PRODUCT MONOGRAPH

Pr TEVA-COMBO STERINEBS®
(salbutamol sulphate and ipratropium bromide Nebulizer Solution)

Each Unit Dose Vial (UDV) contains 0.50 mg of ipratropium bromide (as ipratropium bromide monohydrate) and 2.5 mg salbutamol (as salbutamol sulphate) in 2.5 mL of saline

BRONCHODILATOR

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PrTEVA-COMBO STERINEBS®

(salbutamol sulphate and ipratropium bromide inhalation solution)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Inhalation	Solution Each unit dose vial contains 0.50 mg of ipratropium bromide (as ipratropium bromide monohydrate) and 2.5 mg salbutamol (as salbutamol sulphate) in 2.5 mL of saline	Sodium chloride and hydrochloric acid. *See Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide) Inhalation Solution in unit dose vials is indicated for the management of bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD) who require regular treatment with both ipratropium and salbutamol.

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved.

Pediatrics:

The efficacy and safety in children and adolescents under 18 years has not been established. TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide) Inhalation Solution is not indicated in this patient population.

Geriatrics:

Elderly patients can use TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) at the recommended dose.

CONTRAINDICATIONS

TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) is contraindicated in:

- Patients with a history of hypersensitivity to any of its components or to atropine or its derivatives. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- Patients with cardiac tachyarrhythmias and hypertrophic obstructive cardiomyopathy.

WARNINGS AND PRECAUTIONS

General

The unit dose vials are intended only for inhalation with suitable nebulizing devices and must not be taken orally or administered parenterally.

It is recommended that the nebulized TEVA-COMBO Sterinebs® be administered via a mouth piece. If this is not available and a nebulizer mask is used, it must fit properly.

Systemic Effects

In the following conditions TEVA-COMBO Sterinebs® should only be used after careful risk/benefit assessment: uncontrolled diabetes mellitus, recent myocardial infarction and/or severe organic heart or vascular disorders, hyperthyroidism, pheochromocytoma, risk of narrow-angle glaucoma, prostatic hypertrophy, urinary retention. Care should be taken with patients suffering from coronary insufficiency, arrhythmias and hypertension, convulsive disorders and in patients who are unusually responsive to sympathomimetic amines. Fatalities have been reported following excessive use of inhaled sympathomimetic amines, the exact cause of which is unknown.

Excessive Use and Use with other Sympaticomimetics or Muscarinic Antagonists

As with other inhaled bronchodilators, TEVA-COMBO Sterinebs® should not be used more often or at higher doses than recommended. Concomitant use of salbutamol sulphate and ipratropium bromide inhalation solution with other sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. TEVA-COMBO Sterinebs® should not be administered concomitantly with other medicines containing a muscarinic antagonist, as this has not been studied, and an overdose may result (see DRUG INTERACTIONS).

Anticholinergic Effects

Like other anticholinergic drugs, TEVA-COMBO Sterinebs® should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma:

TEVA-COMBO Sterinebs® should be used with caution in patients with narrow-angle glaucoma.

Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulized solution has not come in contact with the eyes. Patients should be advised that this may result in precipitation or worsening of narrow-angle glaucoma. There have been isolated cases of ocular complications (i.e., mydriasis, increased intraocular pressure, narrow angle closure glaucoma, eye pain) when nebulized ipratropium bromide either alone or in combination with an adrenergic $beta_2$-agonist solution has come in contact with the eyes.

In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of a combined ipratropium/beta2-agonist solution should be avoided unless measures (e.g., use of swimming goggles or use of a nebulizer with a mouthpiece) are taken to ensure that nebulized solution does not reach the eye. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop. Miotic drops alone are not considered to be effective treatment.

Worsening of Urinary Retention:

TEVA-COMBO Sterinebs® should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Carcinogenesis and Mutagenesis

Animal data only (see TOXICOLOGY Section).

Cardiovascular

Special care and supervision are required in patients with idiopathic hypertrophic subvalvular aortic
stenosis, in whom an increase in the pressure gradient between the left ventricle and the aorta may occur, causing increased strain on the left ventricle.

Cardiovascular effects in some patients, as measured by pulse rate, blood pressure, and/or symptoms may be seen with sympathomimetic drugs, including TEVA-COMBO Sterinebs®. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol, one of the components TEVA-COMBO Sterinebs®. In addition, beta-adrenergic agents like salbutamol, have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, TEVA-COMBO Sterinebs® should be used with caution in patients with cardiovascular disorders; especially coronary insufficiency, cardiac arrhythmias, and hypertension. Patients with underlying severe heart disease (e.g. ischaemic heart disease, tachyarrhythmia or severe heart failure) who are receiving TEVA-COMBO Sterinebs® for respiratory disease should be warned to seek immediate medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Endocrine and Metabolism

In common with other beta-adrenergic agents, salbutamol can induce reversible metabolic changes; these are more pronounced during infusions of the drug and include hyperglycemia and hypokalemia.

Potentially serious hypokalemia has been reported and can be aggravated by hypoxia.
Hypokalemia will increase the susceptibility of digitalis-treated patients to cardiac arrhythmias. It is recommended that serum potassium levels be monitored in such situations.

Large doses of intravenous salbutamol have also been reported to aggravate pre-existing diabetes mellitus and may precipitate ketoacidosis.

The relevance of these observations to the use of TEVA-COMBO Sterinebs® is unknown.

