DUOLIN Respules (Levosalbutamol sulphate + Ipratropium bromide)

Composition

DUOLIN Respules
Each 2.5 ml unit-dose vial contains:
Levosalbutamol Sulphate ..................... 1.25 mg
Ipratropium Bromide ......................... 500 mcg
Normal Saline Solution, IP ....................... q.s.

Dosage Form

Solution for inhalation via a nebulizer.

Description

DUOLIN Respules is a combination of the beta₂-adrenergic bronchodilator, levosalbutamol sulphate, and the anticholinergic bronchodilator, ipratropium bromide. Levosalbutamol sulphate is a relatively selective beta₂-adrenergic agonist, whose activation leads to an increase in intracellular adenyl cyclase, the enzyme which catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cAMP).
Ipratropium bromide is an anticholinergic (parasympatholytic) agent, which inhibits vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve.

Pharmacology
Pharmacodynamics

DUOLIN Respules provide the simultaneous delivery of ipratropium bromide and levosalbutamol sulphate allowing effects on both muscarinic and beta$_2$-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly. No pharmacodynamic studies have been carried out on levosalbutamol sulphate and ipratropium bromide combination. Hence pharmacodynamics of levosalbutamol sulphate and ipratropium bromide has been discussed individually.

**Levosalbutamol**

Levosalbutamol is a beta$_2$-adrenergic agent which acts on airway smooth muscle. Activation of beta2-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3’, 5’-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levosalbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levosalbutamol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicated that 10-50% of the beta-receptors in the human heart might be beta$_2$-receptors. The precise function of these receptors, however, is not yet established. Controlled clinical studies and other clinical experience have shown that inhaled levosalbutamol, like other beta-adrenergic agonist drugs, can produce significant cardiovascular effects in some patients. Results from an *in vitro* study of binding to human beta-adrenergic receptors demonstrated that levosalbutamol has approximately 2-fold greater binding affinity than salbutamol and approximately 100-fold greater binding affinity than (S)-salbutamol. In guinea pig airways, levosalbutamol and racemic salbutamol decreased the response to spasmogens (e.g., acetylcholine and histamine), whereas (S)-salbutamol was ineffective. These results suggest that the bronchodilatory effects of racemic salbutamol are attributable to the levosalbutamol.

Intravenous studies in rats with levosalbutamol have demonstrated that levosalbutamol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), salbutamol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

**Ipratropium Bromide**

Ipratropium bromide is an anticholinergic (parasympatholytic) agent, which blocks the muscarinic receptors of acetylcholine. In pre-clinical studies on animals, it appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. It exerts its action by preventing increase in the intracellular concentration of cyclic guanosine monophosphate (cGMP).
The bronchodilation following inhalation of ipratropium bromide is achieved predominantly by locally available drug at the site in bronchial smooth muscles and not by systemically available drug.

Inhalation of 0.04mg 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 nebuliser produces greater bronchodilation, a dose of 0.5mg producing maximal bronchodilation.

Data from the clinical trials demonstrated that, administration of ipratropium bromide using metered dose inhalers, in patients with chronic obstructive pulmonary disease with reversible bronchospasm, significantly improved their pulmonary function. \( \text{FEV}_1 \) increased by 15% or more which occurred within 15 minutes and reached a peak in 1-2 hours, and persisted for approximately 4 hours.

Preclinical and clinical evidence suggest no deleterious effect of ipratropium bromide on airway mucous secretion, mucociliary clearance or gas exchange.

The bronchodilator effect of ipratropium bromide in the treatment of acute bronchospasm associated with asthma has been shown in studies in adults and children over 6 years of age. In most of these studies, ipratropium bromide was administered in combination with an inhaled \( \beta_2 \)-agonist.

### Pharmacokinetics

**DUOLIN Respules** are expected to maximize the response to treatment in patients with chronic obstructive pulmonary disease (COPD), by reducing bronchospasm through two distinctly different mechanisms: sympathomimetic (levosalbutamol sulphate) and anticholinergic/parasympatholytic (ipratropium bromide). Simultaneous administration of both an anticholinergic (ipratropium bromide) and a \( \beta_2 \)-sympathomimetic (levosalbutamol sulphate) is designed to produce greater bronchodilation effects than when either drug is utilized alone at its recommended dosage.

No pharmacokinetic studies have been carried out on levosalbutamol sulphate and ipratropium bromide combination. Hence pharmacokinetics of levosalbutamol sulphate and ipratropium bromide has been discussed individually.

**Levosalbutamol (Adults and Adolescents ≥ 12 Years Old)**

The inhalation pharmacokinetics of levosalbutamol were investigated in a randomized cross-over study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of levosalbutamol and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution (Table. 1) by nebulization using a nebulizer with a Dura-Neb® 2000 compressor.

