DUOLIN LD Respules (Levosalbutamol sulphate + Ipratropium bromide)

Composition

DUOLIN LD Respules
Each 2.5 ml unit-dose vial contains:
Levosalbutamol Sulphate .........................0.63mg
Ipratropium Bromide ............................ 500 mcg
Normal Saline Solution, IP .......................q.s.

Dosage Form

Solution for inhalation via a nebulizer

Description

DUOLIN LD Respules are 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 LD Respules provide the simultaneous delivery of ipratropium bromide and levosalbutamol sulphate allowing effects on both muscarinic and beta₂-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 beta₂-adrenergic agent which acts on airway smooth muscle. Activation of beta2-adrenergic receptors on airway smooth muscle leads to the activation of adenyl cyclase 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.

**Ipratropium Bromide**

Ipratropium bromide is an anticholinergic (parasympatholytic) agent, which blocks the muscarinic receptors of acetylcholine, and, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent increases in the intracellular concentration of cyclic guanosine monophosphate (cGMP), resulting from the interaction of acetylcholine with the muscarinic receptors of bronchial smooth muscle.

The bronchodilation following inhalation of ipratropium bromide is induced by local drug concentrations sufficient for anticholinergic efficacy at the bronchial smooth muscle and not by systemic drug concentrations. 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.

In clinical trials using metered dose inhalers in patients with reversible bronchospasm associated with chronic obstructive pulmonary disease significant improvements in pulmonary function (FEV$_1$ increases of 15% or more) occurred within 15 minutes, 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**

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**

In adults and adolescents ≥ 12 years, 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 salbutamol sulfate inhalation solution 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.
The pharmacokinetic parameters of (R)-and (S)-salbutamol in children with asthma were obtained using population pharmacokinetic analysis. 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.

Ipratropium Bromide

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. Due to the negligible gastro-intestinal absorption of ipratropium bromide the bioavailability of the swallowed dose portion is only approximately 2%. This fraction of the dose does not make a relevant contribution to the plasma concentrations of the active ingredient. The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes).

Limited data on total systemic bioavailability (pulmonary and gastro-intestinal portions), based on renal excretion (0 - 24 hours) of ipratropium bromide, suggests a range of 7 - 28% when delivery is via a nebuliser or a MDI product. It is assumed that this is also a valid range for inhalation from the powder preparation.

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 (Vz) is 338 L (4.6 L/kg). The drug is minimally (less then 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the ammonium structure of the molecule. 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. The major portion of approximately 60% of the systemic available dose is eliminated by metabolic degradation, probably in the liver. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

A portion of approximately 40% of the systemic available dose is cleared via urinary excretion corresponding to an experimental renal clearance of 0.9 L/min. In excretion balance studies after intravenous administration of a radioactive dose, less than 10% of the drug-related radioactivity (including parent compound and all metabolites) is excreted via the biliary-faecal route. The dominant excretion of drug-related radioactivity occurs via the kidneys. 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. Autoradiographic studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. The half-life of elimination is about 2 hours after inhalation or intravenous administration. Ipratropium bromide is minimally bound (0-9% in vitro) to plasma albumin and alpha1-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one-half of the dose is excreted unchanged in the urine.

A pharmacokinetic study with 29 chronic obstructive pulmonary disease (COPD) patients (48–79 years of age) demonstrated that mean peak plasma ipratropium concentrations of 59±20 pg/ml were obtained following a single
administration of 4 inhalations of ipratropium bromide (84 mcg). Plasma ipratropium concentrations rapidly declined to 24±15 pg/ml by 6 hours. When these patients were administered 4 inhalations q.i.d. (16 inhalations/day = 336 mcg) for 1 week, the mean peak plasma ipratropium concentration increased to 82±39 pg/ml with a trough (6 hours) concentration of 28±12 pg/ml at steady state.

### Indications

DUOLIN LD 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

1 respule, nebulized three to four times daily. The dosage should be adapted to the individual requirements of the patient.

### Contraindications

Hypersensitivity to any component of the formulation (levosalbutamol sulphate, ipratropium bromide) or to atropine and its derivatives

### Warnings And Precautions

#### Paradoxical Bronchospasm

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 LD Respules should be discontinued immediately and alternative therapy instituted.

#### Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled products containing sympathomimetic amines.

#### Cardiovascular Effects

Like other beta-adrenergic agonists, DUOLIN LD 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 LD 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 LD 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 LD 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 LD Respules should be stopped at once and alternative treatment should be considered.

Effects Seen With Sympathomimetic Drugs

As with all products containing sympathomimetic amines, DUOLIN LD Respules 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. 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.

Effects Seen With Anticholinergic Drugs

Due to the presence of ipratropium bromide in DUOLIN LD Respules which may cause urinary obstruction, they should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-outflow obstruction. There have been isolated reports of ocular complications (i.e. mydriasis, increased intraocular 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. Thus patients must be instructed in the correct administration of DUOLIN LD Respules and warned against the accidental release of the contents into the eye. 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.

