DUOLIN Respules (Levosalbutamol sulphate + Ipratropium bromide)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Qualitative and Quantitative Composition

Each 2.5 mL unit-dose vial contains:

Levosalbutamol sulphate.....1.25 mg

Ipratropium Bromide ..... 500 mcg

Normal Saline Solution, IP .....q.s.

Each 3 mL unit-dose vial contains:

Levosalbutamol sulphate.....1.25 mg

Ipratropium Bromide ..... 500 mcg

Normal Saline Solution, IP .....q.s.

Dosage Form(s) and Strength(s)

DUOLIN respule is supplied as a unit-dose vial of 2.5 mL & 3 mL sterile solution for nebulization.

Clinical Particulars

Therapeutic Indication

DUOLIN respule is indicated in patients with COPD on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm and who require a second bronchodilator.

Posology and Method of Administration

Adults & children more than 12 years: One respule three times a day [maximum recommended daily dose], every 6 to 8 hours.

DUOLIN respules are for oral inhalation only. Administer by nebulization using a standard jet nebulizer (with a face mask or mouthpiece) connected to an air compressor. Do not exceed the recommended dose.

The use of **DUOLIN** respules can be continued as medically indicated to control recurring bouts of bronchospasm. If a previously effective regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of worsening COPD, which would require reassessment of therapy.

Children under 12 years: There is no experience of the use of **DUOLIN** respules in children under 12 years.

Contraindications

DUOLIN respules are contraindicated in patients with a history of hypersensitivity to any of its components, or to atropine and its derivatives. Reactions have included urticaria, angio-oedema, rash, bronchospasm, anaphylaxis, and oropharyngeal oedema.

Special Warnings and Precautions for Use

Levosalbutamol Sulphate

Paradoxical Bronchospasm

Levosalbutamol sulphate can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, levosalbutamol sulphate inhalation solution should be discontinued immediately and alternative therapy instituted. It should be recognised that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new vial.

Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of levosalbutamol sulphate inhalation solution than usual, this may be a marker of destabilisation of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g. corticosteroids.

Use of Anti-Inflammatory Agents

Levosalbutamol sulphate inhalation solution is not a substitute for corticosteroids. The use of beta-adrenergic agonist alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g. corticosteroids, to the therapeutic regimen.

Cardiovascular Effects

Levosalbutamol sulphate inhalation solution, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and symptoms. Although such effects are uncommon after administration of levosalbutamol sulphate inhalation solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, levosalbutamol sulphate inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Do Not Exceed the Recommended Dose

Do not exceed the recommended dose. Fatalities have been reported in association with excessive

use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of levosalbutamol sulphate or racemic albuterol sulphate. Reactions have included urticaria, angio-oedema, rash, bronchospasm, anaphylaxis, and oropharyngeal oedema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving levosalbutamol sulphate inhalation solution.

Coexisting Conditions

Levosalbutamol sulphate inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator. Changes in blood glucose may occur. Large doses of intravenous racemic albuterol sulphate have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

Hypokalaemia

As with other beta-adrenergic agonist medications, levosalbutamol sulphate inhalation solution may produce significant hypokalaemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Ipratropium Bromide

Caution is advocated in the use of anticholinergic agents in patients with narrow-angle glaucoma, or with prostatic hyperplasia or bladder-outflow obstruction. As patients with cystic fibrosis may be prone to gastrointestinal motility disturbances, ipratropium bromide, as with other anticholinergics, should be used with caution in these patients. Immediate hypersensitivity reactions following the use of ipratropium bromide have been demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, oropharyngeal oedema and anaphylaxis. There have been isolated reports of ocular complications (i.e. mydriasis, increased intra-ocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide, either alone or in combination with an adrenergic beta2-agonist, has come into contact with the eyes during nebulizer therapy.

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 administration of ipratropium bromide. Care must be taken not to allow the solution or mist to enter the eyes. It is recommended that the nebulized solution is administered via a mouthpiece. If this is not available and a nebulizer mask is used, it must fit properly. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

Drug Interactions

Levosalbutamol Sulphate

Short-acting Bronchodilators

Avoid concomitant use of other short-acting sympathomimetic bronchodilators or epinephrine in patients being treated with levosalbutamol sulphate inhalation solution. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-adrenergic agonists such as levosalbutamol sulphate inhalation solution, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g. prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

Diuretics

The ECG changes or hypokalaemia that may result from the administration of non-potassium-sparing diuretics (such as loop and thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. Consider monitoring potassium levels.

Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol sulphate, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levosalbutamol sulphate inhalation solution and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levosalbutamol sulphate inhalation solution.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

Levosalbutamol sulphate inhalation solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levosalbutamol sulphate on the vascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

Ipratropium Bromide

There is evidence that the administration of ipratropium bromide with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect. The risk of acute glaucoma in patients with a history of narrow-angle glaucoma may be increased when nebulized ipratropium bromide and $beta_2$-agonists are administered simultaneously.

Use in Special Populations

Levosalbutamol Sulphate

Pregnancy

Teratogenic effects – pregnancy category C

There are no adequate and well-controlled studies of levosalbutamol sulphate inhalation solution in pregnant women. Because animal reproduction studies are not always predictive of human response, levosalbutamol sulphate inhalation solution should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in newborns of women treated with racemic albuterol sulphate, which contains the levosalbutamol sulphate isomer (active drug substance of levosalbutamol sulphate inhalation solution). However, since multiple medications were taken during some of the pregnancies and there was no consistent pattern of anomalies, it was not possible to establish a relationship between racemic albuterol sulphate use and the occurrence of these congenital anomalies. In animal studies, oral administration of levosalbutamol hydrochloride to pregnant New Zealand White rabbits found no evidence of teratogenicity at doses up to 25 mg/kg/day (approximately 108 times the maximum recommended daily inhalation [MRDI] dose of levosalbutamol hydrochloride for adults on a mg/m^2 basis). However, other studies demonstrated that racemic albuterol sulphate was teratogenic in mice and rabbits at doses comparable to the human therapeutic range. Pregnant mice administered racemic albuterol sulphate subcutaneously had a dose-related increased incidence of cleft palate in their foetuses (4.5% of foetuses at 0.25 mg/kg/day or greater, corresponding to approximately 0.3 times the MRDI dose, 9.3% of foetuses at 2.5 mg/kg/day, approximately 3 times the MRDI dose of levosalbutamol hydrochloride for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg/day (approximately 0.03 times the MRDI dose of levosalbutamol hydrochloride for adults on a mg/m^2 basis). In addition, oral administration of racemic albuterol sulphate to pregnant rabbits resulted in an increased incidence of cranioschisis in foetuses (approximately 215 times the MRDI dose of levosalbutamol hydrochloride for adults on a mg/m^2 basis).

Non-Teratogenic Effects

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulphate demonstrated that drug-related material is transferred from the maternal circulation to the foetus.

Labour and Delivery

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of levosalbutamol sulphate inhalation solution for the treatment of bronchospasm during labour should be restricted to those patients in whom the benefits clearly outweigh the risk. Levosalbutamol sulphate inhalation solution has not been approved for the management of preterm labour. The benefit to risk ratio when levosalbutamol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary oedema, have been reported during or following treatment of premature labour with beta-agonists, including racemic albuterol sulphate.

Nursing Mothers

Plasma concentrations of levosalbutamol sulphate after inhalation of therapeutic doses are very low

in humans. It is not known whether levosalbutamol sulphate is excreted in human milk. Because of the potential for tumourigenicity shown for racemic albuterol sulphate in animal studies and the lack of experience with the use of levosalbutamol sulphate inhalation solution by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother. Caution should be exercised when levosalbutamol sulphate inhalation solution is administered to a nursing woman.

Paediatric Use

There is no data on the use of levosalbutamol sulphate plus ipratropium bromide inhalation solution in children below 12 years of age.

Geriatric Use

Clinical studies of levosalbutamol sulphate inhalation solution did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Only five patients, 65 years of age and older, were treated with levosalbutamol sulphate inhalation solution in a 4-week clinical study (n = 2 for 0.63 mg and n = 3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. In general, patients who are 65 years of age and older should be started at a dose of 0.63 mg of levosalbutamol sulphate inhalation solution. If clinically warranted due to insufficient bronchodilator response, the dose of levosalbutamol sulphate inhalation solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose

Patients with Renal Impairment

Albuterol is known to be substantially excreted by the kidneys, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Ipratropium Bromide

Pregnant Women/Lactating Women

The safety of ipratropium bromide during human pregnancy has not been established. The benefits of using ipratropium bromide during a confirmed or suspected pregnancy must be weighed against the possible hazards to the unborn child. Preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in humans.

