

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DUBLEVENT 0,5 mg + 2,5 mg/2,5 mL Nebulization Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substances:

Each 2.5 mL single-dose ampoule contains 0.52 mg ipratropium bromide monohydrate equivalent to 0.5 mg ipratropium bromide and 3 mg salbutamol sulfate equals to 2.5 mg salbutamol

Excipients:

For each 2.5 mL single-dose ampoule:

Sodium chloride: 22.5 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Single-dose ampoule containing inhalation solution for nebulisation.

A clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DUBLEVENT is indicated for the treatment of reversible bronchospasm associated with obstructive pulmonary disease in patients requiring more than one bronchodilator.

4.2. Posology and method of administration

Posology / Application frequency and duration:

The recommended dose is:

Adults (including elderly patients and children over 12 years):

1 single dose unit ampoule three or four times daily.

Children under 12 years:

There is no experience of the use of DUBLEVENT in children under 12 years

Administration:

Please refer to the “patient information leaflet” for use with a nebuliser.

Since the single dose units contain no preservatives, the medicine inside should be used immediately as soon as the ampoule is opened. It is important to use a new ampoule for each application to avoid microbial contamination. Partly used, open or damaged single dose units

should be discarded.

DUBLEVENT should never be mixed with the other drugs in the nebulizer.

Method of Application:

DUBLEVENT is designed for inhalation only and can be administered with a suitable nebulizer or an intermittent positive pressure ventilator. Single-dose units should not be taken orally or administered parenterally.

See also section 6.6 for application details.

Additional information on special populations

Renal /Hepatic impairment

DUBLEVENT has not been studied in patients with hepatic or renal impairment. It should be used with caution in these patient populations.

Pediatric Population

DUBLEVENT is not indicated in pediatric patients due to insufficient information in children under 12 years of age.

Geriatric population

DUBLEVENT can be used in the elderly at the doses given above.

4.3. Contraindications

DUBLEVENT is contraindicated in patients with hypertrophic obstructive cardio- myopathy or tachyarrhythmia. DUBLEVENT is also contraindicated in patients with a history of hypersensitivity to ipratropium bromide, salbutamol sulfate or to atropine or its derivatives.

4.4. Special warnings and precautions for use

Hypersensitivity Reactions:

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

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 DUBLEVENT 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.

Systemic effects:

In the following conditions DUBLEVENT 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,
- Risk of narrow-angle glaucoma,
- Prostatic hypertrophy
- Bladder-neck obstruction

Cardiovascular effects:

Cardiovascular effects may be seen with sympathomimetic drugs including DUBLEVENT. 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, arrhythmia 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 such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Hypokalaemia:

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.

Gastro-intestinal motility disturbances:

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

Problems with the respiratory system (Dyspnea):

Patients should be warned that in case of acute rapidly worsening dyspnea (difficulty breathing), they should seek immediate medical attention. Patients should also be warned that they should seek medical advice when a decrease in response becomes evident.

As with other inhalation therapies, paradoxical bronchospasm may occur and be accompanied by an increase in wheezing and shortness of breath soon after dosing. Paradoxical bronchospasm responds to a fast-acting inhaled bronchodilator and must be treated promptly. In this case, DUBLEVENT should be discontinued immediately, the patient should be evaluated and, if necessary, alternative therapy instituted.

Doping Test

The use of COMBIVENT may lead to positive results with regards to salbutamol in tests for non clinical substance abuse, (e.g. in the context of athletic performance enhancement (doping)).

Lactic acidosis

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 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.

4.5. Interaction with other medicinal products and other forms of interaction

The chronic co-administration of DUBLEVENT with other anticholinergic drugs has not been studied. Therefore, the chronic co-administration of DUBLEVENT with other anticholinergic drugs is not recommended.

The use of additional beta-agonists, xanthine derivatives and corticosteroids may enhance the effect of DUBLEVENT. 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.

Additional information on special populations

There is no specific data.

Pediatric population:

There is no specific data.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Women with childbearing potential / Contraception

Women of childbearing potential should use contraceptives that are considered medically effective during treatment.

Pregnancy

There are no adequate data from the use of ipratropium bromide and salbutamol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Lactation

DUBLEVENT should not be used in nursing mothers unless the expected benefits outweigh the risks to the newborn.

Reproduction / Fertility

No studies have been conducted on the effect on human fertility with DUBLEVENT. There were no adverse effects on fertility in preclinical studies with ipratropium bromide and salbutamol (see section 5.3).

