**1. Name of the medicinal product**

Aerotropa Nebulizer Solution.

**2. Qualitative and quantitative composition**

Each single-dose container (2.5 ml) contains 500 mcg ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as salbutamol sulfate).

For the full list of excipients, see section 6.1.

**3. Pharmaceutical form**

Nebulizer Solution.

AEROTROPA Nebulizer Solution is clear colorless to yellowish solution.

**4. Clinical particulars**

**4.1 Therapeutic indications**

AEROTROPA Nebulizer Solution is indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium bromide and salbutamol.

**4.2 Posology and method of administration**

Posology

The recommended dose is:

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

The contents of one single-dose container three or four times daily.

*Paediatric population (under 12 years)*

The safety and efficacy of AEROTROPA Nebulizer Solution in children aged under 12 years have not been established. AEROTROPA Nebulizer Solution is not recommended in children below 12 years of age.

Method of administration

Inhalation use.

1.4.1 Summary of Product Characteristics

Drug delivery characteristics were studied in vitro using an eFlow rapid electronic nebulizer and a PARI LC Sprint nebulizer:

| **Nebulizer** | **Droplet size distribution** [micrometer] | | | **Drug delivery rate** [microgram/minute] | **Total drug delivered** [microgram] |
|---|---|---|---|---|---|
| | **D10** | **D50*** | **D90** | | |
| eFlow rapid electronic nebulizer | 2.5 | 4.7 | 10.4 | Salbutamol: 361.2<br>Ipratropium: 73.6 | Salbutamol: 1185.7<br>Ipratropium: 240.6 |
| PARI LC Sprint nebulizer (used with PARI Boy SX compressor) | 1.4 | 4.2 | 13.2 | Salbutamol: 137.9<br>Ipratropium: 28.1 | Salbutamol: 1031.7<br>Ipratropium: 206.7 |

***** Median Mass Diameter

No information is available in respect of pulmonary inhalation and deposition patterns across nebulizer systems that have not been studied.

The use of an alternative untested nebulizer system may alter the pulmonary deposition of the active substances, this in turn may alter the efficacy and safety of the product and dose adjustment may then become necessary.

**Instructions for use with the eFlow rapid electronic nebulizer:**

1. The nebulizer should be prepared by following the manufacturer's instructions.

2. A new single-dose container should be carefully separated from the strip.

3. The remaining single-dose containers should be put back in the sachet and the sachet should be closed by crimping over the lap. The sachet should be stored in the carton.

4. The single-dose container should be held upright and opened by simply twisting off the top.

5. Unless otherwise indicated the contents of one single-dose container should be squeezed into the nebulizer chamber.

6. The nebulizer chamber should be closed by placing the cap on the nebulizer chamber so that the slots in the side of the cap are positioned above the notches in the chamber. Pressing gently the cap should be turned clockwise as far as it will go. The closing mechanism is functioning correctly if the cap seal

rises with the turning motion to form a seal. It should be checked that all parts are connected tightly and that the nebulizer chamber is sealed.

7. The patient should hold the nebulizer handset in his/her hand and sit in an upright position and relax. The mouthpiece should be taken between the teeth and the lips should be closed around it. The lips should not touch the blue expiratory valve. The ON/OFF button on the control unit should be pressed. A green LED beside the ON/OFF button lights up and an audible signal (1 beep) is emitted to indicate proper functioning. The patient should be instructed to inhale and exhale through the mouthpiece as slowly and deeply as possible.

8. The nebulizer device switches off automatically when the nebulizer solution is used up. When inhalation has been completed successfully a tick will appear on the display. Any remaining solution (about 1 ml cannot be nebulized and remains in the nebulizer chamber) should be discarded.

9. When the inhalation session has ended the power adapter plug should be disconnected from the socket.

**Instructions for use with the PARI LC Sprint nebulizer:**

1. The nebulizer is operated with the PARI Boy SX compressor and should be prepared by following the manufacturer's instructions.

2. A new single-dose container should be carefully separated from the strip.

3. The remaining single-dose containers should be put back in the sachet and the sachet should be closed by crimping over the lap. The sachet should be stored in the carton.

4. The single-dose container should be held upright and opened by simply twisting off the top.

5. The closure on the nebulizer upper section should be released by pressing the thumb against the underside of the cap.

6. Unless otherwise indicated the contents of one single-dose container should be squeezed into the nebulizer chamber.

7. The cap of the nebulizer should be closed. The cap should snap into place. All parts of the nebulizer should be firmly connected to each other.