It is not known whether ipratropium bromide is excreted into breast milk. It is unlikely that ipratropium bromide would reach the infant to an important extent; however, caution should be exercised when ipratropium bromide is administered to nursing mothers.

Patients with Hepatic Impairment

Use of levosalbutamol sulphate and ipratropium bromide inhalation solution has not been studied in patients with hepatic impairment. It should be used with caution in these patient populations.

Effect on Ability to Drive and Use Machines

None known.

Undesirable Effects

Levosalbutamol Sulphate

Serious adverse reactions include paradoxical bronchospasm, cardiovascular effects, immediate hypersensitivity reactions, and hypokalaemia.

Clinical Trials Experience:

Adverse reactions reported (≥2% of patients) in a 4-week, controlled clinical trial in adults and adolescents aged12 years and older were allergic reactions, flu syndrome, chills, chest pain, accidental injury, pain, back pain, tachycardia, migraine, dyspepsia, leg cramps, dizziness, hypertonia, nervousness, tremor, anxiety, increased cough, viral infection, rhinitis, sinusitis and turbinate oedema.

In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received levosalbutamol sulphate inhalation solution 1.25 mg compared with the other active treatment groups.

Most frequently reported adverse reactions (≥2% in any treatment group) and those reported more frequently than in placebo during the double-blind period (6 to 11 years old) were abdominal pain, accidental injury, asthenia, fever, headache, pain, viral infection, diarrhoea, lymphadenopathy, myalgia, asthma, pharyngitis, eczema, rash, urticaria and otitis media.

The following adverse reactions, considered potentially related to levosalbutamol sulphate inhalation solution, occurred in less than 2% of the 292 subjects who received levosalbutamol sulphate inhalation solution and more frequently than in patients who received placebo in any clinical trial – ECG abnormal, ECG change, hypertension, hypotension, syncope, diarrhoea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea, lymphadenopathy, leg cramps, myalgia, anxiety, hyperaesthesia of the hand, insomnia, paraesthesia, tremor, eye itch.

Post-marketing Experience:

In addition to the adverse reactions reported in clinical trials, the following adverse reactions have been observed in post-approval use of levosalbutamol sulphate inhalation solution. Because these reactions 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 drug exposure. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angio-oedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, extra-systoles), asthma, chest pain, cough increased, dysphonia, dyspnoea, gastro-oesophageal reflux disease (GERD), metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, and urticaria. In addition, levosalbutamol sulphate inhalation solution, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx.

Ipratropium Bromide

The most common non-respiratory adverse reactions reported in clinical trials are headache, nausea (with or without vomiting) and dryness of the mouth.

Common (>1/100, <1/10):

Nervous system disorders: Headache.

Respiratory, thoracic and mediastinal disorders: Cough, local irritation.

Gastrointestinal disorders: Dryness of the mouth, nausea and disturbances in gastrointestinal motility (constipation, diarrhoea and vomiting).

Uncommon (>1/1000, <1/100):

Immune system disorders: Urticaria.

Eye disorders: Accommodation disturbances, narrow-angle glaucoma.

Cardiac disorders: Tachycardia.

Respiratory, thoracic and mediastinal disorders: Spasms of larynx.

Skin and subcutaneous tissue disorders: Exanthema

Rare (>1/10,000, <1/1000):

Immune system disorders: Anaphylactic reactions, angio-oedema on the tongue, lips and face.

Eye disorders: Increased intraocular pressure, pain in the eyes, mydriasis.

Cardiac disorders: Palpitations, supraventricular tachycardia, atrial fibrillation.

Respiratory, thoracic and mediastinal disorders: Bronchospasms induced by the inhalation.

Renal and urinary disorders: Urinary retention.

Reporting of Side Effects

If case of any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to Cipla Ltd on **1800 267 7779**. By reporting side effects, you can help provide more information on the safety of this product.

Overdose

Levosalbutamol Sulphate

The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation and/or occurrence or exaggeration of any of the symptoms, including seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalaemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of levosalbutamol sulphate inhalation solution.