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 DUBLEVENT. 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 attributed to the anticholinergic and beta2-sympathomimetic properties of DUBLEVENT. Like all drugs administered by inhalation, DUBLEVENT may cause symptoms of local irritation. Adverse drug reactions were identified from data obtained in clinical trials and pharmacovigilance studies during the post-approval use period.

The most frequently reported adverse events in clinical trials were headache, throat irritation, cough, dry mouth, gastrointestinal motility disorders (including constipation, diarrhea and vomiting), nausea and dizziness.

The following undesirable effects have been reported in clinical trials involving 3488 patients:

Undesirable effects are classified according to the following frequencies:

Very common	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1.000$ to $< 1/100$
Rare	$\geq 1/10.000$ to $< 1/1.000$
Very rare	$< 1/10.000$

Not known

Frequency cannot be estimated from the available data

Immune system diseases

Rare: Anaphylactic reaction, hypersensitivity, angioedema of the tongue, lips and face

Metabolism and nutrition disorders

Rare: Hypokalaemia

Unknown: Lactic acidosis (see section 4.4)

Psychiatric disorders

Uncommon: Nervousness

Rare: Mental disorder

Nervous system disorders

Uncommon: Dizziness, headache, tremor

Eye disorders

Rare: Accommodation disorder, corneal oedema, glaucoma¹, eye pain¹, increased intraocular pressure¹, mydriasis¹, blurred vision, conjunctival hyperaemia, halo vision

Cardiac disorders

Uncommon: Palpitations, tachycardia

Rare: Arrhythmia, atrial fibrillation, myocardial ischaemia, supraventricular tachycardia

Respiratory, thoracic and mediastinal disorders

Uncommon: Cough, dysphonia, throat irritation

Rare: Bronchospasm, paradoxical bronchospasm², dry throat, laryngospasm, pharyngeal oedema

Gastrointestinal disorders

Uncommon: Dry mouth, nausea

Rare: gastrointestinal motility disorder (diarrhoea, constipation, vomiting), mouth oedema, stomatitis

Skin and subcutaneous tissue disorders

Uncommon: Skin reactions

Rare: Hyperhidrosis, rash, urticaria, pruritus

Musculoskeletal and connective tissue disorders

Rare: Muscle spasms, muscular weakness, myalgia

Böbrek ve idrar yolu hastalıkları

Rare: Urinary retention³

General disorders and administration site conditions

Rare: Asthenia

Investigations

Uncommon: Systolic blood pressure increased

Rare: Diastolic blood pressure decreased

¹Ocular complications have been reported when aerolised ipratropium bromide, either alone or in combination with an adrenergic beta₂-agonist, has come into contact with the eyes (see section 4.4).

²As 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. DUBLEVENT should be discontinued immediately, the patient should be assessed and alternative therapy instituted if necessary (see section 4.4)

³The risk of urinary retention may be increased in patients with pre-existing urinary outflow tract obstruction.

4.9. Overdose and treatment

Symptoms

Acute effects of overdosage with ipratropium bromide are mild and transient (such as dry mouth, visual accommodation disorders) due to its poor systemic absorption after either inhalation or oral administration. Any effects of overdosage are therefore likely to be related to the salbutamol component.

Symptoms of an overdose with salbutamol include: tachycardia, palpitations, tremor, hypertension, hypokalaemia, hypotension, widening of the pulse pressure, arrhythmias, anginal pain and flushing. Metabolic acidosis has also been observed with overdosage of salbutamol.

The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but caution should be used in administering these drugs to patients with a history of bronchospasm.

Metabolic acidosis has also been observed with overdosage 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 tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergics in combination with anticholinergics

ATC code: R03AL02

Ipratropium bromide has anticholinergic (parasympatholytic) properties. In non-clinical studies, it appears to inhibit vagally mediated reflexes by antagonising the action of acetylcholine, the transmitter agent released from the vagus nerve.

The bronchodilation following inhalation of ipratropium bromide is primarily local and site specific to the lung and not systemic in nature.

Salbutamol is a beta2-adrenergic agent which acts on airway smooth muscle resulting in relaxation. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges.

DUBLEVET provides the simultaneous delivery of ipratropium bromide and salbutamol sulfate allowing effects on both muscarinic and beta2-adrenergic receptors in the lung leading to increased bronchodilation over that provided by each agent singly.