Gastrointestinal

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

Immune

Hypersensitivity reactions including urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema may occur after administration of ipratropium bromide or salbutamol sulphate. In clinical trials and post-marketing experience with ipratropium containing products, hypersensitivity reactions such as skin rash, pruritus, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported (see ADVERSE REACTIONS). If such a reaction occurs, therapy with TEVA-COMBO Sterinebs® should be stopped at once and alternative treatment should be considered (see CONTRAINDICATIONS).

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see WARNINGS AND PRECAUTIONS, Anticholinergic Effects).

Renal

Worsening of Urinary Retention (see WARNINGS AND PRECAUTIONS, Anticholinergic Effects).

Respiratory

Paradoxical Bronchospasm:
Severe life threatening paradoxical bronchospasm has been reported in patients receiving beta2agonists. If it occurs, therapy with TEVA-COMBO Sterinebs® should be discontinued immediately and alternative therapy instituted.
Dyspnea:

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

Special Populations

Pregnant Women:

The safety of TEVA-COMBO Sterinebs® in pregnancy has not been established. There are no adequate and well-controlled studies of TEVA-COMBO Sterinebs® in pregnant women. Animal reproduction studies have not been conducted with TEVA-COMBO Sterinebs®.

Salbutamol sulphate, a component of TEVA-COMBO Sterinebs®, has been shown to be teratogenic in mice and rabbits when inhalation Maximum Recommended Human Daily Dose (MRHDD) was exceeded (see TOXICOLOGY section).

For ipratropium bromide, nonclinical studies have shown no embryotoxic or teratogenic effects following inhalation or intranasal application at doses considerably higher than those recommended in man.

Because animal reproduction studies are not always predictive of human response, TEVA-COMBO Sterinebs®, should be used during pregnancy only if the potential benefit justifies the potential risk to the unborn child.

Labour and Delivery:

Although there have been no reports concerning the use of inhaled salbutamol during labour and delivery, intravenously administered salbutamol given at high doses may inhibit uterine contractions. While this effect is extremely unlikely as a consequence of using inhaled formulations, it should be kept in mind. Oral salbutamol has been shown to delay preterm labour in some reports but there are no well-controlled studies which demonstrate that it will stop preterm labour or prevent labour at term. When given to pregnant patients for relief of bronchospasm, cautious use of TEVA-COMBO Sterinebs® is required to avoid interference with uterine contractility.

Nursing Women:

Since salbutamol is probably excreted in breast milk and because of the potential for tumorigenicity shown for salbutamol in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

No specific studies have been conducted on the excretion of ipratropium bromide in breast milk. It is considered unlikely that ipratropium bromide would reach the infant to an important extent, especially when administered by inhalation. However, caution should be exercised when TEVA-COMBO Sterinebs® is administered to nursing mothers. The benefits of TEVA-COMBO Sterinebs® use during lactation should therefore be weighed against possible effects on the infant.

Pediatrics:
The efficacy and safety in children and adolescents under 18 years has not been established. TEVA-COMBO Sterinebs® is not indicated for pediatric patients.

Geriatrics:
Elderly patients can use TEVA-COMBO Sterinebs® at the recommended dose.

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 TEVA-COMBO Sterinebs®. 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.

Monitoring and Laboratory Tests

The use of Salbutamol sulphate and ipratropium bromide inhalation solution UDV may lead to positive results with regards to salbutamol in tests for nonmedical substance abuse, e.g. in the context of athletic performance enhancement (doping).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

TEVA-COMBO Sterinebs® contains salbutamol, a beta-adrenergic agonist, and ipratropium bromide, an anticholinergic.
Use of salbutamol may be associated with:

- Paradoxical bronchospasm (see WARNINGS AND PRECAUTIONS, Respiratory)
- Cardiovascular effects (see WARNINGS AND PRECAUTIONS, General and Cardiovascular)
- Hypersensitivity reactions, including anaphylaxis (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Immune)

- Hypokalemia (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism)

Use of ipratropium bromide may result in:

- Ocular effects (see WARNINGS AND PRECAUTIONS, General and Ophthalmologic)
- Urinary retention (see WARNINGS AND PRECAUTIONS)

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reaction information concerning Salbutamol sulphate and ipratropium bromide inhalation solution UDV is derived from a total of 1070 COPD patients randomized and treated with either Salbutamol sulphate and ipratropium bromide inhalation solution UDV (222 patients); ipratropium bromide + salbutamol sulfate (100 patients); ipratropium bromide (327 patients) or salbutamol sulfate (421 patients).

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.

Adverse reactions, judged by the investigator to be possibly related to drug treatment, as well as adverse events occurring in one or more patients in any group in the controlled clinical trials, appear in the following tables.