Treatment consists of discontinuation of levosalbutamol sulphate inhalation solution together with appropriate symptomatic therapy. The judicious use of a cardio-selective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is

insufficient evidence to determine if dialysis is beneficial for overdosage of levosalbutamol sulphate inhalation solution.

Ipratropium Bromide

Palpitation and increases in heart rate have been produced with inhaled doses of 5 mg. Side effects have not been caused by single inhaled doses of 2 mg in adults and 1 mg in children. Single oral doses of 30 mg of ipratropium bromide caused anticholinergic side effects, but these did not require treatment. Severe overdose is characterised by atropine-like symptoms such as tachycardia, tachypnoea, high fever and central nervous system effects such as restlessness, confusion and hallucinations. These symptoms should be treated symptomatically. The use of physostigmine is not recommended because of worsening of cardio-toxic symptoms and induction of convulsions.

Pharmacological Properties

Mechanism of Action

Levosalbutamol Sulphate

Activation of beta$_2$-adrenergic receptors on airways smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which, in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Levosalbutamol sulphate relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. Levosalbutamol sulphate acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. While it is recognised that beta-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10–50% of which are beta-adrenergic receptors. However, all beta-agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Ipratropium Bromide

Ipratropium bromide is a competitive antagonist of muscarinic acetylcholine receptors. It exhibits its greatest potency on bronchial receptors, whether given intravenously or inhaled, but causes no tachycardia. No anticholinergic effects have been observed on cardiac function, bladder function or in the eye. Ipratropium bromide is able to inhibit reflex-induced bronchoconstriction following exercise, inhalation of cold air and the early response to inhaled antigens. It also reverses the bronchoconstriction induced by inhaled cholinergic agonists.

Pharmacodynamic Properties

Levosalbutamol Sulphate

Adults and Adolescents (12 Years of Age and Older)

In a randomised, double-blind, placebo-controlled, cross-over study, 20 adults with mild-to-moderate asthma received single doses of levosalbutamol sulphate inhalation solution (0.31 mg, 0.63 mg, and 1.25 mg) and racemic albuterol sulphate inhalation solution (2.5 mg). All doses of active treatment

produced a significantly greater degree of bronchodilation (as measured by percent change from pre-dose mean forced expiratory volume (FEV) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator responses to 1.25 mg of levosalbutamol sulphate inhalation solution and 2.5 mg of racemic albuterol sulphate inhalation solution were clinically comparable over the 6-hour evaluation period, except for a slightly longer duration of action (>15% increase in FEV from baseline) after administration of 1.25 mg of levosalbutamol sulphate inhalation solution. Systemic beta-adrenergic adverse effects were observed with all active doses and were generally dose-related for (R)-albuterol. Levosalbutamol sulphate inhalation solution at a dose of 1.25 mg produced a slightly higher rate of systemic beta-adrenergic adverse effects than the 2.5 mg dose of racemic albuterol sulphate inhalation solution. In a randomised, double-blind, placebo-controlled, cross-over study, 12 adults with mild-to-moderate asthma were challenged with inhaled methacholine chloride 20 and 180 minutes following administration of a single dose of 2.5 mg of racemic albuterol sulphate, 1.25 mg of levosalbutamol sulphate inhalation solution, 1.25 mg of (S)-albuterol, or placebo using a Pari LC Jet™ nebulizer. Racemic albuterol sulphate, levosalbutamol sulphate inhalation solution and (S)-albuterol had a protective effect against methacholine-induced bronchoconstriction 20 minutes after administration, although the effect of (S)-albuterol was minimal. At 180 minutes after administration, the bronchoprotective effect of 1.25 mg of levosalbutamol sulphate inhalation solution was comparable with that of 2.5 mg of racemic albuterol sulphate. At 180 minutes after inhalation solution was comparable with that of 2.5 mg of racemic albuterol sulphate. At 180 minutes after administration, 1.25 mg of (S)-albuterol had no bronchoprotective effect. In a clinical study in adults with mild-t--moderate asthma, comparable efficacy (as measured by change from baseline FEV_1) and safety (as measured by heart rate, blood pressure, ECG, serum potassium, and tremor) were demonstrated after a cumulative dose of 5 mg of levosalbutamol sulphate inhalation solution (four consecutive doses of 1.25 mg administered every 30 minutes) and 10 mg of racemic albuterol sulphate inhalation solution (four consecutive doses of 2.5 mg administered every 30 minutes).

