Duolin Respules:

1. **Brand Name**
   Duolin Respules

2. **Generic name**
   Salbutamol + Ipratropium Bromide

3. **Dosage Form**
   Solution for inhalation via a nebulizer: Salbutamol Sulphate 2.5 mg + Ipratropium Bromide 500 mcg

4. **Indication & Usage**
   Duolin Respules is a combination of the beta2-adrenergic bronchodilator, salbutamol sulphate, and the anticholinergic bronchodilator, ipratropium bromide.
   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.

5. **Dosage & 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.

6. **Adverse reactions**
   Since Duolin Respules contains both ipratropium and salbutamol, the side effects of both the components should be expected.

   Salbutamol:
   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, diarrhea, dry mouth, dry throat, gastroenteritis, nausea, lymphadenopathy, myalgia, hypoesthesia of the hand, insomnia, paresthesia and eye itch.
   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 hypokalemia 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 salbutamol. 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, and 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, salbutamol, 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), gastro-intestinal disorders [dryness of mouth, nausea and disturbances in gastrointestinal motility (constipation, diarrhea 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 (hypokalemia); 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.

7. 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 (salbutamol sulphate, ipratropium bromide) or to atropine and its derivatives.

8. Drug interactions

Anticholinergic Agents:
The chronic co-administration of salbutamol 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 anesthetics such as halothan e may increase the susceptibility to the cardiovascular effects of beta-agonists.

Beta-Receptor Blocking Agents:
These agents and salbutamol 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 beta1-selective agents are recommended for use.

Diuretics:
The ECG changes and/or hypokalemia 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:
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 salbutamol sulphate on the cardiovascular system may be potentiated.

9. Warnings & 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 salbutamol products and can be life-threatening. 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

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 colored images, in association with red eyes from conjunctival congestion and corneal edema 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 salbutamol and/or ipratropium bromide may occur after the administration of Duolin Respules, as demonstrated by rare cases of urticaria (including giant urticaria), angioedema, skin rash, pruritus, oropharyngeal edema, 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.

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.

Hypokalemia

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

Gastro-Intestinal Motility Disturbances

Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances.

Dyspnea

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

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10. Pregnancy & Lactation

Pregnancy

There are no adequate and well-controlled studies of Duolin Respules in pregnant women. Duolin Respules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Plasma levels of salbutamol after inhalation of therapeutic doses are very low in humans, but it is not known whether salbutamol is secreted in human milk. 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.

11. Storage condition

Store below 25°C.
Do not freeze.
Protect from light.
Do not use if the solution is discolored.
Keep out of the reach of children.

12. Packaging

Each box contains 20 respules, 2.5 ml of each.

13. License Holder

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14. Marketing Authorization Holder in IRAN

Koushan Pharmed