Table 1:
Number (Percent) Of Patients With Adverse Reactions Occurring in 1% or More of Patients By Treatment Group, Body System And Preferred Term

	Salbutamol sulphate and ipratropium bromide inhalation solution UDV N (%)	Ipratropium + Salbutamol N (%)	Ipratropium N (%)	Salbutamol N (%)
Total Treated	222 (100)	100 (100)	327 (100)	421 (100)
Total with any possible related event	24 (10.8)	15 (15.0)	34 (10.4)	47 (11.2)
Cardiac disorders				
Hypertension	0	1 (1.0)	0	1 (0.2)
Gastrointestinal disorders				
Mouth (dry)	4 (1.8)	3 (3.0)	7 (2.1)	9 (2.1)
Nausea	0	0	3 (0.9)	5 (1.2)
Nervous system disorders				
Headache	2 (0.9)	4 (4.0)	3 (0.9)	7 (1.7)
Dizziness	1 (0.5)	2 (2.0)	0	3 (0.7)
Dysphonia	3 (1.4)	0	1 (0.3)	1 (0.2)
Nervousness	1 (0.5)	1 (1.0)	0	8 (1.9)
Respiratory, thoracic and mediastinal disorders				
Coughing	2 (0.9)	2 (2.0)	6 (1.8)	1 (0.2)
Skin and subcutaneous tissue disorders				
Rash	0	1 (1.0)	0	2 (0.5)
Special Senses Other				
Taste perversion	1 (0.5)	2 (2.0)	0	2 (0.5)

Table 2:
Number (Percent) Of Patients With Adverse Events[1]- By Treatment Group, Body System And Preferred Term

	Salbutamol sulphate and ipratropium bromide inhalation solution UDV N (%)	Ipratropium + Salbutamol N (%)	Ipratropium N (%)	Salbutamol N (%)
Total Treated	222	100	327	421
Total with any possible related event	24 (10.8)	15 (15.0)	34 (10.4)	47 (11.2)
Body as a Whole-General				
Rigors	0	0	1 (0.3)	1 (0.2)
Body odour	0	0	0	1 (0.2)
Fatigue	0	0	1 (0.3)	2 (0.5)
Hot flashes	1 (0.5)	0	0	0
Oedema (legs)	1 (0.5)	0	0	0
Back pain	0	0	0	1 (0.2)
Influenza-like symptoms	0	0	1 (0.3)	0
Chest pain	0	0	1 (0.3)	0
Pain	0	0	1 (0.3)	0
Cardiovascular				
Cardiac failure	0	0	0	1 (0.2)
Syncope	0	0	0	1 (0.2)
Central & Peripheral Nervous System				
Somnolence	1 (0.5)	0	2 (0.6)	0
Confusion				1 (0.2)
Paraesthesia	0	0	1 (0.3)	1 (0.2)
Hypoaesthesia	0	0	1 (0.3)	1 (0.2)
Insomnia	0	0	1 (0.3)	1 (0.2)
Gastro-intestinal System				
Diarrhoea	0	0	0	1 (0.2)
Anorexia	0	0	0	1 (0.2)
Flatulence	0	0	0	1 (0.2)
Stomatitis ulcerative	0	0	0	1 (0.2)
Saliva (increased)	0	0	1 (0.3)	0
Psychiatric				
Agitation	1 (0.5)	0	0	0
Amnesia	0	0	0	1 (0.2)
Anxiety	0	0	0	1 (0.2)
Depression	0	0	1 (0.3)	0
Resistance Mechanism				
Moniliasis	1 (0.5)	0	0	0
Respiratory System-Lower				
Dyspnoea	2 (0.9)	0	6 (1.8)	8 (1.9)
Bronchitis	0	0	1 (0.3)	7 (1.7)
Sputum (increased)	1 (0.5)	0	2 (0.6)	3 (0.7)
Haemoptysis	0	0	0	1 (0.2)
Respiratory System-Upper				
Rhinitis	0	0	3 (0.9)	0
Pharyngitis	2 (0.9)	0	4 (1.2)	3 (0.7)

Table 2:
Number (Percent) Of Patients With Adverse Events[1]- By Treatment Group, Body System And Preferred Term

	Salbutamol sulphate and ipratropium bromide inhalation solution UDV N (%)	Ipratropium + Salbutamol N (%)	Ipratropium N (%)	Salbutamol N (%)
Special Senses Other				
Taste perversion	1 (0.5)	2 (2.0)	0	2 (0.5)
Vision Disorders				
Conjunctivitis	1 (0.5)	0	0	0

[1] not considered to have a causal relationship to treatment

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye disorders: Vision (abnormal), eye pain

Cardiac disorders: Arrhythmia, palpitation, tachycardia, ECG abnormal specific

Musculoskeletal and connective tissue disorders: Myalgia

Nervous system disorders: Tremor

Resistance mechanism disorders: Infection (fungal)

Respiratory, thoracic and mediastinal disorders: Bronchospasm

Skin and subcutaneous tissue disorders: Sweating increased, pruritis, urticaria

Urinary system disorders: Micturation frequency, dysuria, urinary retention

Additional adverse reactions reported during treatment with salbutamol sulphate and ipratropium bromide inhalation solution include hypertension, nervousness, tachycardia, tremor, palpitations, and urinary retention especially in susceptible patients.

Additional adverse events observed during treatment with salbutamol sulphate and ipratropium bromide inhalation solution include fatigue, abdominal pain, dyspepsia, sinusitis, and dysuria.

Post-Market Adverse Drug Reactions

Many of the listed undesirable effects can be assigned to the anticholinergic and $beta_2$- sympathomimetic properties of salbutamol sulphate and ipratropium bromide inhalation solution. As with all inhalation therapy salbutamol sulphate and ipratropium bromide inhalation solution may show symptoms of local irritation. Adverse drug reactions were identified from data obtained in pharmacovigilance during post approval use of the drug.

World-wide safety data, including post-marketing data, spontaneous reports, literature reports list below the most frequent undesirable effects of salbutamol sulphate and ipratropium bromide inhalation solution according to system organ class.