Ipratropium Bromide

Inhalation of 0.04 mg of ipratropium from a metered dose aerosol causes bronchodilation, the maximal effect is seen after 30-60 minutes, with a duration of 4 hours. This is a dose-related effect and use of a nebulizer produces greater bronchodilation, with a dose of 0.5 mg producing maximal bronchodilation.

Pharmacokinetic Properties

Levosalbutamol Sulphate

Adults and Adolescents (12 Years of Age and Older)

The inhalation pharmacokinetics of levosalbutamol sulphate inhalation solution were investigated in a randomised crossover study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of levosalbutamol sulphate inhalation solution and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulphate inhalation solution by nebulization, using a PARI LC Jet nebulizer. Following administration of a single 1.25 mg dose of levosalbutamol sulphate inhalation solution, exposure to levosalbutamol sulphate (AUC of 3.3 ng•hr/mL) was approximately 2-fold higher than following administration of a single 2.5 mg dose of racemic albuterol sulphate inhalation solution (AUC of 1.7 ng•hr/mL). Following administration of a cumulative 5 mg dose of levosalbutamol sulphate inhalation solution (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic albuterol sulphate inhalation solution (2.5 mg given every 30 minutes for a total of four doses), C_{max} and AUC of (R)-albuterol were comparable.

Mean (SD) Values for Pharmacokinetic Parameters in Healthy Adults

	Single Dose		**Cumulative Dose**	
	Levosalbutamol sulphate inhalation solution (1.25 mg)	Racemic albuterol sulphate (2.5 mg)	Levosalbutamol sulphate inhalation solution (5 mg)	Racemic albuterol sulphate (10 mg)
C_{max} (ng/mL) (R)-albuterol	1.1 (0.45)	0.8 (0.41)*	4.5 (2.20)	4.2 (1.51)*
T_{max} (h)† (R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (–0.18‡, 1.25)	0.2 (–0.28‡, 1.00)
AUC (ng•h/mL) (R)-albuterol	3.3 (1.58)	1.7 (0.99)*	17.4 (8.56)	16.0 (7.12)*
T½ (h) (R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

* Values reflect only (R)-albuterol and do not include (S)-albuterol.

† Median (min, max) reported for T_{max}.

‡ A negative T_{max} indicates C_{max} occurred between first and last nebulizations.

Metabolism and Elimination

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol sulphate enantiomers in humans is SULT1A3 (sulphotransferase). When racemic albuterol sulphate was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pre-treatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that (R)-albuterol is preferentially metabolised in the gastrointestinal tract, presumably by SULT1A3. The primary route of elimination of albuterol sulphate enantiomers is through renal excretion (80–100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the faeces. Following intravenous administration of racemic albuterol sulphate, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

Use in Special Populations

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of levosalbutamol sulphate inhalation solution has not been evaluated.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of racemic albuterol sulphate was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in racemic albuterol sulphate clearance. Caution should be used when administering high doses of levosalbutamol sulphate inhalation solution to patients with renal impairment

Ipratropium Bromide

Depending on the formulation and the inhalation technique, approximately 10-30% of the inhaled dose reaches the lungs. A major part of the dose is swallowed. Because of the negligible gastrointestinal absorption, the bioavailability of the swallowed dose is only about 2% of the total dose administered. The part of the dose that reaches the lungs has an almost complete systemic bioavailability and reaches the circulation within a few minutes. From data on renal excretion (0-24 hours), the total systemic bioavailability of inhaled ipratropium bromide is estimated to be 7-28% (averages from three studies). It can be assumed that this interval is valid for the solution for nebulizer as well. The kinetic parameters have been calculated from plasma concentrations after intravenous administration. The plasma concentration falls rapidly. The volume of distribution (Vz) is 338 L (approximately 4.6 L/kg). Ipratropium bromide has a low degree of protein-binding (<20%). Because of its ammonium ion structure, ipratropium bromide does not pass the blood-brain barrier. The elimination of ipratropium bromide is biphasic. The half-life of elimination of the drug and metabolites is 3.6 hours. The half-life of the terminal elimination phase is about 1.6 hours.