8. The patient should sit in an upright position and relax. The compressor should be switched on. The mouthpiece should be taken between the teeth and the lips should be closed around it. The patient should be instructed to breathe in through the mouthpiece as slowly and deeply as possible and to breathe out in their own time.

9. The inhalation should be continued until the solution in the nebulizer chamber is used up (signalled by a change in the sound of the nebulizer).

10. The compressor should be switched off as soon as inhalation is finished. Any remaining solution in the nebulizer chamber (some solution will remain after inhalation) should be discarded.

**For eFlow rapid electronic nebulizer and PARI LC Sprint nebulizer:**

The manufacturer's instructions should be followed for cleaning the nebulizer. It is important that the nebulizer is kept clean.

The full instructions for use of the nebulizer in the leaflet provided with the nebulizer system should be read before starting the inhalation.

As the single-dose containers contain no preservatives it is important that the contents are used immediately after opening and a fresh single-dose container is used for each administration to avoid microbial contamination. Partly used, opened or damaged single-dose containers should be discarded.

**4.3 Contraindications**

Patients with hypertrophic obstructive cardiomyopathy or tachyarrhythmia.

Patients with known hypersensitivity to the active substances or to atropine or its derivatives or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

If it is necessary to use higher doses than recommended to control the symptoms of bronchoconstriction (or bronchospasm) the patient's treatment plan should be reassessed.

Dyspnoea

Patients should be instructed to consult a doctor immediately in the event of acute, rapidly worsening dyspnoea or if a reduced response to treatment becomes apparent.

Hypersensitivity

Immediate hypersensitivity reactions may occur after administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis.

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

Ocular complications

There have been rare reports of ocular complications when aerosolised ipratropium bromide, either alone or in combination with a beta$_2$-adrenergic agonist, has been inadvertently sprayed into the eye. Patients must therefore be instructed in the correct use of AEROTROPA with their nebulizer and warned not to allow the solution or mist to enter the eyes. To avoid inadvertent entry of drug into the eye, it is preferable to administer the nebulized solution using a mouthpiece rather than a face mask.

Such ocular complications may include, mydriasis, blurring of vision, increased intraocular pressure, eye pain and narrow-angle glaucoma (including acute narrow- angle glaucoma). Patients who may be susceptible to glaucoma should be warned specifically about the need for ocular protection. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals.

Eye pain or discomfort, blurred vision, visual halos or coloured images, in association with red eyes from conjunctival congestion or corneal oedema may be signs of acute narrow-angle glaucoma. Should any combination of these symptoms develops, treatment with miotic eye drops should be initiated and the patient should seek specialist advice immediately.

Systemic effects

In the following conditions AEROTROPA Nebulizer Solution should only be used after careful risk/benefit assessment: inadequately controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, prostatic hypertrophy, bladder-neck obstruction and risk of narrow-angle glaucoma.

Cardiovascular effects

Cardiovascular effects may be seen with sympathomimetic drugs, including medicinal products containing salbutamol. There is some evidence from post- marketing data and published literature of rare occurrences of myocardial ischemia associated with salbutamol.

Patients with underlying severe heart disease (e.g. ischemic heart disease, arrhythmias 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 either respiratory or cardiac in origin.

Hypokalemia

Potentially serious hypokalemia 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.

Hypokalemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin. Additionally, hypoxia may aggravate the effects of hypokalemia on cardiac rhythm. It is recommended that serum levels of potassium 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, should be used with caution in these patients.

Lactic acidosis

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulized 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 AEROTROPA Nebulizer Solution may lead to positive results in doping tests.

Pediatric population

AEROTROPA Nebulizer Solution should not be used in children under 12 years of age (see section 4.2).

Dental caries

Dental caries has been reported with salbutamol use. It is recommended, particularly in children, to pay attention to proper oral hygiene and perform regular dental checkups.

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

The chronic co-administration of AEROTROPA Nebulizer Solution with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of AEROTROPA Nebulizer Solution with other anticholinergic drugs is not recommended.

The effect of other anticholinergic products may be potentiated.

Concurrent use of additional beta-agonists, corticosteroids, anticholinergics and xanthine derivatives may enhance the effect of AEROTROPA Nebulizer Solution on airway function and may increase the severity of side effects. Due to opposing pharmacodynamic interaction with the salbutamol element, a potentially serious reduction in effect may occur during concurrent administration of beta-blockers.