Cardiac disorders: Atrial fibrillation, myocardial ischaemia, palpitations, arrhythmia, tachycardia, supraventricular tachycardia

Eye disorders: Glaucoma, eye pain, intraocular pressure increased, mydriasis, vision blurred, accommodation disorder, corneal oedema, conjunctival hyperaemia, halo vision

Gastrointestinal disorders: Oedema mouth, dry mouth, nausea, gastrointestinal motility disorder, vomiting, throat irritation, diarrhoea, constipation, stomatitis

General disorders and administration site conditions: Asthenia

Immune system disorders: Anaphylactic reaction, hypersensitivity

Investigations: blood pressure diastolic decreased, blood pressure systolic increased

Metabolism and nutrition disorders: Hypokalaemia

Musculoskeletal and connective tissue disorders: Muscle spasms, myalgia, muscular weakness

Nervous system disorders: Dizziness, headache, tremor

Psychiatric disorders: Mental disorder, nervousness

Renal and urinary disorders: Urinary retention

Respiratory, thoracic and mediastinal disorders: Bronchospasm, cough, dysphonia, laryngospasm, pharyngeal oedema, dry throat, bronchospasm paradoxical

Skin and subcutaneous tissue disorders: Angioedema, hyperhidrosis, skin reactions such as rash, pruritus and urticaria

Literature reports regarding adverse events associated with the use of ipratropium bromide or
salbutamol nebulizer solution singly or in combination have been reported and include, cases of taste perversion, bronchitis, angina, lightheadedness, drowsiness, insomnia, vertigo, CNS stimulation, weakness (asthenia), itching, flushing, alopecia, gastrointestinal distress, vomiting, diarrhea, edema, constipation and urinary difficulty.

DRUG INTERACTIONS

It is strongly recommended not to mix TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) solution with other drugs in the same nebulizer.

Overview

In patients receiving other anticholinergic drugs, TEVA-COMBO Sterinebs® should be used with caution because of possible additive effects. Xanthine derivatives and $beta_2$-adrenergic agents may increase the side effects of TEVA-COMBO Sterinebs®.

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

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 are monitored in such situations.

The ECG changes and/or hypokalemia which 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 TEVA-COMBO Sterinebs®, with non-potassium sparing diuretics. Consider monitoring potassium levels.

Other sympathomimetic bronchodilators or epinephrine should not be used concomitantly with
TEVA-COMBO Sterinebs®. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects. Such concomitant use must be individualized and not given on a routine basis. If regular co-administration is required then alternative therapy must be considered.
TEVA-COMBO Sterinebs® should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or within 2 weeks of discontinuation of such agents because the action of salbutamol on the vascular system may be potentiated. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants (see WARNINGS AND PRECAUTIONS, Cardiovascular).

Beta-receptor blocking agents and salbutamol inhibit the effect of each other. A potentially serious reduction in bronchodilator effect may occur during concurrent administration of beta-blockers.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment should be initiated and administered under medical supervision, e.g. in the hospital setting. Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved.

TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) dosage should be individualized, and patient response should be monitored to determine the requirement for more than a single bronchodilator by the prescribing physician on an ongoing basis. Patients should be advised to consult a physician or the nearest hospital immediately in the case of acute or rapidly worsening dyspnoea if additional inhalations of salbutamol sulphate and ipratropium bromide solution do not produce an adequate improvement.

Counselling on smoking cessation should be the first step in treating patients with chronic bronchitis who smoke. Smoking cessation produces symptomatic benefits and has been shown to confer a survival advantage by slowing or stopping the progression of chronic bronchitis and emphysema.

Recommended Dose and Dosage Adjustment

The recommended dosage is 1 unit dose vial (0.50 mg ipratropium bromide (as ipratropium monohydrate) and 2.5 mg salbutamol (as salbutamol sulfate) in 2.5 mL) three or four times daily.

TEVA-COMBO Sterinebs® in unit dose vials may be administered from a suitable nebulizer or an intermittent positive pressure ventilator.

Since the unit dose vials contain no preservative, it is important that the contents are used soon after opening and that a fresh vial is used for each administration to avoid microbial contamination. Partly used, opened or damaged unit dose vials should be discarded.

It is strongly recommended not to mix salbutamol sulphate and ipratropium bromide inhalation solution with other drugs in the same nebulizer.

Instructions for Use
The unit dose vials are intended only for inhalation with suitable nebulizing devices and must not be taken orally or administered parenterally. The content of the unit dose vials does not need to be diluted for nebulization.

Dilution Instructions
If necessary, before use, doses may be diluted to a total nebulization volume of 3-5 mL with preservative free 0.9% sterile sodium chloride solution and used immediately. Discard any unused solution. Nebulize over 10-15 minutes at gas flow of 6-10L/min. Repeat every six hours as necessary.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptoms and Signs
The effects of overdosage are expected to be related primarily to salbutamol because acute overdosage with ipratropium bromide is unlikely since ipratropium bromide is not well absorbed systemically after aerosol or oral administration. Expected symptoms of overdosage with ipratropium bromide (such as dry mouth, visual accommodation disorders) are mild and transient in nature. However, should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

The expected symptoms with salbutamol overdosage are those of excessive beta-adrenergic stimulation, such as: tachycardia, palpitations, tremor, cardiac arrhythmia, hypokalemia, hypertension, hypotension, widening of pulse pressure, anginal pain, flushing and, in extreme cases, sudden death.

