PROFESSIONAL INFORMATION FOR

DUOLIN RESPULES

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DUOLIN RESPULES 0,5 mg/2,5 mg in 2,5 mL, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2,5 mL solution (in a single dose respule) contains ipratropium bromide micronized equivalent to ipratropium bromide (anhydrous) 0,5 mg and salbutamol sulphate equivalent to salbutamol 2,5 mg.

Sugar free.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Solution.

DUOLIN RESPULES are clear polyethylene bottles (respules) containing 2,5 mL of a clear, colourless solution free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUOLIN RESPULES is indicated for the treatment of reversible bronchospasm associated with obstructive pulmonary disease.

4.2 Posology and method of administration

Posology

Do not exceed recommended doses.

In the case of acute or rapidly worsening dyspnoea, a medical practitioner should be consulted immediately (see **section 4.4**).

Adults (including elderly patients) and children over the age of 12 years

Treatment of acute symptoms

One unit dose (one respule) provides prompt relief in most cases.

In severe cases, if an attack has not been relieved by one respule, two respules may be required. In this situation, the patient should seek prompt medical attention.

Maintenance treatment

One respule three or four times a day.

Paediatric population

Children under the age of 12 years

There is no experience in the use of DUOLIN RESPULES in children under the age of 12 years (see **section 4.3**).

Method of administration

Oral inhalation. DUOLIN RESPULES solution for inhalation may be administered via a suitable nebuliser or an intermittent positive pressure ventilator. The respules should not be taken orally (swallowed) or administered parenterally (see **"Instructions for use"**).

Instructions for use

1. Prepare the nebuliser according to the instructions of the manufacturer or medical practitioner.
2. Tear one respule from the strip.
3. Open the respule by twisting the top.
4. Squeeze the contents into the nebuliser reservoir.
5. Assemble the nebuliser and use as directed.
6. Discard any solution left in the nebuliser, as well as any partly used, opened respules.
7. Clean the nebuliser according to the manufacturer's instructions.

Since DUOLIN RESPULES contains no preservatives, it is important that the contents are used immediately after opening and that a fresh respule is used for each administration to avoid microbial contamination. Partly used, open or damaged respules should be discarded.

DUOLIN RESPULES should be used undiluted.

It is strongly recommended that DUOLIN RESPULES solution for inhalation should not be mixed with other medicines in the same nebuliser reservoir.

4.3 Contraindications

DUOLIN RESPULES is contraindicated in:

- Patients with known hypersensitivity to salbutamol sulphate, ipratropium bromide, atropine or its derivatives, or to any of the excipients in DUOLIN RESPULES (see **section 6.1**),
- Patients with tachydysrhythmias,
- Patients with hypertrophic obstructive cardiomyopathy,

- Children under 12 years, as safety has not been established (see **section 4.2**).

4.4 Special warnings and precautions for use

Do not exceed the recommended maximum doses.

Following administration of DUOLIN RESPULES solution for inhalation, immediate hypersensitivity reactions may occur, as demonstrated by less frequent cases of urticaria, rash, angioedema, oropharyngeal oedema and bronchospasm (see **section 4.8**).

There have been reports of ocular complications (i.e. blurring of vision, mydriasis, increased intraocular pressure, narrow-angle glaucoma and eye pain) (see **section 4.8**) when aerosolised ipratropium bromide, either alone, or in combination with a β_2-agonist, as in DUOLIN RESPULES, has escaped into the eyes.

DUOLIN RESPULES must be used correctly, by giving proper instruction to patients. Care must be taken to avoid eye exposure to DUOLIN RESPULES solution or mist. It is recommended that administration of the nebulised solution be done via a mouthpiece. A nebuliser mask that fits properly should be used if a mouthpiece is not available. Patients who may be susceptible to glaucoma should be warned specifically to protect their eyes.

Signs of acute narrow-angle glaucoma, in association with red eyes from conjunctival congestion and corneal oedema, may include eye pain or discomfort, blurred vision, visual halos or coloured images. Treatment should be commenced with miotic drops and specialist advice should be obtained immediately if any combination of these ocular symptoms develop.

Fatalities have been reported following excessive use of inhaled β_2-agonists. DUOLIN RESPULES should be given with caution in patients with:

- Recent myocardial infarction.
- Cardiovascular disorders, such as ischaemic heart disease, severe cardiac decompensation, dysrhythmias, severe hypertension, since these patients may require special care and supervision, with particular emphasis on dosage limits.
- Hyperthyroidism, since patients with uncontrolled hyperthyroidism are usually more sensitive to β_2-agonists, as contained in DUOLIN RESPULES.
- Diabetes mellitus, since close blood glucose monitoring is recommended due to the increased risk of hyperglycaemia (see **section 4.8**). In common with other β-adrenoceptor agonists, salbutamol, as contained in DUOLIN RESPULES, can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose, and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.
- Phaeochromocytoma.