Following administration of a single 1.25 mg dose of levosalbutamol, exposure to (R)-salbutamol (AUC of 3.3 ng•hr/mL) was approximately 2-fold higher than following administration of a single 2.5 mg dose of racemic salbutamol inhalation solution (AUC of 1.7 ng•hr/mL). Following administration of a cumulative 5 mg dose of levosalbutamol (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic salbutamol inhalation solution (2.5 mg given every 30 minutes for a total of four doses), Cmax and AUC of (R)-salbutamol were comparable.

<p>| Table. 1: Levo-salbutamol pharmacokinetic comparison |</p>
<table>
<thead>
<tr>
<th></th>
<th>Single Dose</th>
<th>Cumulative Dose</th>
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<tbody>
<tr>
<td></td>
<td>Levosalbutamol 1.25 mg</td>
<td>Racemic Salbutamol 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>Levosalbutamol 5 mg</td>
<td>Racemic Salbutamol 10 mg</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>(R)-salbutamol 1.1 (0.45)</td>
<td>0.8 (0.41) **</td>
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<tr>
<td></td>
<td>(R)-salbutamol 0.8 (0.41) **</td>
<td>4.5 (2.20)</td>
</tr>
<tr>
<td></td>
<td>(R)-salbutamol 4.2 (1.51) **</td>
<td>4.2 (1.51)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>(gamma) (R)-salbutamol 0.2 (0.17, 0.37)</td>
<td>0.2 (0.17, 1.50)</td>
</tr>
<tr>
<td></td>
<td>(R)-salbutamol 0.2 (-0.18 *, 1.25)</td>
<td>0.2 (-0.28 *, 1.00)</td>
</tr>
<tr>
<td>$\text{AUC}$ (ng-h/mL)</td>
<td>(R)-salbutamol 3.3 (1.58)</td>
<td>1.7 (0.99) **</td>
</tr>
<tr>
<td></td>
<td>(R)-salbutamol 17.4 (8.56)</td>
<td>16.0 (7.12) **</td>
</tr>
<tr>
<td>$t_{\text{1/2}}$ (h)</td>
<td>(R)-salbutamol 3.3 (2.48)</td>
<td>1.5 (0.61)</td>
</tr>
<tr>
<td></td>
<td>(R)-salbutamol 4.0 (1.05)</td>
<td>4.1 (0.97)</td>
</tr>
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</table>

*Children 6-11 years old*

The pharmacokinetic parameters of (R)- and (S)-salbutamol in children with asthma were obtained using population pharmacokinetic analysis (Table. 2). In children, AUC and Cmax of (R)-salbutamol following administration of 0.63 mg of levosalbutamol were comparable to those following administration of 1.25 mg racemic salbutamol inhalation solution. When the same dose of 0.63 mg of levosalbutamol was given to children and adults, the predicted Cmax of (R)-salbutamol in children was similar to that in adults (0.52 vs. 0.56 ng/mL), while predicted AUC in children (2.55 ng•hr/mL) was about 1.5-fold higher than that in adults (1.65 ng•hr/mL). These data support lower doses for children 6-11 years old compared with the adult doses.

Table 2: (R)-Salbutamol exposure in adults, adolescents, and paediatric subjects
### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
<th>Value 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng·hr/mL)</td>
<td>1.36</td>
<td>2.55</td>
<td>2.65</td>
<td>5.02</td>
<td>1.65&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>0.303</td>
<td>0.521</td>
<td>0.553</td>
<td>1.08&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.56&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> The values are predicted by assuming linear pharmacokinetics.
<sup>b</sup> The data obtained from Table 1.
<sup>c</sup> Area under the plasma concentration curve from time 0 to infinity.
<sup>d</sup> Maximum plasma concentration

### Ipratropium Bromide

#### Absorption

Based on a cumulative excretion value (CRE0-24h) of about 3-4%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 9%.

Ipratropium bromide is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as assessed by blood level and renal excretion studies. The elimination half-life of drug and metabolites is about 3 to 4 hours after inhalation or intravenous administration. Ipratropium bromide does not cross the blood-brain barrier.

Following inhalation, dose portions from 10 to 30%, depending on the formulation, device and inhalation technique, are generally deposited in the lungs. The major part of the dose is swallowed and passes through the gastro-intestinal tract.

#### Distribution

Kinetic parameters describing the distribution of ipratropium bromide were calculated from plasma concentrations after intravenous administration. A rapid biphasic decline in plasma concentrations is observed. The volume of distribution at steady state (V<sub>dss</sub>) is approximately 176 L (= 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier.