Lactic acidosis 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.

Treatment
Treatment with salbutamol sulphate and ipratropium bromide inhalation solution should be discontinued. Acid-base and electrolyte monitoring should be considered. Supportive and symptomatic treatment is indicated. Dialysis is not an appropriate treatment. The judicious use of a cardioselective beta-blocker may be considered, taking into account a possible risk of bronchospasm.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) is a combination of the anticholinergic bronchodilator, ipratropium bromide, and the $beta_2$-adrenergic bronchodilator, salbutamol sulphate.

Ipratropium Bromide

Ipratropium bromide is a quaternary ammonium compound with anticholinergic (parasympatholytic) properties. In nonclinical studies, it appears to inhibit vagally mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released from the vagus nerve. Anticholinergics prevent the increase in intracellular concentration of Ca^{++} which is caused by interaction of acetylcholine with the muscarinic receptor 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.

On inhalation, the onset of action is noted within 5 to 15 minutes, with a peak response between 1 and 2 hours, lasting about 2 additional hours, with subsequent decline from the peak. Bronchodilation is still evident 8 hours after inhalation.

Salbutamol

Salbutamol produces bronchodilation through stimulation of $beta_2$-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of muscle fibres. Salbutamol relaxes all smooth muscle from the trachea to the terminal bronchioles and protects against bronchoconstrictor challenges (i.e. methacholine and histamine). This action is manifested by an increase in pulmonary function as demonstrated by spirometric measurements. A measurable decrease in airway resistance is typically observed 5 to 15 minutes after inhalation of salbutamol. The maximum improvement in pulmonary function usually occurs after 60 to 90 minutes, and significant bronchodilator activity has been observed to persist from 3 to 6 hours.

TEVA-COMBO Sterinebs® provides the simultaneous release of ipratropium bromide and salbutamol sulphate allowing the additive effect on both muscarinic and $beta_2$-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 salbutamol sulphate and ipratropium bromide inhalation solution has a greater bronchodilator effect than either of its components and there was no potentiation of adverse events.

Pharmacodynamics

Ipratropium Bromide

Large, single inhaled doses of ipratropium bromide have been given to man without any signs of toxicity. After the administration of 400 μg to 10 healthy subjects, no changes were detected in pulse rate, blood pressure, intra ocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in a similar study no change in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhalation to healthy volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients have not revealed any systemic anticholinergic effects.

In one study, 14 patients were treated for 45 days with either ipratropium bromide 40 μg q.i.d. or
ipratropium bromide 40 μg q.i.d. plus oral fenoterol 5 mg q.i.d. No changes in visual acuity, intra ocular pressure, pupil size or accommodation of vision occurred. Micturition function studies in 20 male patients showed no differences in urinary flow, total flow time and time until maximum flow between placebo and ipratropium bromide 40 μg t.i.d. administered for 3 days.

A wide variety of challenge studies has been conducted using ipratropium bromide as a protective agent. In pharmacologically induced bronchospasm, ipratropium bromide, in clinical doses, was very effective against methacholine and acetylcholine, moderately effective against propranolol but had no effect against histamine or serotonin. Studies in exercise induced bronchospasm have yielded variable results. Some investigations have indicated that ipratropium bromide has little or no effect but other studies have shown that some patients, at least, were protected against bronchospasm induced by exercise. Likewise, the protection against cold air induced bronchospasm has been variable.

The Lung Health Study

The Lung Health Study was a randomized multi centre clinical trial carried out from October 1986 to April 1994 in North America. It was designed to test the

effectiveness of intervention-smoking cessation and bronchodilator administration in smokers aged 35-60 years who have mild obstructive pulmonary disease. The main outcome or end point was the rate of change and cumulative change in FEV_1 over a 5-year period.

A total of 5887 male and female smokers, aged 35 to 60 years, with spirometric signs of early chronic obstructive pulmonary disease were recruited. Participants were randomized to one of the following groups: (1) smoking intervention plus bronchodilator, (2) smoking intervention plus placebo, or (3) no intervention.

Smoking intervention consisted of an intensive 12-session smoking cessation program combining behaviour modification and use of nicotine gum, with continuing 5-year maintenance program to minimize relapse. Two puffs ipratropium bromide was prescribed three times daily from a metered-dose-inhaler.

The results showed that participants in the two smoking intervention groups showed significantly smaller declines in FEV_1 than did those in the control group. Most of this difference occurred during the first year following entry into the study and was attributable to smoking cessation, with those who achieved sustained smoking cessation experiencing the largest benefit. The benefit associated with the use of the ipratropium bromide vanished after the ipratropium bromide was discontinued at the end of the study.

In summary, the results showed that smoking intervention reduced the rate of decline in FEV_1 in middle aged smokers with mild airways obstruction who remained non-smokers throughout the 5 years. The other intervention, administration of ipratropium bromide, did not alter the rate of decline in lung function. There was a small one time improvement in lung function associated with the onset of ipratropium use, but this disappeared rapidly when ipratropium use was discontinued at the end of the study. Otherwise, the regular use of ipratropium bromide had no effect on the rate of decline of lung function over 5 years in patients studied.

Salbutamol

In controlled clinical trials, the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximum mid-expiratory flow rate (MMEF) and FEV_1. MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes following two inhalations of salbutamol and that clinically significant improvement generally

continues for three to four hours in most patients. In clinical trials some patients with asthma showed a therapeutic response (defined as maintaining FEV_1 values 15% or more above baseline) that was still apparent at six hours. Continued effectiveness of salbutamol was demonstrated over a 13-week period in these same trials.

