouth | Uncommon |
| Nausea | Uncommon |
| Gastrointestinal motility disorder | Rare |
| e.g. Diarrhoea | Rare |
| Constipation | Rare |
| Vomiting | Rare |
| Mouth oedema | Rare |
| Stomatitis | Rare |
| **Skin and subcutaneous tissue disorders** | |
| Skin reactions | Uncommon |
| Hyperhidrosis | Rare |
| Rash | Rare |
| Urticaria | Rare |
| Pruritus | Rare |
| **Musculoskeletal and connective tissue disorders** | |
| Muscle spasms | Rare |
| Muscular weakness | Rare |
| Myalgia | Rare |
| **Renal and urinary disorders** | |
| Urinary retention (3) | Rare |
| **General disorders and administration site conditions** | |
| Asthenia | Rare |
| **Investigations** | |
| Systolic blood pressure increased | Uncommon |
| Diastolic blood pressure decreased | Rare |

(1) ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta2-agonist, has come into contact with the eyes.

(2) 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. Salbutamol and Ipratropium Bromide Nebulizer Solution should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary.
(3) the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

**4.9 Overdose**

Acute effects of overdosage with ipratropium bromide are mild and transient (such as dry mouth, visual accommodation disorders) due to its poor systemic absorption after either inhalation or oral administration. Any effects of overdosage are therefore likely to be related to the salbutamol component. Manifestations of overdosage with salbutamol may include tachycardia, anginal pain, hypertension, palpitations, tremor, hypokalaemia, 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.
Treatment with Salbutamol and Ipratropium Bromide Nebulizer Solution should 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 should be used in administering these drugs to patients with a history of bronchospasm.

**5. Pharmacological properties**

**5.1 Pharmacodynamic Properties**

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

ATC code: R03AL02

Mode of action

Ipratropium bromide has anticholinergic (parasympatholytic) properties. In non-clinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve.

Pharmacodynamics

The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature. Salbutamol is a beta2-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. Salbutamol and Ipratropium Bromide Nebulizer Solution provide the simultaneous delivery of ipratropium bromide and salbutamol sulfate allowing effects on both muscarinic and beta2-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

Paediatric population

Salbutamol and Ipratropium Bromide Nebulizer Solution has not been studied in the paediatric population.

## 5.2 Pharmacokinetic Properties

Absorption characteristics of the combination ipratropium bromide – salbutamol sulfate

Co-administration of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component and therefore the additive activity of Salbutamol and Ipratropium Bromide Nebulizer Solution is due to the combined local effect on the lung following inhalation.

**Ipratropium**

Absorption

Based on a cumulative excretion value (CRE0-24h) of about 3-13%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 28%.

Distribution

Kinetic parameters describing the disposition of ipratropium bromide 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). The drug is minimally (less than 20%) bound to plasma proteins. Non-clinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Biotransformation

After administration via inhalation approximately 87%-89% of a dose is metabolised, the major portion probably in the liver by oxidation.

Elimination

Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/ min.

After administration via inhalation about 3.2% of drug 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 half-life for elimination of drug-related radioactivity following inhalation is 3.2 hours.

**Salbutamol**

Absorption

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or the 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 Salbutamol and Ipratropium Bromide Nebulizer Solution.

Distribution

Kinetic parameters were calculated from plasma concentrations after I.V. administration. The apparent volume of distribution (Vz) is approximately 156 L (≈ 2.5 L/kg). Only 8% of the drug is bound to plasma proteins. In nonclinical trials, levels of approximately 5% of the plasma level of salbutamol are found in the brain. However, this amount probably represents the distribution of the substance in the extracellular water of the brain.

Biotransformation and Elimination

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

mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291mL/min.
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. After oral administration urinary excretion of unchanged drug and sulfate conjugate were 31.8% and 48.2% of the dose, respectively.

**5.3 Preclinical safety data**
None stated.

**6.0 Pharmaceutical particulars**

**6.1 List of Excipients**
Sodium chloride BP, Disodium Edetate BP, Sodium Citrate BP, Citric Acid Monohydrate BP, Water for Injections BP.

**6.2 Incompatibilities**
None stated.

**6.3 Shelf life**
24 months from the date of manufacturing.

**6.4 Special precautions for storage**
Do not store above 30ºC. Protect from light. Do not refrigerate or freeze.

**6.5 Nature and contents of container**
4 x 5 x 2.5 mL LDPE Respules packed in a carton along with pack

**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**
The product should be used with a respirator or nebulizer only, under the direction of a physician. It is not to be injected or administered orally.
Remove a strip of combipack respules from the carton. Use a fresh respule for each dose.
1. Tear one respule from the combipack.
2. To open the respules twist off the cap as shown in the figure.
3. Squeeze the content into the reservoir of the nebulising chamber.
4. Discard the respule after use.
Shake well before use. Keep out of reach of children.
Store the respule in foil pouch at all times. Once the foil pouch is opened the respules should be used within one month.

**7. Marketing Authorization Holder**
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**8. Marketing Authorization Number(s)**
TAN 22 HM 0371

**9. Date of first authorization/renewal of the authorization**
21/09/2022

## 10. Date of revision of the text

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