5.2. Pharmacokinetic properties

Ipratropium

Absorption:

Based on a cumulative excretion value (CRE_{0-24h}) of about 3-4%, the range of total systemic bioavailability of inhaled doses of ipratropium bromide is estimated at 7 to 9%.

Distribution:

Kinetic parameters describing the disposition of ipratropium bromide 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. Non-clinical data indicate that the quaternary amine ipratropium does not cross the placental or the blood-brain barrier. The main urinary metabolites bind poorly to the muscarinic receptor and have to be regarded as ineffective.

Biotransformation:

The total clearance of ipratropium is 2.3 L/min and its renal clearance is 0.9 L/min. After inhalation, approximately 87-89% of the dose is metabolized, probably primarily by oxidation in the liver.

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. Its principal urinary metabolites bind weakly to muscarinic receptors and have been evaluated as ineffective.

Linearity/Nonlinearity:

There is no specific data.

Salbutamol

Absorption:

Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or the 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 DUBLEVENT.

Distribution:

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 crosses the blood-brain barrier, reaching a concentration of approximately 5% of plasma concentrations.

Biotransformation and Elimination

Following this single inhaled administration, approximately 27% of the estimated mouthpiece dose is excreted unchanged in the 24-hour urine. The mean terminal half life is approximately 4 hours with a mean total clearance of 480 mL/min. A mean renal clearance is 291 mL/min. Salbutamol is conjugatively metabolised to salbutamol 4'-O-sulfate. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolised and is therefore cleared from the body more rapidly than the S(+)-enantiomer. Urinary excretion is complete after approximately 24 hours following intravenous administration. Most of the excreted dose is the parent compound (64.2) and 12% is excreted as sulfate conjugate. The urinary excretion of unchanged drug and sulfate conjugate after oral administration is 31.8% and 48.2% of the dose, respectively.

Linearity/Nonlinearity:

There is no specific data.

Absorption properties of the combination of ipratropium bromide and salbutamol sulfate:

Co-administration of ipratropium bromide and salbutamol sulfate does not potentiate the systemic absorption of any of these components. Therefore, the additive activity of DUBLEVENT is due to the combined local effect on the lung after inhalation.

5.3. Preclinical safety data

The acute toxicity of the ipratropium/salbutamol combination after single inhalation administration was studied in rats and dogs. Up to the highest doses technically possible (rat: 887/5397 microgram/kg body weight [ipratropium bromide/salbutamol], dog: 165/862 microgram/kg body weight [ipratropium bromide/salbutamol]) there was no indication of

systemic toxic effects and the compound locally well tolerated. Approximate LD50 values after intravenous administration for individual substances have been calculated to be between 12 and 20 mg/kg body weight for ipratropium bromide and 60 to 70 mg/kg body weight for salbutamol, depending on the species ipratropium bromide is tested for (mouse, rat, and dog).

Two 13-week inhalation toxicity studies were conducted with the combination of ipratropium bromide and salbutamol in rats and dogs, respectively. In these studies, it was revealed that the heart is the target organ. At doses of 31.3/183.4 to 375.5/2188.4 micrograms/kg body weight/day ipratropium bromide/salbutamol, a dose-independent increase in heart weights of rats was observed, but this was not accompanied by any detectable histopathological changes. In dogs, doses of 32.3/197.6 to 129.2/790.4 micrograms/kg body weight/day ipratropium bromide/salbutamol slightly increased heart rates and, at higher doses, left ventricular papillary muscles, sometimes accompanied by mineralization, histopathologically detectable scars and/or fibrosis were observed.

The findings from the aforementioned studies should be regarded as the well-known effects of beta-adrenergics such as salbutamol.

Also, the toxicological profile of the second component (ipratropium bromide) has been well known for many years and are typical anticholinergic effects such as dryness of the mucous membranes of the head, mydriasis, keratoconjunctivitis sicca in dogs only (dry eye), decreased tone and inhibition of motility in the gastrointestinal tract (rat).

Reproductive toxicity studies are available for both single components of the ipratropium/salbutamol combination. Salbutamol caused cleft palates in mice at high doses. This phenomenon is well known and occurs after administration of other beta-adrenergic compounds. Currently, this effect is assumed to be due to an increase in maternal corticosterone and may be considered the result of a general stress that is not significant for other species. In addition, preclinical findings that raise suspicions that salbutamol may have teratogenic properties have been taken into account in the restrictions regarding its use in women.

Apart from these findings, studies with salbutamol and ipratropium bromide revealed only marginal effects, if any, in embryos, fetuses, and offspring, and these effects occurred only within the range of maternal toxicity.