In clinical studies, two inhalations of salbutamol taken approximately 15 minutes before exercise prevented exercise-induced bronchospasm, as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients. One of these studies also evaluated the duration of the prophylactic effect to repeated exercise challenges which was evident at four hours in the majority of patients and at six hours in approximately one third of the patients.

The ability of salbutamol to produce bronchodilation in humans has been demonstrated in many
spirometric and plethysmographic studies. Following a challenge with acetylcholine aerosol, in a study examining the effects of salbutamol in airway resistance following challenge testing in 12 patients, the mean airway resistance increased 250%. After salbutamol aerosol (200 μg), the mean airway resistance decreased to 78% of the initial value.

Challenges with grass pollen or house dust aerosols in five and eight patients, respectively, increased activity resistance 265% and 255%, respectively. Administration of salbutamol decreased airway resistance to initial levels.

Controlled clinical studies and other clinical experience have shown that inhaled salbutamol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. Fatalities have been reported following excessive use of inhaled sympathomimetic agents, the exact cause of which is unknown.

When salbutamol was administered as a metered-dose inhaler preparation to six normal volunteers, at doses of three or seven inhalations of 100 mcg, it was observed that three inhalations of salbutamol did not alter serum potassium while seven inhalations resulted in a decrease in serum potassium from 4.4 to 3.8 mEq/L. Thus, the recommended dose of salbutamol aerosol (two inhalations) would not be expected to alter serum potassium levels.

Prolonged use of salbutamol Inhalation Aerosol in most patients caused no significant changes in ECG pattern, blood sugar, liver and kidney functions and hematological values.

The hemodynamic effects of intravenous salbutamol were studied in patients with mitral valve disease. At the dose of 1 μg/kg, salbutamol reduced mean aortic pressure by 7 mmHg, increased the cardiac output by 0.6 L/minute and reduced systemic vascular resistance by 7 units. It caused no change in left ventricular ejection time. At the dose of 2 μg/kg, salbutamol increased the mean oxygen uptake by 21 mL/minute, narrowing the mean arteriovenous oxygen difference by 10 mL/minute. Salbutamol has no effect on the pulmonary ventilation/perfusion ratio; therefore, unlike
isoprenaline, it does not increase hypoxia during acute asthmatic attacks.

Pharmacokinetics

Ipratropium Bromide

Absorption:
Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 μg administered from a pressurized metered dose inhaler. The peak plasma concentration (mean C_{max} = 32 pg/mL) is reached within 5 minutes after inhalation. The therapeutic effect of ipratropium bromide is produced by a local action in the airways. Therefore time courses of bronchodilation and systemic pharmacokinetics do not run in parallel. The plasma concentration-versus-time curve was similar to that seen after oral administration, likely reflecting the large fraction of inhaled dose which is deposited on the pharyngeal mucosa and swallowed.

Intravenous administration of 1.0 mg in man showed a rapid distribution into tissues (half-life of an alpha phase approximately five minutes), and a terminal half-life (beta phase) of 3-4 hours. Plasma concentrations after inhaled ipratropium bromide were about 1000 times lower than equipotent oral or intravenous doses (15 and 0.15 mg, respectively).

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 to 13% of an inhaled dose. Based on these data, the apparent systemic bioavailability of oral and inhaled doses of ipratropium bromide is estimated at 2% and 7 to 28% respectively. Taking this into account, swallowed dose portions of ipratropium bromide do not relevantly contribute to systemic exposure.

Distribution:

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 (Vdss) is approximately 176 L (≈2.4 L/kg). The drug is minimally (less than 20%) bound to plasma proteins. Nonclinical data indicate that the quaternary amine ipratropium does not cross the blood-brain barrier.

Metabolism:
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 metabolized, the major portion probably in the liver by oxidation.

Elimination:
Up to 8 metabolites of ipratropium bromide have been detected in man, dog and rat. 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.

Thirty-nine percent of the active ingredient is excreted renally after intravenous administration, 4.4% - 13.1% after inhalation from a metered dose inhaler is excreted as unchanged compound in urine.

In a crossover pharmacokinetic study in 12 healthy male volunteers comparing the pattern of absorption and excretion of a single-dose of salbutamol sulphate and ipratropium bromide inhalation solution to the two active components individually, the co-nebulization of ipratropium bromide and salbutamol sulphate does not potentiate the systemic absorptions of either component.

Salbutamol

Absorption and Distribution:
Salbutamol is rapidly and completely absorbed following oral administration either by the inhaled or gastric route and has an oral bioavalability of approximately 50%. Mean peak plasma salbutamol

concentrations of 492 pg/ml occur within three hours after inhalation of salbutamol sulphate and ipratropium bromide solution. Kinetic parameters were calculated from plasma concentrations after i.v. administration. The apparent volume of distribution (Vz) is approximately 156 L (≈2.5 L/kg). Only 8% of the drug is bound to plasma proteins. In nonclinical trials, levels of approximately 5% of the plasma level of salbutamol are found in the brain. However, this amount probably represents the distribution of the substance in the extracellular water of the brain.