Due to its ipratropium bromide content, DUOLIN RESPULES should be administered with caution in patients with:

- Urinary retention, bladder-neck obstruction and prostatic hypertrophy (see **section 4.8**).
- Glaucoma (narrow-angle) – an acute attack may be precipitated if the inhalation is inadvertently sprayed into the eyes.

From post-marketing data and published literature, there is some evidence of incidences of myocardial ischaemia associated with salbutamol, as contained in DUOLIN RESPULES. Patients receiving salbutamol for respiratory disease, who also suffer from severe underlying heart disease (e.g. ischaemic heart disease, severe heart failure or arrhythmia), should be warned to seek medical advice if chest pain or other symptoms of worsening heart disease are

experienced. Attention should be paid to assessment of symptoms, such as chest pain and dyspnoea, as they may be of either cardiac or respiratory origin.

The β_2-agonist in DUOLIN RESPULES may lead to potentially serious hypokalaemia. In severe airway obstruction, particular caution is advised, as the hypokalaemic effect may be potentiated by simultaneous treatment with xanthine derivatives, diuretics and steroids (see **section 4.5**). Additionally, the effects of hypokalaemia on cardiac rhythm may be aggravated by hypoxia and acidosis. Hypokalaemia may result in an increased susceptibility to dysrhythmias in patients receiving digoxin (see **section 4.5** and **section 4.8**). It is recommended that serum potassium levels are monitored in such situations.

Patients with cystic fibrosis may be more prone to gastrointestinal motility disturbances (see **section 4.8**).

A medical practitioner should be consulted immediately in the case of acute, rapidly worsening dyspnoea. In addition, if a reduced response becomes obvious, the patient should be warned to seek medical advice. The patient's therapy plan should be reviewed by a medical practitioner, if higher than recommended doses of DUOLIN RESPULES are required to control symptoms.

Paradoxical bronchospasm has been reported following bronchodilator therapy with an immediate increase in wheezing and shortness of breath after dosing (see **section 4.8**). In addition, regular use of inhaled, short-acting β_2-agonists, such as salbutamol (as opposed to on an as-needed basis), has been demonstrated to increase airway hyperresponsiveness to various stimuli and to lead to the possible development of tolerance to the bronchoprotective effect.

Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated promptly. DUOLIN RESPULES should be stopped immediately, the patient should be assessed and alternative treatment instituted if necessary.

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see **section 4.8** and **section 4.9**). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting (see **section 4.9**).

When testing for non-clinical substance abuse, e.g. in the context of athletic performance enhancement (doping), the use of salbutamol as in DUOLIN RESPULES, may lead to positive results.

Porphyria

Safety has not been established in porphyria.

4.5 Interaction with other medicines and other forms of interaction

- Concurrent use of other anticholinergics or other medicines with anticholinergic effects may potentiate the effects of ipratropium bromide in DUOLIN RESPULES or *vice versa*.
- Concurrent use of β-blockers may result in mutual inhibition of therapeutic effects.
- The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of DUOLIN RESPULES. The concurrent use of xanthine derivatives (e.g. theophylline) with β-adrenergic agonists as well as systemically

absorbed anticholinergics, may increase the severity of the side-effects due to DUOLIN RESPULES (see **section 4.4**).

- Diuretics (non-potassium sparing), digitalis glycosides (digoxin), methylxanthines and corticosteroids may increase the hypokalaemic effect of β_2-agonists, as contained in DUOLIN RESPULES, and lead to an increased disposition to dysrhythmias in patients treated with digitalis glycosides (digoxin). Monitor serum potassium levels. Potentiation of β-agonist induced hypokalaemia should be taken into consideration, particularly in patients with severe airway obstruction (see **section 4.4**).
- Since the action of the β_2-adrenergic agonist in DUOLIN RESPULES may be enhanced in patients taking monoamine oxidase inhibitors or tricyclic antidepressants, DUOLIN RESPULES should be administered with caution.
- An increase in susceptibility to the cardiovascular effects of the β-agonist in DUOLIN RESPULES may be caused by inhalation of halogenated hydrocarbon anaesthetics, such as halothane, trichloroethylene and enflurane.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in breastfeeding has not been established.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects on the ability to drive and the use of machines. However, during treatment with DUOLIN RESPULES, patients should be advised that they may experience undesirable effects such as accommodation disorder, dizziness, blurred vision and mydriasis (see **section 4.8**). If patients experience any of these side-effects, potentially hazardous tasks, such as driving or operating machines, should be avoided.