Both individual substances have been studied in numerous *in-vivo* and *in-vitro* tests. Neither salbutamol nor ipratropium bromide showed any signs of mutagenic properties.

Salbutamol and ipratropium bromide have been separately investigated for their neoplastic properties in various *in-vivo* carcinogenicity studies.

An increased incidence of mesovarium leiomyoma was observed after oral administration of salbutamol in mice, but not rats and dogs, at doses greater than 100 times the inhalation doses used in humans. It has been found that the development of leiomyoma can be prevented by simultaneous administration of beta-blockers. It has been evaluated that these findings are species-specific and do not have clinical significance, and as a result, they will not cause any

restriction in the clinical use of salbutamol.

No carcinogenic potential was revealed when ipratropium bromide was administered orally in mice and rats.

No data were found regarding any immunotoxicological effects caused by the ipratropium/salbutamol combination or its individual active ingredients.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Sodium chloride

Hydrochloric acid

Water for injection

6.2. Incompatibilities

DUBLEVENT has no known incompatibility.

6.3. Shelf-life

24 months

6.4. Special precautions for storage

Store below 25°C. Do not freeze. Keep vials in the outer carton in order to protect from light.

Do not use if solution is discoloured.

As single-dose units do not contain preservatives, the medicine inside should be used immediately as soon as the ampoule is opened.

6.5. Nature and contents of container

DUBLEVENT contains 20 amber glass ampoules of 3 mL (containing 2.5 mL solution) in the box.

6.6. Special precautions for disposal of waste materials derived from the medicinal product and other handling

No special requirements.

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Only clear, particle-free products with intact packaging integrity should be used.

Partially used solutions should not be stored.

7. MARKETING AUTHORIZATION HOLDER

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Vakıflar OSB Mahallesi, Sanayi Caddesi No:22/1 Ergene/Tekirdağ/TURKEY

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8. MARKETING AUTHORIZATION NUMBER

2022/496

9. DATE OF FIRST LICENSE/RENEWAL OF THE LICENSE

Date of first license: 31.08.2022

Date of renewal of the license:

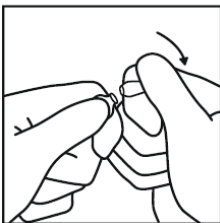
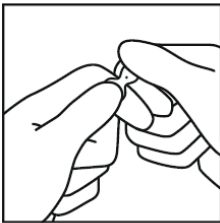
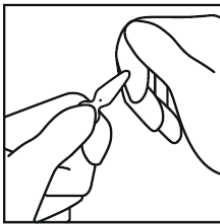
10. DATE OF REVISION OF THE TEXT

Administration Instruction:

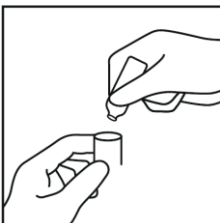
Single-dose ampoules are for inhalation use only with a suitable nebulizer device and should not be taken orally or administered parenterally.

Read through numbers 1 to 5 first, before starting to use your nebuliser.

1. Get your nebuliser ready by following the manufacturer’s or physician’s instructions. Ask your doctor if you are not sure how to use it.
2. Break the ampoule at the marked ringed/dotted area.
 - Always hold it upright while you do this.
 - Do not use if it is already open or if the liquid inside is discoloured.



3. Pour all the contents of single dose ampoule into the nebuliser reservoir (storage area)



- Your doctor will tell you if you need to use a different amount
 - If your doctor has told you that your medicine needs to be diluted, you will be given “sterile sodium chloride 0.9% solution”. Your doctor will tell you how to do this. It is used immediately after dilution.
4. Assemble the parts of the nebuliser and inhale as directed by your doctor.
 5. After use, discard any solution that may have remained in the reservoir and nebuliser;
 - Follow the manufacturer’s instructions on how to clean.
 - It is important to keep your nebulizer clean.

If any of the liquid or mist accidentally gets into your eyes you may get painful, stinging or red eyes, dilated pupils, blurred vision, see colours or lights. If this happens, talk to your doctor for

advice. If you get problems with your eyes at any other time, talk to your doctor for advice.

Since single-dose ampoules do not contain preservatives, it is important to use the ampoule immediately after opening and to open a new ampoule for each application in order to prevent contamination with microbes. Partially used, opened or damaged single-dose ampoules should be discarded.

You should be especially careful not to mix DUBLEVENT with other medicines in the same nebulizer.