After inhalation of recommended doses of salbutamol, plasma drug levels are very low. When 100
μg of tritiated salbutamol aerosol was administered to two normal volunteers, plasma levels of drug-radioactivity were insignificant at 10, 20 and 30 minutes following inhalation. The plasma concentration of salbutamol may be even less as the amount of plasma drug-radioactivity does not differentiate salbutamol from its principal metabolite, a sulphate ester. In a separate study, plasma salbutamol levels ranged from less than 0.5 ng/mL to 1.6 ng/mL in ten asthmatic children one hour after inhalation of 200 μg of salbutamol.

Approximately 10% of an inhaled salbutamol dose is deposited in the lungs. Eighty-five percent of the remaining salbutamol administered from a metered-dose inhaler is swallowed; however, since the dose is low (100 to 200 μg), the absolute amount swallowed is too small to be of clinical significance. Salbutamol is only weakly bound to plasma proteins. Results of animal studies indicate that following systemic administration, salbutamol does not cross the blood-brain barrier but does cross the placenta using an *in vitro* perfused isolated human placenta model. It has been found that between 2% and 3% of salbutamol was transferred from the maternal side to the fetal side of the placenta.

Metabolism and Elimination:
Following a 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 and a mean renal clearance of 291 mL/min.

Salbutamol is metabolized in the liver. Salbutamol is conjugatively metabolized to salbutamol 4' -O-sulphate which has negligible pharmacologic activity. Salbutamol may also be metabolized by oxidative deamination and/or conjugation with glucuronide. The R(-)-enantiomer of salbutamol (levosalbutamol) is preferentially metabolized 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% were 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.
Salbutamol and its metabolites are excreted in the urine (> 80%) and the feces (5% to 10%). Plasma levels are insignificant after administration of aerosolized salbutamol; the plasma half-life ranges from 3.8 to 7.1 hours.

Ipratropium Bromide and Salbutamol Sulphate UDV

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

Special Populations and Conditions

Pediatrics

The efficacy and safety in children and adolescents under 18 years has not been established. COPD does not occur in children under 18 years of age.

Hepatic Insufficiency

TEVA-COMBO Sterinebs® has not been studied in patients with hepatic insufficiency.

Renal Insufficiency

TEVA-COMBO Sterinebs® has not been studied in patients with renal insufficiency.

STORAGE AND STABILITY

Unopened unit dose vials of TEVA-COMBO Sterinebs® should be stored at controlled room temperature (between 15° C and 25° C). Store in the original foil pouch to protect from light. Do not use if solution is discoloured. Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-COMBO Sterinebs® (Salbutamol Sulphate and Ipratropium Bromide inhalation solution) is supplied in plastic single dose units in strips of 5 with a foil overwrap, each containing 0.50 mg

ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as salbutamol sulphate) in a 2.5 mL isotonic preservative-free solution for inhalation. There are 4 strips per carton for a carton size of 20 unit dose vials.

Non-medicinal ingredients include sodium chloride and hydrochloric acid.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

TEVA-COMBO Sterinebs® (salbutamol sulphate and ipratropium bromide inhalation solution) is a combination product containing two active ingredients, ipratropium bromide and salbutamol sulphate.

Drug Substance

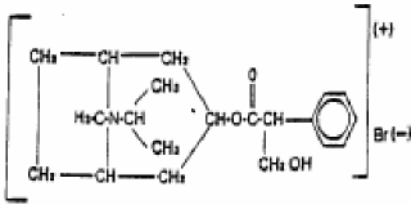
Proper name: ipratropium bromide monohydrate

Chemical name: (8r)-3α-Hydroxy-8-isopropyl-1αH, 5αH-tropanium bromide(±)-tropate monohydrate

Molecular formula: $C_{20}H_{30}NO_3Br$

Molecular mass: 412.37

Structural formula:



Physicochemical properties: White crystalline substance with a bitter taste. Freely soluble in water and alcohol; insoluble in chloroform and ether. In neutral and acid solutions the substance is rather stable. In alkaline solutions the ester bond is rapidly hydrolyzed. Melting point, 230° C with decomposition.

Drug Substance

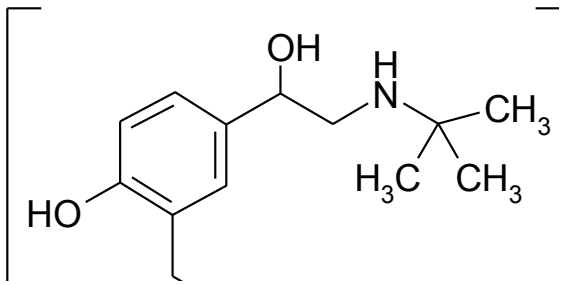
Proper name: Salbutamol sulphate

Chemical name: 1,3-benzenedimethanol,α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-,sulphate (2:1) (salt)

Molecular formula: $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$

Molecular weight: 576.7

Structural formula:



Physicochemical properties: White to off-white crystalline powder soluble in ethanol, sparingly soluble in water and very soluble in chloroform.

CLINICAL TRIALS

In a pivotal 85 day multi-centre, randomized, double-blind, parallel trial, 652 patients with Chronic Obstructive Pulmonary Disease (COPD) were evaluated for the bronchodilator efficacy of
salbutamol sulphate and ipratropium bromide inhalation solution (222 patients) in comparison to its components, ipratropium bromide (214 patients) and salbutamol sulphate (216 patients). In this study, salbutamol sulphate and ipratropium bromide inhalation solution produced significant improvements in pulmonary function as demonstrated by increases in FEV_1 of 15% or more compared with baseline. The median time to onset of a 15% increase in FEV_1 was 15 minutes for each treatment group. The median time to peak was one hour for salbutamol sulphate and ipratropium bromide inhalation solution, and ranged from one to two hours for the ipratropium group and 30 minutes to 1 hour for the salbutamol group. The median duration of effect was 3-5 hours for salbutamol sulphate and ipratropium bromide inhalation solution compared to 4 hours for ipratropium bromide and 2-3 hours for salbutamol sulphate.