The average total clearance has been estimated to be 2.3 L/min. About 60% of the systemic available dose is metabolised, probably in the liver. The main metabolites that are found in the urine have a low affinity for muscarinic receptors and do not possess significant anticholinergic activity.

About 40% of the systemic available dose is excreted via the kidneys, which corresponds to a renal clearance of 0.9 L/min. From studies using radioactively labelled ipratropium bromide, less than 10% of the dose (ipratropium bromide and metabolites) is excreted via bile and faeces. The major part of the radio labelled dose is excreted via the kidneys.

Nonclinical Properties

Animal Toxicology or Pharmacology

Levosalbutamol Sulphate

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although there have been no carcinogenesis studies with levosalbutamol hydrochloride, racemic albuterol sulphate has been evaluated for its carcinogenic potential. In a 2-year study in Sprague-Dawley rats, dietary administration of racemic albuterol sulphate resulted in a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses of 2 mg/kg/day and greater (approximately 4 times the MRDI dose of levosalbutamol hydrochloride for adults and approximately 5 times the MRDI dose of levosalbutamol hydrochloride for children on a mg/m^2 basis). In an 18-month study in CD-1 mice and a 22-month study in the golden hamster, dietary administration of racemic albuterol sulphate showed no evidence of tumourigenicity. Dietary doses in CD-1 mice were up to 500 mg/kg/day (approximately 540 times the MRDI dose of levosalbutamol hydrochloride for adults and approximately 630 times the MRDI dose of levosalbutamol hydrochloride for children on a mg/m^2 basis) and doses in the golden hamster study were up to 50 mg/kg/day (approximately 90 times the MRDI dose of levosalbutamol hydrochloride for adults on a mg/m^2 basis and approximately 105 times the MRDI dose of levosalbutamol hydrochloride for children on a mg/m^2 basis). Levosalbutamol hydrochloride was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Levosalbutamol hydrochloride was not clastogenic in the *in vivo* micronucleus test in mouse bone marrow. Racemic albuterol sulphate was not clastogenic in an *in vitro* chromosomal aberration assay in CHO cell cultures. No fertility studies have been conducted with levosalbutamol hydrochloride. Reproduction studies in rats using racemic

albuterol sulphate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg/day (approximately 108 times the maximum recommended daily inhalation dose of levosalbutamol sulphate hydrochloride for adults on a mg/m^2 basis).

Ipratropium Bromide

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity.

Description

Levosalbutamol Sulphate

The IUPAC name of levosalbutamol sulphate is 4-[(1R)-2-(tert-butylamino)-1-hydroxye-hyl]-2-(hydroxymethyl)phenol; sulphuric acid. It has a molecular weight of 337.39 g/mol and the empirical formula is $C_{13}H_{23}NO_7S$ (Figure 1).

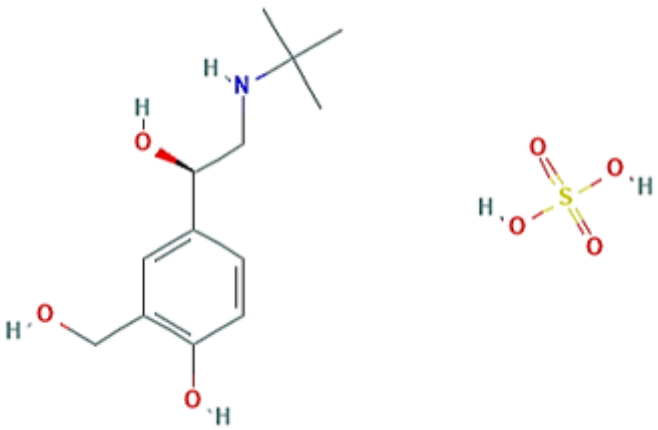

Figure 1: Chemical Structure of Levosalbutamol Sulphate

Ipratropium Bromide

Ipratropium bromide is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo [3.2.1]-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8methyl-8-(1-methylethyl)-bromide, a synthetic quaternary ammonium compound, chemically related to atropine. It has a molecular weight of 430.4 and the empirical formula is $C_{20}H_{30}BrNO_3 \bullet H_2O$. It is a white crystalline substance, freely soluble in water and lower alcohols, and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons (Figure 2).