4.8 Undesirable effects

Summary of the safety profile

The anticholinergic and β_2-sympathomimetic properties of DUOLIN RESPULES are responsible for several of the listed undesirable effects. DUOLIN RESPULES may show symptoms of local irritation.

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

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Side effects**
Infections and infestations	*Frequency unknown*	Infection and inflammation in children including viral infection, rhinitis, tonsillitis and gastroenteritis.

Immune system disorders	*Less frequent*	Hypersensitivity reactions (see **section 4.4**) including paradoxical bronchospasm, angioedema of the tongue, lips and face, oropharyngeal oedema, urticaria, rash, hypotension and collapse, anaphylactic reaction.
Metabolism and nutritional disorders	*Less frequent*	Hyperglycaemia (with large doses), hypokalaemia (after large doses) leading to dysrhythmias (see **"Cardiac disorders"** and **section 4.4**).
	Frequency unknown	Lactic acidosis (see **section 4.4**).
Psychiatric disorders	*Less frequent*	Agitation, restlessness, anxiety, sleep disturbances, nervousness, mental disorder.
Nervous system disorders	*Less frequent*	Tremor.
	Frequent	Dizziness, headache.
Eye disorders	*Less frequent*	Mydriasis, increased intraocular pressure, narrow-angle glaucoma, eye pain, blurred vision, visual halos or coloured images when solution for inhalation has escaped into eyes in patients with narrow-angle glaucoma (see **section 4.4**), accommodation disorder, corneal oedema, conjunctival hyperaemia.

Cardiac disorders	*Less frequent*	Palpitations, tachycardia, dysrhythmias, atrial fibrillation, myocardial ischaemia, supraventricular tachycardia.
Vascular disorders	*Less frequent*	Increases in blood pressure, increased systolic blood pressure, decreased diastolic blood pressure (see **section 4.4**).
Respiratory, thoracic and mediastinal disorders	*Frequent*	Dysphonia, throat irritation.
	Less frequent	Bronchospasm (cough, shortness of breath, chest tightness, wheezing) (see **section 4.4**), laryngospasm, pharyngeal oedema (see **"Immune system disorders"**), paradoxical bronchospasm (see **section 4.4)**, dry throat.
Gastrointestinal disorders	*Frequent*	Dry mouth, nausea, vomiting, constipation, gastrointestinal motility disorder, (e.g. diarrhoea).
	Less frequent	Dyspepsia, abdominal pain, mouth oedema (see **"Immune system disorders"**), stomatitis.
Skin and subcutaneous tissue disorders	*Less frequent*	Rash, urticaria, pruritus, sweating/hyperhidrosis, skin reactions.
Musculoskeletal and connective	*Frequent*	Skeletal muscle tremor.

tissue disorders	*Less frequent*	Muscle cramps, muscle spasms, muscular weakness, myalgia.
Renal and urinary disorders	*Less frequent*	Urinary retention (see **section 4.4**).
General disorders and administrative site conditions	*Less frequent*	Asthenia.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

Expected symptoms of overdose are primarily related to salbutamol and are those of excessive β-adrenergic stimulation.

The most prominent effects are headache, hyperglycaemia (blurred vision, increased hunger or thirst, increased urination), hypotension, hypertension, metabolic acidosis (shortness of breath), hypokalaemia, skeletal muscle tremor, tachycardia, palpitations, widening of the pulse pressure, anginal pain, dysrhythmias, and flushing (see **section 4.4** and **section 4.8**).

Metabolic acidosis has been observed with an overdose of salbutamol, including lactic acidosis, which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of

tachypnoea despite resolution of other signs of bronchospasm, such as wheezing) may be indicated in the setting of overdose. (see **section 4.4** and **section 4.8**).

Expected symptoms of overdose with ipratropium bromide (such as visual accommodation disorders/disturbances and dry mouth) are mild and transient in nature, in view of the wide therapeutic range and due to its poor systemic absorption after either inhalation, topical or oral administration. Effects of overdose are therefore likely to be related to the salbutamol component of DUOLIN RESPULES.

Treatment of overdosage

Treatment with DUOLIN RESPULES should be discontinued. Acid base and electrolyte monitoring should be considered.

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

Specific antidotes are β-receptor blockers, preferably β_1-selective (cardio selective β-blocking medicines). However, the possibility of an increased risk of bronchial obstruction must be taken into consideration. The dose should therefore be carefully adjusted in patients suffering from bronchial asthma or with a history of bronchospasm.

Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 10.2.1 Bronchodilators – inhalants.

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics for obstructive airway diseases.

ATC code: R03AL02.

