

New Zealand Datasheet

1 PRODUCT NAME

Duolin® 100 mcg / 20 mcg metered dose aerosol inhaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Salbutamol 100 mcg / Ipratropium bromide 20 mcg per inhalation.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Duolin Inhaler consists of a white homogenous suspension of micronised substances in a CFC-free (HFA-227) propellant mixture filled in an aluminium canister with a metering valve. Each metered dose contains salbutamol 100 mcg (equivalent to 120 mcg salbutamol sulphate), and ipratropium bromide 20 mcg (equivalent to 21 mcg of ipratropium bromide monohydrate). Duolin Inhaler uses a metered dose inhaler that has a grey actuator and mouthpiece with a light blue cap. Each inhaler contains 200 doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Duolin Inhaler is indicated for the treatment of reversible bronchospasm associated with obstructive airway diseases in patients who require more than a single bronchodilator.

4.2 Dose and method of administration

Adults (including elderly patients): Two inhalations four times daily. The dose may be increased as required up to a maximum of 12 inhalations in 24 hours.

Children: There has been no experience with the use of Duolin Inhaler in children below the age of 12 years.

Duolin Inhaler has not been studied in patients with hepatic or renal insufficiency. It should be used with caution in those patient populations.

In asthma, concomitant anti-inflammatory therapy should be considered.

In patients who find coordination of a pressurised metered-dose inhaler difficult, a spacer device may be used with Duolin Inhaler. Please follow the instruction for use provided with the spacer.

Patients should be advised to consult a doctor or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea (difficulty in breathing) if additional inhalations do not produce an adequate improvement.

4.3 Contraindications

Duolin Inhaler is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any other component of the product and in patients with hypertrophic obstructive cardiomyopathy and tachyarrhythmia.

4.4 Special warnings and precautions for use

In the case of acute, rapidly worsening dyspnoea, a doctor should be consulted immediately.

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

There have been isolated reports of ocular complications (e.g. mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain) when aerosolised ipratropium bromide either alone or in combination with an adrenergic beta2-agonist containing ipratropium bromide have escaped into the 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. Patients should be instructed in the correct administration of Duolin Inhaler and care must be taken to prevent Duolin from entering the eye. Patients who may be predisposed to glaucoma should be warned specifically to protect their eyes.

In the following situations Duolin Inhaler should only be used after careful risk / benefit assessment, especially when doses higher than recommended are used: Insufficiently controlled diabetes mellitus, recent myocardial infarction, severe organic heart or vascular disorders, hyperthyroidism, phaeochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.

Cardiovascular effects may be seen with sympathomimetic drugs, including Duolin Inhaler. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, tachyarrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms (e.g. dyspnoea and chest pain), as they may be of either respiratory or cardiac origin.

Potentially serious hypokalaemia may result from prolonged and / or high dose beta2-agonist therapy. Additionally, hypoxia may aggravate the effects of hypokalaemia on cardiac rhythm.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances.

If higher than recommended doses of Duolin Inhaler are required to control symptoms, the patient's therapy plan should be reviewed by a doctor.

The use of Duolin Inhaler may lead to positive results with regards to salbutamol in tests for nonclinical substance abuse e.g. in the context of athletic performance enhancement (doping).

Duolin Inhaler contains a very small amount of lactose (less than 0.04 mcg per actuation). For people that are intolerant to lactose, this small amount does not normally cause problems. Caution should be taken for those with severe milk protein allergies.

4.5 Interaction with other medicines and other forms of interaction

The concurrent administration of other beta-mimetics, systemically absorbed anticholinergics and xanthine derivatives may increase the side effects.

Beta-agonist induced hypokalaemia may be increased by concomitant treatment with xanthine derivatives, glucocorticosteroids and diuretics. This should be taken into account particularly in patients with severe airway obstruction.

Hypokalaemia may result in an increased susceptibility to arrhythmias in patients receiving digoxin. It is recommended that serum potassium levels be monitored in such situations.

A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.

Beta-adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta-adrenergic agonists may be enhanced.

Inhalation of halogenated hydrocarbon anaesthetics such as halothane, trichloroethylene and enflurane may increase the susceptibility to the cardiovascular effects of beta-agonists.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Duolin Inhaler during human pregnancy is not established. The usual precautions regarding the use of drugs in pregnancy, especially during the first trimester, should be observed. The inhibitory effect of Duolin Inhaler on uterine contraction should be taken into account.

Duolin Inhaler during a confirmed or suspected pregnancy must be weighed against possible hazards to the unborn child.

For ipratropium bromide, preclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man. For salbutamol sulphate, non-inhalation preclinical studies did not indicate direct or indirect harmful effects unless the inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (please refer to section Toxicology).

No studies on the effect on human fertility have been conducted for Duolin Inhaler. Preclinical studies performed with ipratropium bromide and salbutamol showed no adverse effect on fertility (please refer to section Toxicology).