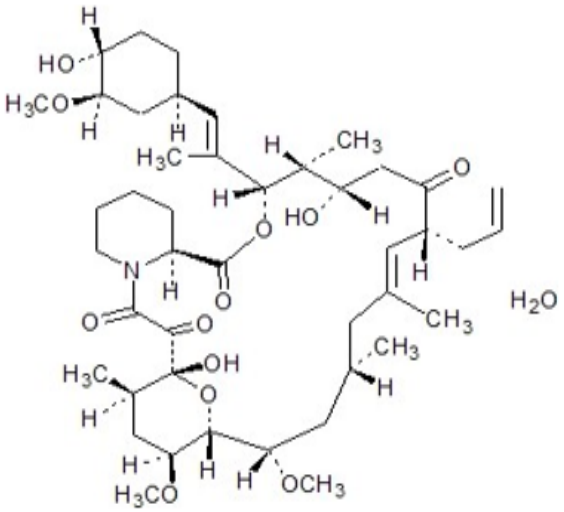

Figure 2: Chemical Structure of Ipratropium Bromide

Pharmaceutical Particulars

Incompatibilities

The drug compatibility (physical and chemical), efficacy, and safety of levalbuterol inhalation solution when mixed with other drugs in a nebulizer have not been established. Ipratropium solution can be diluted only with sterile 0.9% sodium chloride solution.

Shelf-Life

As on the pack.

Packaging Information

DUOLIN respules..... Available as unit-dose vial of 2.5 mL

DUOLIN respules..... Available as unit-dose vial of 3 mL

Available in a pack of 8 strips. Each strip contains 5 unit-dose vials of 2.5 mL [8 x 5 x 2.5 mL].

Available in a pack of 8 strips. Each strip contains 5 unit-dose vials of 3 mL [8 x 5 x 3 mL].

Storage and Handling Instructions

Store below 25°C. Do not freeze. Protect from light. The respule should be opened only before actual use and any solution remaining after use should be discarded.

Patient Counselling Information

● **What is DUOLIN respules?**

DUOLIN respules are a combination of two medicines called bronchodilators. Levosalbutamol sulphate, a beta-adrenergic agonist, and ipratropium bromide, which is an anticholinergic, work together to help open the airways in your lungs. **DUOLIN** respules are used to help treat airways

narrowing (bronchospasm) that happens with COPD (chronic obstructive pulmonary disease) in adult patients who need to use more than one bronchodilator medicine.

● Who should not use DUOLIN respules?

Do not use **DUOLIN** respules if you are allergic or hypersensitive to ipratropium bromide 0.5 mg and levosalbutamol sulphate 1.25 mg or to atropine. Counsel patients to report any hypersensitivity reactions to their physician. The active ingredients are levosalbutamol sulphate and ipratropium bromide.

● What should I tell my doctor before I start using DUOLIN respules?

Tell your doctor about all of your conditions, including if you

- have an allergic reaction to levosalbutamol sulphate and ipratropium;
- have heart problems – this includes coronary artery disease and heart rhythm problems;
- have high blood pressure;
- have diabetes;
- have or had seizures;
- have a thyroid problem called hyperthyroidism;
- have an eye problem called narrow-angle glaucoma;
- have liver or kidney problems;
- have problems urinating due to bladder-neck blockage or an enlarged prostate (men);
- are pregnant or planning to become pregnant. It is not known if **DUOLIN** respules can harm your unborn baby. You and your doctor must decide if **DUOLIN** respules are right for you during a pregnancy; and/or
- are breastfeeding. It is not known if ipratropium bromide 0.5 mg and levosalbutamol sulphate 1.25 mg passes into your milk or if it can harm your baby. You and your doctor should decide whether you should take **DUOLIN** respule or breastfeed, but not both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Ipratropium bromide 0.5 mg and levosalbutamol sulphate 1.25 mg and other medicines can interact. This may cause serious side effects. Especially tell your doctor if you take the following:

- Other medicines that contain anticholinergics such as ipratropium bromide. This also includes medicines used for Parkinson's disease.
- Other medicines that contain beta-agonists such as albuterol sulphate. These are usually used to treat airway narrowing (bronchospasm).
- Medicines called beta-blockers. These are usually used for high blood pressure or heart problems.
- Medicines called ‘water pills’ (diuretics).
- Medicines for depression called monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants.