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.

Use in Hepatic or Renal Diseases

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

Ocular Complications

There have been rare reports 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 LD 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.

In the following conditions DUOLIN LD Respules should only be used after careful risk/benefit assessment: insufficiently controlled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, prostatic hypertrophy and risk of narrow-angle glaucoma.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in severe airway obstruction as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm (especially in patients receiving
digoxin). It is recommended that serum potassium levels are monitored in such situations. Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances. 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**

Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is, therefore, advised in the co-administration of DUOLIN LD Respules with other drugs having anticholinergic properties.

**Beta-Adrenergic Agents**

Caution is advised in the co-administration of DUOLIN LD Respules and other sympathomimetic agents due to the increased risk of adverse cardiovascular effects.

**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 LD 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 LD Respules.

**Monoamine Oxidase Inhibitors or Tricyclic Antidepressants**

DUOLIN LD 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 levosalbutamol and ipratropium combination in pregnant women. Because animal reproduction studies are not always predictive of human response, DUOLIN LD Respules should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

### Lactation

It is not known whether the components of DUOLIN LD Respules are excreted in human milk. Although lipid-insoluble quaternary bases pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken as a nebulized solution. Plasma levels of levosalbutamol after inhalation of therapeutic doses are very low in humans, but it is not known whether levosalbutamol is excreted in human milk. Because of the potential for tumorigenicity shown for levosalbutamol sulphate in some animal studies, a decision should be made...
whether to discontinue nursing or discontinue Duolin LD Respules, taking into account the importance of the drug to the mother.

**Paediatric Use**

Safety and effectiveness of DUOLIN LD Respules in patients below 18 years of age have not been established.

**Geriatric Use**

Safety and effectiveness of DUOLIN LD Respules in elderly patients (65 years of age and older) have not been established. Data on the use of levosalbutamol in patients 65 years of age and older is very limited. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of levosalbutamol. If clinically warranted due to insufficient bronchodilator response, the dose of levosalbutamol may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose.

**Undesirable Effects**

Since DUOLIN LD Respules contains both ipratropium and levosalbutamol, the side effects of both the components should be expected. Efficacy and safety of levosalbutamol and ipratropium combination in chronic obstructive pulmonary disease (COPD) provides significant improvement in lung function and generally well tolerated.

**Levosalbutamol**

Common side effects reported by greater than 2% in adults and adolescents 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, hypertension, hypotension, syncope, diarrhoea, dry mouth, dry throat, gastroenteritis, nausea, lymphadenopathy, myalgia, hypesthesia of the hand, insomnia, paresthesia and eye itch. Common side effects observed in more than 2% of children were abdominal pain, accidental injury, asthenia, fever, headache, pain, viral infections, diarrhoea, lymphadenopathy, myalgia, asthma, pharyngitis, rhinitis, rash, urticaria; whereas in less than 2% were cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis. In children, frequently occurring adverse events were accidental injury, vomiting, bronchitis, pharyngitis. 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 slightly low. Potentially serious hypokalaemia may result from beta-2-agonist therapy. This effect may be potentiated by hypoxia. Particular 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, gastrooesophageal 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

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

The common adverse effects (>1/100, < 1/10) include: nervous system disorders (headache), respiratory, thoracic and mediastinal disorders (cough, local irritation), gastro-intestinal disorders. The uncommon adverse effects (>1/1,000, < 1/100) include: immune system disorders (urticaria), eye disorders (accommodation disturbances, narrow angle glaucoma), cardiac disorders (tachycardia), respiratory, thoracic and mediastinal disorders (spasm of the larynx), skin and subcutaneous disorders (exanthema). The rare adverse effects (>1/10,000, 1/1000) seen include: immune system disorders (anaphylactic reactions, angio-oedema on 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 (bronchospasm induced by the inhalation), renal and urinary disorders (urinary retention).

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 LD Respules are expected to be related primarily to levalbuterol, since ipratropium bromide is not well absorbed systemically after oral or aerosol administration. 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 and insomnia. As with all sympathomimetic aerosol medications, cardiac arrest and, even, death may be associated with the abuse of DUOLIN LD Respules. The judicious use of cardio selective beta-receptor blockers may be considered, bearing in mind that such medication can produce bronchospasm.

Palpitation and increases in heart rate have been produced with inhaled doses of 5 mg ipratropium. 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 characterized by atropine-like symptoms like tachycardia, tachypnea, high fever and central effects like restlessness, confusion and hallucinations. These symptoms should be treated symptomatically. The use of phystostigmine is not recommended because of worsening of cardiotoxic symptoms and induction of convulsions.

Packaging Information

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

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