Breast feeding

It is not known whether salbutamol sulphate and ipratropium bromide are excreted in breast milk. Although lipid-insoluble quaternary cations pass into breast milk, it is considered unlikely that ipratropium bromide would reach the infant to an important extent when administered by inhalation. However, because many drugs are excreted in breast milk, caution should be exercised when Duolin Inhaler is administered to nursing mothers.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that they may experience undesirable effects such as dizziness, accommodation disorder, mydriasis and blurred vision during treatment with Duolin Inhaler. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above-mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Many of the listed undesirable effects can be assigned to the anticholinergic and beta2-sympathomimetic properties of Duolin Inhaler. As with all inhalation therapy, Duolin Inhaler may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance during post approval use of the drug.

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

Immune system disorders:

Anaphylactic reaction
Hypersensitivity

Metabolism and nutrition disorders:

Hypokalaemia

Psychiatric disorders:

Mental disorder
Nervousness

Nervous system disorders:

Dizziness
Headache
Tremor

Eye disorders:

Glaucoma
Eye pain
Intraocular pressure increased
Mydriasis
Vision blurred
Accommodation disorder
Corneal oedema
Conjunctival hyperaemia
Halo vision

Cardiac disorders:

Arrhythmia
Atrial fibrillation
Myocardial ischaemia
Palpitations
Tachycardia
Supraventricular tachycardia

Respiratory, thoracic and mediastinal disorders:

Bronchospasm
Bronchospasm paradoxical
Laryngospasm
Pharyngeal oedema
Cough
Dysphonia
Dry throat

Gastrointestinal disorders:

Oedema mouth
Dry mouth
Throat irritation
Diarrhoea
Gastrointestinal motility disorder
Constipation
Nausea
Vomiting
Stomatitis

Skin and subcutaneous tissue disorders:

Skin reactions such as:
Rash
Pruritus
Urticaria
Angioedema
Hyperhidrosis

Musculoskeletal and connective tissue disorders:

Muscle spasms
Muscular weakness
Myalgia

Renal and urinary disorders:

Urinary retention

General disorders and administration site conditions:

Asthenia

Investigations:

Blood pressure diastolic decreased
Blood pressure systolic increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

The effects of overdosage are expected to be primarily related to salbutamol. The expected symptoms with overdosage are those of excessive beta-adrenergic-stimulation, the most prominent being tachycardia, palpitation, tremor, hypertension, hypotension, widening of the pulse pressure, anginal pain, arrhythmias, and flushing.

Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disorders) are mild and transient in nature in view of the wide therapeutic range and topical administration.

Treatment

Administration of sedatives, tranquillisers, in severe cases intensive therapy.

Beta-receptor blockers, preferably beta1-selective, are suitable as specific antidotes; however, a possible increase in bronchial obstruction must be taken into account and the dose should be adjusted carefully in patients suffering from bronchial asthma.

Contact the Poisons Information Centre (phone: 0800 764 766) for advice on management of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Duolin Inhaler contains two active bronchodilating substances, salbutamol sulphate and ipratropium bromide.

Salbutamol sulphate is a beta2-adrenergic agonist which acts on airway smooth muscle resulting in muscle relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and aids to prevent bronchoconstriction when challenged.

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In preclinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase of intracellular concentration of Ca⁺⁺ which is caused by interaction of acetylcholine with muscarinic receptors on bronchial smooth muscle. Ca⁺⁺ release is mediated by the second messenger system consisting of IP3 (inositol triphosphate) and DAG (diacylglycerol). The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Duolin Inhaler provides the simultaneous release of ipratropium bromide and salbutamol allowing the synergistic efficacy on the muscarinic and beta2-adrenergic receptors in the lung resulting in a bronchodilation which is superior to that provided by each single agent.

Controlled studies in patients with reversible bronchospasm have demonstrated that Duolin Inhaler has a greater bronchodilator effect than either of its components and there was no potentiation of adverse events.

5.2 Pharmacokinetic properties

From a pharmacokinetic perspective, the efficacy observed in the Inhalation Aerosol pulmonary clinical trials is due to a local effect on the lung following inhalation.

Following inhalation, 10% to 39% of a dose is generally deposited in lungs, depending on the formulation, inhalation technique and device, while the remainder of the delivered dose is deposited in the mouthpiece, mouth and the upper part of the respiratory tract (oropharynx). The portion of the dose deposited in the lungs reaches the circulation rapidly (within minutes). The amount of the active substance deposited in the oropharynx is slowly swallowed and passes the gastrointestinal tract. Therefore, the systemic exposure is a function of both oral and lung bioavailability.

Ipratropium

Cumulative renal excretion (0-24 hrs) of ipratropium (parent compound) is approximated to 46% of an intravenously administered dose, below 1% of an oral dose and approximately 3-4% of an inhaled dose. Based on this data, the total systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7-9% respectively. Taking this

into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Kinetic parameters describing the disposition of ipratropium were calculated from plasma concentrations after i.v. administration. A rapid biphasic decline in plasma concentrations is observed. The apparent volume of distribution at steady-state (V_{dss}) is approximately 176 L (≈ 2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Preclinical studies with rats and dogs revealed that the quaternary amine ipratropium does not cross the blood-brain barrier.