Beta-adrenergic agents 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 cardiovascular side effects of $beta_2$-agonists. These patients should therefore be monitored closely.

Alternatively, discontinuation of AEROTROPA prior to surgical operation should be considered.

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, diuretics and steroids.

Potentially serious arrhythmias may occur during concomitant administration of digoxin and AEROTROPA. The interaction risk is aggravated by hypokalemia and should be monitored regularly. Hypokalemia can bring about increased sensitivity to arrhythmias in patients being treated with digoxin (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

Pregnancy

There are no adequate data from the concomitant use of ipratropium bromide and salbutamol in pregnant women (in early stages of pregnancy). In animal studies there has been evidence of some harmful effects on the foetus at very high dose levels. The potential risk for humans is unknown. AEROTROPA should not be used during pregnancy unless clearly necessary and caution should be exercised when prescribing to pregnant women (especially in the first trimester). At the end of pregnancy, the inhibitory effect of AEROTROPA Nebulizer Solution on uterine contraction should be taken into account.

Breast-feeding

It is unknown whether ipratropium bromide is excreted into human breast milk. Salbutamol is excreted in human breast milk. There is insufficient/limited information on the excretion of AEROTROPA

Nebulizer Solution in human or animal breast milk. A risk to the suckling child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with AEROTROPA should be made taking into account the benefit of breast-feeding to the child and the benefit of AEROTROPA Nebulizer Solution to the mother.

Fertility

No studies on the effect on human fertility have been conducted for AEROTROPA Nebulizer Solution.

Animal studies reveal no special hazard for humans based on conventional studies of toxicity to reproduction (see section 5.3).

**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 the treatment with AEROTROPA Nebulizer Solution. If patients experience the above-mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machines.

**4.8 Undesirable effects**

Summary of the safety profile

Many of the listed undesirable effects can be assigned to the anticholinergic and $beta_2$ sympathomimetic properties of the medicinal product. As with all inhalation therapy AEROTROPA may show symptoms of local irritation.

Adverse reactions were identified from data obtained in clinical trials and post- approval data of nebulizer solutions containing the combination ipratropium bromide and salbutamol.

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

Tabulated list of adverse reactions

Based on the MedDRA system organ class and frequencies, adverse events are listed in the table below.

Frequencies are defined as:

very common ($\geq 1/10$)

common (≥1/100 to <1/10)

uncommon (≥1/1,000 to <1/100)

rare (≥1/10,000 to <1/1,000)

very rare (<1/10,000)

not known (cannot be estimated from the available data)

The following side effects have been reported based on clinical trials involving 3488 patients.

| **System organ class** | **Frequency** | **Symptom** |
|---|---|---|
| Immune system disorders | Rare | Anaphylactic reaction,<br>Hypersensitivity,<br>Angioedema of the face, lips and tongue |
| Metabolism and nutritional disorders | Rare | Hypokalemia |
| | Not known | Lactic acidosis (see section 4.4) |
| Psychiatric disorders | Uncommon | Nervousness |
| | Rare | Mental disorders |
| Nervous system disorders | Uncommon | Headache,<br>Dizziness,<br>Tremor |
| Eye disorders | Rare | Accommodation disorders,<br>Corneal oedema,<br>Glaucoma(1),<br>Eye pain(1), |

| | | |
|---|---|---|
| | | Mydriasis[1],<br>Blurred vision,<br>Conjunctival hyperemia,<br>Increased intraocular pressure[1],<br>Halo vision |
| Cardiac disorders | Uncommon | Palpitations,<br>Tachycardia |
| | Rare | Arrhythmia,<br>Atrial fibrillation,<br>Supraventricular tachycardia,<br>Myocardial ischemia |
| Respiratory, thoracic and mediastinal disorders | Uncommon | Cough,<br>Dysphonia,<br>Throat irritation |
| | Rare | Bronchospasm,<br>Laryngospasm,<br>Paradoxical bronchospasm[2],<br>Dry throat,<br>Pharyngeal oedema |
| Gastrointestinal disorders | Uncommon | Dry mouth,<br>Nausea |
| | Rare | Gastrointestinal motility disorder, e.g.: |

| | | |
|---|---|---|
| | | Diarrhoea,<br>Constipation,<br>Vomiting;<br>Mouth oedema,<br>Stomatitis |
| | Not known | Dental caries |
| Skin and subcutaneous tissue disorders | Uncommon | Skin reactions |
| | Rare | Hyperhidrosis,<br>Rash,<br>Pruritus,<br>Urticaria |
| Musculoskeletal, connective tissue and bone disorders | Rare | Myalgia,<br>Muscle spasms,<br>Muscular weakness |
| Renal and urinary disorders | Rare | Urinary retention(3) |
| General disorders and administration site conditions | Rare | Asthenia |
| Investigations | Uncommon | Systolic blood pressure increased |
| | Rare | Diastolic blood pressure decreased |