#### Biotransformation

The half-life of the terminal elimination phase is about 1.6 hours. The mean total clearance of the drug is determined to be 2.3 L/min and renal clearance of 0.9L/min. The major portion of approximately 87-89% of the systemic available dose is eliminated by metabolic degradation, probably 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 for this route of administration. The half-life for elimination of drug-related radioactivity following inhalation is 3.2 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.
Most of an administered dose is swallowed, as is shown by faecal excretion studies. Ipratropium bromide is a quaternary amine. It is not readily absorbed into the systemic circulation either from the surface of the lungs or from the gastrointestinal tract, as confirmed by blood level and renal excretion studies.

### Indications

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

### Dosage And Administration

**Adults (including elderly patients and children over 12 years):**
1 respule, three times daily.

**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 hypertrophic obstructive cardio-myopathy or tachyarrhythmia. DUOLIN Respules are also contraindicated in patients with history of hypersensitivity to any component of the formulation (levosalbutamol sulphate, ipratropium bromide) or to atropine and its derivatives.

### Warnings And Precautions

#### 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.

Paradoxical bronchospasm has been observed with both inhaled ipratropium bromide and levosalbutamol products and can be life-threatening. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial. If this occurs, DUOLIN Respules should be discontinued immediately, patients should be assessed and alternative therapy instituted.

#### Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled products containing sympathomimetic amines.
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 DUOLIN Respules and warned not to allow the solution or mist to enter the eyes. This is particularly important in patients who may be pre-disposed 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. Antiglaucoma therapy is effective in the prevention of acute narrow-angle glaucoma in susceptible individuals and patients who may be susceptible to glaucoma should be warned specifically on the need for ocular protection.

Cardiovascular Effects

Like other beta-adrenergic agonists, DUOLIN Respules can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon for DUOLIN Respules 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. Large doses of intravenous racemic salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. The clinical significance of these findings is unknown. Therefore, DUOLIN Respules, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension, in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions to levosalbutamol and/or ipratropium bromide may occur after the administration of DUOLIN Respules, as demonstrated by rare cases of urticaria (including giant urticaria), angio-oedema, skin rash, pruritus, oropharyngeal oedema, bronchospasm, anaphylaxis, pruritus and laryngospasm. If such a reaction occurs, therapy with DUOLIN Respules should be stopped at once and alternative treatment should be considered.

Systemic Effects Seen with Sympathomimetic Drugs

As with all products containing sympathomimetic amines, DUOLIN Respules should be used with caution after careful risk/benefit assessment in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, recent myocardial infarction and hypertension; in patients with convulsive disorders, hyperthyroidism, diabetes mellitus, pheochromocytoma; and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous racemic salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. Additionally, beta-agonists may cause a decrease in serum potassium in some patients, possibly
through intracellular shunting which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

- **Systemic Effects Seen with Anticholinergic Drugs**

DUOLIN Respules should be used with caution in patients with a risk of narrow-angle glaucoma, prostatic hyperplasia or bladder-outflow obstruction.

- **Use in Hepatic or Renal Diseases**

DUOLIN Respules have not been studied in patients with hepatic or renal impairment. It should be used with caution in these patient populations.

- **Hypokalaemia**

Potentially serious hypokalaemia may result from beta2-agonist therapy. 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.

The safety and efficacy of Levosalbutamol have been established in pediatric patients 6 years of age and above in an adequate and well controlled clinical trial, however, its safety and effectiveness in patients 6 years and below have not been established.

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.

- **Drug Interactions**

*Anticholinergic Agents*

The chronic co-administration of levosalbutamol and ipratropium bromide with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of DUOLIN with other anticholinergic drugs is not recommended.

*Beta-Adrenergic Agents*

Caution is advised in the co-administration of DUOLIN Respules and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects. The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of DUOLIN. 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.

**Beta-Receptor Blocking Agents**

These agents and levosalbutamol sulphate inhibit the effect of each other. Beta-receptor blocking agents should be used with caution in patients with hyper-reactive airways or under certain circumstances e.g. as prophylaxis after myocardial infarction, they should be administered with caution. Also, relatively selective beta-1-selective agents are recommended for use.

**Diuretics**

The ECG changes and/or hypokalaemia that may result from the administration of non-potassium-sparing diuretics (such as loop or 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-agonist-containing drugs, such as DUOLIN Respules, with non-potassium-sparing diuretics.

**Digoxin**

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic salbutamol, 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 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 DUOLIN Respules.

**Monoamine Oxidase Inhibitors or Tricyclic Antidepressants**

DUOLIN Respules 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 cardiovascular system may be potentiated.

**Pregnancy**

There are no adequate and well-controlled studies of DUOLIN Respules in pregnant women. Because animal reproduction studies are not always predictive of human response, DUOLIN Respules should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

**Use in Labor and Delivery**

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of DUOLIN Respules for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.
Levosalbutamol has not been approved for the management of preterm labor. The benefit:risk ratio when Levosalbutamol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta2-agonists, including racemic salbutamol.