Mechanism of action and Pharmacodynamic effects

Ipratropium

Ipratropium bromide has anticholinergic (parasympatholytic) properties. Ipratropium bromide is a competitive muscarinic receptor antagonist, which inhibits vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve, at the neuroeffector sites, thus preventing the effects of acetylcholine by competing with and blocking its binding at neuroeffector sites.
Ipratropium is a synthetic quaternary ammonium compound that does not cross the blood-brain barrier. When ipratropium is inhaled, its action is primarily confined to the mouth and airways and not systemic in nature.

Salbutamol

Salbutamol is a short-acting beta-two (β_2)-selective agonist that relaxes bronchial smooth muscle and airway muscle. β-adrenergic agonists activate pulmonary β_2- receptors that relax bronchial smooth muscle and decrease airway resistance. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

Paediatric population

DUOLIN RESPULES has not been studied in the paediatric population (see **section 4.3**).

5.2 Pharmacokinetic properties

Ipratropium

Absorption

Systemic absorption of inhaled ipratropium is low, either from the surface of the lung or from the gastrointestinal tract. After inhalation, maximal responses usually develop over 30 to 90 minutes, lasting for four to six hours.

The range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 28 %, based on a cumulative excretion value ($CRE_{0\text{-}24h}$) of about 3 to 13 %.

Distribution

Kinetic parameters, calculated from plasma concentrations after intravenous (I.V.) administration, describe the disposition of ipratropium bromide. In plasma concentrations, a rapid biphasic decline was observed.

The apparent volume of distribution is approximately 176 L (~ 2,4 L/kg) at steady-state (V_{dss}). The medicine is minimally (less than 20 %) bound to plasma proteins. Ipratropium bromide, a quaternary ammonium compound, is not expected to cross the placental or the blood-brain barrier.

Biotransformation and elimination

Ipratropium has a total clearance of 2,3 L/min and a renal clearance of 0,9 L/min. Approximately 87 % to 89 % of a dose is metabolised, probably mainly in the liver by oxidation, after administration via inhalation.

About 3,2 % of drug-related radioactivity, i.e. parent compound and metabolites, were eliminated in urine, after administration via inhalation. Total radioactivity excreted via the faeces was for this route of administration. After inhalation of ipratropium, the elimination half-life of drug-related radioactivity is 3,2 hours. The main urinary metabolites have to be regarded as ineffective, due to poor binding to the muscarinic receptor.

Salbutamol

Absorption

Salbutamol is rapidly and completely absorbed after oral dosing either by the inhaled or the gastric route and has an oral bioavailability of about 50 %. Within three hours after inhalation of the combination product of ipratropium bromide and salbutamol sulphate, mean peak plasma salbutamol concentrations of 492 pg/mL occur.

Significant bronchodilation occurs within minutes of inhalation of a therapeutic dose, persisting for three to four hours.

Only about 10 % of an inhaled dose reaches the lungs, the remainder is swallowed and ultimately may be absorbed.

Distribution

Following I.V. administration, kinetic parameters were calculated from plasma concentrations. The apparent volume of distribution (V_z) is about 156 L (~ 2,5 L/ kg). Only 8 % of the medicine is bound to plasma proteins.

Intravenous salbutamol crosses the blood-brain barrier and will reach concentrations of about 5 % of the plasma concentrations. However, this amount probably represents the distribution of the substance in the extracellular water of the brain.

Biotransformation and elimination

Salbutamol is excreted unchanged and as inactive metabolites in the urine. 24 hours following a single inhaled administration, approximately 27 % of the estimated mouthpiece dose is excreted unchanged in the urine. The mean terminal half-life of salbutamol is approximately 4 hours, with a mean total clearance of 480 mL/min and a mean renal clearance of 291 mL/min.

Salbutamol is metabolised by conjugation to salbutamol 4'-O-sulphate. The S(+)- enantiomer is cleared from the body less rapidly than the preferentially metabolised R(–)-enantiomer of salbutamol (levosalbutamol). After oral administration, urinary excretion of unchanged medicine and sulphate conjugate were 31,8 % and 48,2 % of the dose, respectively.

Combination product

Co-nebulisation of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorption of either component and, therefore, the additive activity of the combination is due to the combined local effect on the lung after inhalation.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

Sodium chloride

Sulphuric acid (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light. Do not freeze.

Do not use if the solution is discoloured.

6.5 Nature and contents of container

DUOLIN RESPULES are packed as single dose units (plastic vials/respules made from LDPE granules) in strips of 5 in a triple laminated foil pouch and in an outer carton containing 10, 25, 30, 60, or 90 respules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBERS

37/10.2.1/0012

Namibia: NS2 06/10.2.1/0292

Botswana: S2 BOT1102010A

Botswana: S2 BOT1102010B

Botswana: S2 BOT1102010C

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation:12 November 2004

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

06 February 2026