(1) ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta$_2$-agonist, has come into contact with the eyes - see section 4.4.

(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. AEROTROPA should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary - see section 4.4.

(3) the risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

The following other side effects have also been reported rarely for nebulizer solutions containing ipratropium bromide and salbutamol: restlessness, hyperactivity in children, anxiety, depression, extrasystoles, dyspnoea.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

**4.9 Overdose**

Symptoms

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, hypokalemia, hypotension, widening of the pulse pressure, arrhythmias, flushing, chest pain, restlessness and dizziness.

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.

Patients should therefore be monitored closely for potential unwanted effects from overdosage of salbutamol.

Treatment

Treatment with AEROTROPA Nebulizer Solution should be discontinued. Acid base and electrolyte monitoring should be considered.

The preferred antidote for overdosage with salbutamol is a cardio selective beta- blocking agent, but caution should be used in administering these drugs to patients with a history of bronchospasm.

Hypokalemia may occur following overdose with salbutamol and therefore serum potassium levels should be monitored.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases, ATC code: R03AL02

Mode of action and pharmacodynamics

Ipratropium bromide is an anticholinergic agent, which inhibits vagally-mediated reflexes by antagonising the muscarinic action of acetylcholine. The bronchodilation following inhalation of ipratropium bromide is primarily local and specific to the lung and not systemic in nature.

Salbutamol is a beta$_2$-adrenergic agonist, 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.

AEROTROPA provides the simultaneous delivery of ipratropium bromide and salbutamol sulphate producing effects on both muscarinic and beta$_2$- adrenergic receptors in the lung. This provides increased bronchodilation over that provided by each agent singly.

### 5.2 Pharmacokinetic properties

***Absorption characteristics of the combination ipratropium bromide - salbutamol sulfate***

Co-nebulization of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of either component. The increased pharmacodynamic activity of AEROTROPA Nebulizer Solution is due to the combined local effect of both substances on the lung.

***Ipratropium***

Absorption

Based on a cumulative excretion value of about 3-4%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 9%.

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.

Ipratropium bromide like any other quaternary ammonium compound is not expected to readily cross the blood brain 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 87-89% of a dose is metabolised probably mainly in the liver by oxidation.

Elimination

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 69.4% for this route of administration. The half-life for elimination of drug-related radioactivity following inhalation is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

***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 AEROTROPA 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

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.

Elimination

Following a 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 291 ml/min.

Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64.2%) and 12.0% were excreted as sulfate conjugate. 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**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenic potential or toxicity to reproduction.

**6. Pharmaceutical particulars**

**6.1 List of excipients**

Sodium chloride for injection.

Disodium edetate.

Hydrochloric Acid.

Water for injections.

**6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products in the same nebulizer.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

Store at Temperature not exceeding 30°C.

Do not freeze. Store in the original package in order to protect from light and evaporation.

Do not use if solution is discoloured.

**6.5 Nature and contents of container**

***Primary Packaging***

Transparent glass ampoules Type I, each of 2.5 ml solution.

***Secondary Packaging***

AEROTROPA Nebulizer Solution is applied in a chromo-duplex carton box containing a patient leaflet and two plastic drawers (of 5 transparent glass ampoules each).

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

For single use only. Use immediately after first opening the single-dose container. Discard immediately after first use.

Partly used, opened or damaged single-dose containers should be disposed of in accordance with local requirements.

**7. Marketing authorization holder**

European Egyptian Pharmaceutical Industries.

Kilo 25 Alexandria-Cairo Desert Road, Amriya, Alexandria, Egypt.

**8. Marketing authorization number(s)**

29125/2020.

**9. Date of first authorization/renewal of the authorization**

25/6/2020.

**10. Date of revision of the text**

August 2020