Ask your doctor or pharmacist if you are not sure if you take any of these types of medicines. Know the medicines you take. Keep a list of them and show it to your doctor and pharmacists when you get a new medicine.

●How should I use DUOLIN respules?

- Talk to your doctor or pharmacist if you have any questions.
- Take **DUOLIN** respules exactly as prescribed by your doctor. Do not change your dose or how

often you use **DUOLIN** respules without talking to your doctor. Inhale **DUOLIN** respules using a mouthpiece and a suitable nebulizer.
- **DUOLIN** respules may help to open your airways for up to 5 hours after taking this medicine. If **DUOLIN** respules do not help your airways narrowing (bronchospasm) or your bronchospasm gets worse, call your doctor right away or get emergency help if needed.
- **Frequency of use:** Inform patients not to increase the dose more frequently than recommended without consulting their physician. If patients find that treatment becomes less effective for symptomatic relief, symptoms become worse, or they need to use the product more frequently than usual, they should seek medical attention immediately.

● What should I avoid while using DUOLIN respules?

Avoid any contact of the respule solution with your eyes. Be careful not to spray **DUOLIN** respules in your eyes while you are using your nebulizer. Exposure to **DUOLIN** respules can cause the following short-term eye problems:

- Enlarged pupils
- Blurry vision
- Eye pain

DUOLIN respules can cause a serious eye problem called narrow-angle glaucoma or worsen the narrow-angle glaucoma you already have.

Concomitant drug use: Inform patients using levosalbutamol sulphate inhalation solution, that other inhaled drugs and asthma medications should be taken only as directed by their physician.

● What are the possible side effects with DUOLIN respules?

Worsening of the narrowing in your airways (bronchospasm): This side effect can be life-threatening and has happened with both of the medicines that are in ipratropium bromide 0.5 mg and levosalbutamol sulphate 1.25 mg. Stop **DUOLIN** respules and call your doctor right away or get emergency help if your breathing problems get worse while or after using **DUOLIN** respules.

- Hypersensitivity: Query patients about previously experienced hypersensitivity to levosalbutamol sulphate or racemic albuterol sulphate and counsel patients to report any hypersensitivity reactions to their physician.
- Serious and life-threatening allergic reactions: Symptoms of a serious allergic reaction include
  - hives, rash;
  - swelling of your face, eyelids, lips, tongue, or throat, and trouble swallowing;
  - worsening of your breathing problems such as wheezing, chest tightness or shortness of breath; and,
  - shock (loss of blood pressure and consciousness)

The most common side effects with **DUOLIN** respules include lung disease, sore throat, chest pain, constipation, diarrhoea, bronchitis, urinary tract infection, leg cramps, nausea, upset stomach, voice changes, palpitation, chest pain, fast heart rate, headache, dizziness, tremor, nervousness and pain.

These are not all the side effects with **DUOLIN** respules. For a complete list, ask your doctor or pharmacist.

● How should I store DUOLIN respules?

- Store **DUOLIN** respules below 25°C. Protect from light.

- Do not use after the expiration date stamped on the container. Open the foil pouch just prior to administration. Once the foil pouch is opened, use the contents of the vial immediately. Keep the unused vials in the foil pouch or carton.
- Safely discard **DUOLIN** respules that are out-of-date or no longer needed.
- Keep **DUOLIN** respules and all medicines out of the reach of children.

General advice about **DUOLIN** respules

- **Pregnancy:** Advise patients who are pregnant or nursing to contact their physician about the use of **DUOLIN** respules.
- Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use **DUOLIN** respules for a condition for which it was not prescribed. Do not give **DUOLIN** respules to other people, even if they have the same symptoms you have, It may harm them.

This leaflet summarises the most important information about **DUOLIN** respules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **DUOLIN** respules that is written for healthcare professionals.

To report SUSPECTED ADVERSE REACTIONS, contact your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to Cipla Ltd on **1800 267 7779**. By reporting adverse events, you can help provide more information on the safety of this product.

Details of The Manufacturer

Cipla LTD. Verna Industrial Estate, Goa 403722, INDIA.

Details of Permission or Licence Number with Date

Duolin respule 2.5 mL: Manufacturing License No. 536 and dated 07.03.2011

Duolin respule 3 mL: Manufacturing License No. M/719/2016 and dated 22.12.2020

Date of Revision

29/07/2021