Lactation

Plasma levels of Levosalbutamol after inhalation of therapeutic doses are very low in humans, but it is not known whether Levosalbutamol is secreted in human milk. Because of the potential for tumorigenicity shown for racemic salbutamol in animal studies and the lack of experience with the use of DUOLIN Respules 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 DUOLIN Respules is administered to a nursing woman.

Undesirable Effects

Since DUOLIN Respules contains both ipratropium and levosalbutamol, the side effects of both the components should be expected.

Levosalbutamol

Common side effects reported by greater than or equal to 2% in adults and adolescents in a 4-week controlled clinical trial were pain, flu syndrome, accidental injury, tachycardia, migraine, dyspepsia, leg cramps, dizziness, nervousness, tremor, anxiety, as well as certain respiratory effects such as increased cough, viral infection, rhinitis, sinusitis and turbinate edema. Other undesirable effects observed in less than 2% of the subjects were chills, chest pain, changes in ECG, leg cramps, dyspepsia, anxiety, hyperesthesia of the hand, insomnia, paresthesia, tremor, hypertension, hypotension, syncope, diarrhoea, dry mouth, dry throat, gastroenteritis, nausea, lymphadenopathy, myalgia, hysteresis of the hand, insomnia, paresthesia and eye itch. Common side effects observed in more than or equal to 2 % of children (6-11 years old) were accidental injury, asthenia, fever, headache, pain, viral infections, diarrhoea, lymphadenopathy, myalgia, asthma, pharyngitis, rhinitis, rash, urticaria. The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low. Changes in heart rate and plasma glucose and potassium levels were low. Potentially serious hypokalaemia may result from beta2-agonist therapy. This effect may be potentiated by hypoxia. Caution is advised in severe asthma in such cases, monitoring of serum potassium levels is recommended. In addition to the adverse events reported in clinical trials, the following adverse events have been observed in post approval use of levosalbutamol. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles), asthma, chest pain, cough increased, dysphonia, dyspnea, gastroesophageal reflux disease (GERD), metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, and urticaria. Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

In addition, levosalbutamol, 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

As with all inhalation therapy, DUOLIN may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval of the drug.

In a clinical trial involving 3488 patients, administered with Ipratropium bromide and salbutamol, following were the side effects seen.

The common adverse effects (>1/100, \< 1/10) include: nervous system disorders (headache), respiratory, thoracic and mediastinal disorders (cough, local irritation), gastrointestinal disorders [dryness of mouth, nausea and disturbances in gastrointestinal motility (constipation, diarrhoea and vomiting) and dizziness.

The uncommon adverse effects include (>1/1,000, \< 1/100) nervous system disorder (nervousness, dizziness, headache, tremor); cardiac disorder (palpitations, tachycardia, increased systolic blood pressure); respiratory, thoracic and mediastinal disorders (cough, dysphonia, throat irritation); gastrointestinal disorders (dry mouth, nausea), skin disorder (skin reaction).

The rare adverse effects (>1/10,000, \< 1/1,000) include: immune system disorders (Anaphylactic reaction, hypersensitivity, Angioedema of tongue, lips and face), metabolic disorder (hypokalaemia); eye disorders (accommodation disturbances, narrow angle glaucoma, corneal edema, eye pain, increased intraocular pressure, mydriasis, blurred vision, conjunctival hyperemia, halo vision), cardiac disorders (arrhythmia, atrial fibrillation, myocardial ischemia, supraventricular tachycardia), respiratory, thoracic and mediastinal disorders (bronchospasm, paradoxical bronchospasm, dry throat, pharyngeal edema, spasm of the larynx), skin and subcutaneous disorders (hyperhidrosis, rash, urticaria, pruritus), gastrointestinal disorder (diarrhea, constipation, vomiting, mouth edema, stomatitis), musculoskeletal disorder (muscle spasm, muscular weakness, myalgia), renal disorder (urinary retention), Asthenia and decrease in diastolic blood pressure.

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.

By reporting side effects, you can help provide more information on the safety of this product.

Overdosage

The effects of overdosage with DUOLIN Respules are expected to be related primarily to Levosalbutamol, since ipratropium bromide is not well absorbed systemically after oral or aerosol administration. Therefore, the effects of overdosage of ipratropium bromide are mild and transient (such as dry mouth, visual accommodation disorders). The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of symptoms such as seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmia, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia and insomnia. As with all sympathomimetic aerosol medications, cardiac arrest and, even, death may be associated with the abuse of DUOLIN Respules. The judicious use of cardioselective beta-receptor blockers may be considered, bearing in mind that such medication can produce bronchospasm.

Storage And Handling
Store below 25°C. Do not freeze. Protect from light.

Packaging Information

DUOLIN Respules........ available as respule of 2.5 ml

Last updated: July 2018
Last reviewed: July 2018

DUOLIN Respules

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