The half-life of the terminal elimination phase is approximately 1.6 hours. Ipratropium has a total clearance of 2.3 L/min and a renal clearance of 0.9 L/min. After intravenous administration, approximately 60% of a dose is metabolised probably mainly in the liver by oxidation.

In an excretion balance study, cumulative renal excretion (6 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 72.1% after intravenous administration, 9.3% after oral administration and 3.2% after inhalation. Total radioactivity excreted via the faeces was 6.3% following intravenous application, 88.5% following oral dosing and 69.4% after inhalation. Regarding the excretion of drug-related radioactivity after intravenous administration, the main excretion occurs via the kidneys. The half-life for elimination of drug-related radioactivity (parent compound and metabolites) is 3.6 hours. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Salbutamol

Salbutamol is rapidly and completely absorbed following administration either by the inhaled or gastric route and has an oral bioavailability of approximately 50%. Mean peak plasma salbutamol concentrations of 492 pg/ml occur within three hours after inhalation of Duolin Inhaler. Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine. Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (V_z) is approximately 156 L (≈ 2.5 L/kg). Only 8% of the drug is bound to plasma proteins. Salbutamol will cross the blood brain barrier reaching concentrations amounting to about 5% of the plasma concentrations. The mean terminal half-life is approximately 4 hours with a mean total clearance of 480 mL/min and a mean renal clearance of 291 mL/min.

Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulphate. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer. Following intravenous administration, urinary excretion was complete after approximately 24 hours. The majority of the dose was excreted as parent compound (64.2%) and 12.0% was excreted as sulphate conjugate. After oral administration, urinary excretion of unchanged drug and sulphate conjugate were 31.8% and 48.2% of the dose, respectively.

Co-administration of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and therefore the additive activity of Duolin Inhaler is due to the combined local effect on the lung following inhalation.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, propellant HFA-227.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 24 months (2 years) from manufacture. The expiry date is the last day of the expiry month.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Do not expose the aerosol canister to high temperatures. Do not force open even when empty.

6.5 Nature and contents of container

Aerosol, aluminium aerosol can with metered dose valve and actuator – 200 doses.

6.6 Special precautions for handling and disposal

Instructions for Use/Handling

Testing your inhaler:

Before first use, the Duolin Inhaler should be shaken and the mouthpiece cover removed and the canister depressed twice to release two actuations into the air. If the inhaler has not been used for more than one week the canister should be depressed twice to re-prime the inhaler.

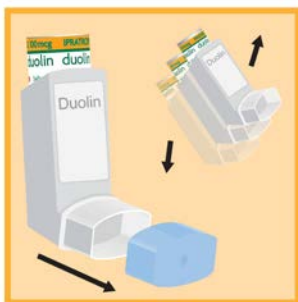


Using your inhaler:

The correct operation of the inhaler is essential for successful therapy.

1. Remove the mouthpiece cover.

Shake the inhaler well before each use. If the inhaler has not been used for more than one week depress the canister twice to prime the inhaler.



2. Breathe out deeply through your mouth.
Hold the inhaler, with the inhaler upright and your thumb on the base and either one or two fingers on top of the canister and place the mouthpiece of the inhaler in your mouth and close lips over the mouthpiece (do not bite it).



3. Start breathing in as deeply as possible. As you breathe in, depress the canister to release one dose, while continuing to breathe in steadily and deeply.
4. Hold your breath for 10 seconds, or for as long as it is comfortable. Then remove the mouthpiece from your mouth and breathe out slowly.
5. If another dose is required, it is recommended that you wait for at least one minute and then repeat steps 2 to 4.
6. After use, replace the mouthpiece cover.

IMPORTANT: Do not rush steps 3 to 4. It is important that you start to breathe in slowly just before releasing the dose.

Practice in front of a mirror for the first few times. If you see “mist” coming from the top of your inhaler or the sides of your mouth you should start again from stage 2. This escaping “mist” indicates incorrect technique.

Cleaning

Note: The mouthpiece should always be kept clean to maintain the proper functioning of the inhaler. Clean your inhaler at least once per week as follows:

1. Gently pull the metal canister out of the plastic body of the inhaler. Remove the mouthpiece cover.
2. Immerse the plastic body and the mouthpiece cover in warm water.
3. Rinse the plastic body and mouthpiece cover under running tap water.
4. Shake well to remove excess water. Leave to dry in a warm place.
5. Replace the canister and mouthpiece cover correctly.

DO NOT PUT THE METAL CANISTER INTO WATER.

Note: If soap or detergent is used, the mouthpiece should be thoroughly rinsed in clear water. When cleaning the inhaler always make sure that you have a spare inhaler ready to use.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

REX Medical Ltd
PO Box 18-119
Glen Innes 1743
AUCKLAND
admin@rexmed.co.nz
Ph (09) 574 6060
Fax (09) 574 6070

9 DATE OF FIRST APPROVAL

18 November 2010

10 DATE OF REVISION OF THE TEXT

15 February 2019
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Summary table of changes:

Section changed	Summary of new information
All	Format update
4.4	Caution regarding lactose content.
6.6	Updated graphics