In a supportive 90 day, multi-center, randomized, double-blind, parallel trial, 195 COPD patients were randomly treated by compressor-driven nebulizer using salbutamol (2.5 mg in 3 mL UDV) with either 0.3 mL placebo or 0.3 mL ipratropium bromide solution (500 μg), 3 times daily for 3 months. In this study, ipratropium bromide and salbutamol sulphate produced significant improvements in pulmonary function as demonstrated by increase in FEV1 of 15% or more compared to baseline. The median time to onset of a 15% increase in FEV1 was 15 minutes for both groups. Peak effect was reached 1-2 hours in the ipratropium bromide solution/salbutamol combination, compared with 1 hour in the placebo/salbutamol combination. The median duration of action was 5-7 hours for the ipratropium bromide solution / salbutamol combination compared with 3-4 hours for placebo/salbutamol combination.

These studies demonstrated that each component of salbutamol sulphate and ipratropium bromide inhalation solution contributed to the efficacy of the combination, especially during the first 4 hours after administration, and that salbutamol sulphate and ipratropium bromide inhalation solution was significantly more effective than ipratropium bromide or salbutamol sulphate administered alone.

DETAILED PHARMACOLOGY

Mechanism of Action

Salbutamol Sulphate and Ipratropium Bromide inhalation solution

Salbutamol sulphate and ipratropium bromide inhalation solution is a combination of the anticholinergic ipratropium bromide and the $beta_2$-adrenergic agonist salbutamol sulfate. The mechanisms of action described below for the individual components apply to salbutamol sulphate and ipratropium bromide inhalation. The two classes of medications are both bronchodilators. Simultaneous administration of both an anticholinergic and a $beta_2$-sympathomimetic is designed to produce a greater bronchodilator effect than when either drug is utilized alone at its recommended
dosage. The efficacy of salbutamol sulphate and ipratropium bromide inhalation is likely to be due to a local effect on the muscarinic and $beta_2$-adrenergic receptors in the lung.

Ipratropium Bromide

Ipratropium bromide is an anticholinergic agent which, when delivered by aerosol, exerts its effect primarily in the bronchial tree. It abolishes acetylcholine induced bronchospasm in the guinea pig and dog after intravenous administration of ED_{50} of 0.15 and 0.40 μg/kg with a transient effect on blood pressure. By inhalation, approximately 25 μg ipratropium bromide produces a 50% inhibition of acetylcholine-induced bronchospasm in the dog with no detectable effect on blood pressure but with an increased duration of action compared to intravenous administration. Histologic evaluation of human bronchial mucosae following chronic inhalation of ipratropium bromide showed no alterations of epithelial, ciliated or goblet cells. Short term mucociliary clearance in normal and bronchitic subjects was not adversely affected by 200 μg of inhaled ipratropium bromide.

The anticholinergic effects of ipratropium bromide were evaluated in several other organ systems following oral, subcutaneous, intravenous and inhalation administration. In dogs, a 50% increase in heart rate resulted from a s.c. dose of about 0.011 mg/kg, equipotent to atropine, but the equieffective oral dose of ipratropium was 58 times greater. By inhalation, no increase in heart rate or pathologic changes in ECG pattern were recorded at dose up to 8 mg. In another study, blood pressure and heart rate in the dog could be modulated after intravenous (i.v.) administration of low doses of ipratropium but metered aerosol administration of 100 puffs (40 μg/puff) was required to produce an 11% increase in heart rate.

Salivary secretion in the rat, mouse and dog was effectively inhibited by low parenteral doses of
ipratropium bromide (0.001 to 0.032 μg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration to dogs of about 65 puffs (40 μg/puff) produced a 50% decrease in salivary flow. Similarly, effects on gastric secretion in the rat showed at least a 100-fold difference between effective enteral and subcutaneous doses.

Mydriatic effects of ipratropium bromide in mice were approximately equipotent to atropine after
s.c. doses but were 10-20 times less after oral administration. Tests in the rabbit indicated that doses up to 100 mg/kg had no effect on the central nervous system.

Ipratropium bromide administered s.c. inhibited the secretory effects of the cholinergic antagonist,

oxitropium, in mice. It also inhibited spasmolytic effects equivalent to or greater than atropine in isolated guinea pig gut. *In vitro* tests with isolated rectum of the guinea pig demonstrated the effectiveness of ipratropium bromide in suppressing the spasmogenic effects of acetylcholine and pilocarpine. It was ineffective against histamine or barium chloride induced spasm. Ipratropium bromide exerted anticholinergic effects on the *in situ* bladder and intestine preparations of the dog.
Intravenous doses were 500 times more potent than oral doses or intraduodenal administration.

Salbutamol

In vitro studies and *in vivo* pharmacologic studies have demonstrated that salbutamol has a preferential effect on $beta_2$-adrenergic receptors. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that there is a population of $beta_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these, however, is not yet established.

The pharmacologic effects of beta-adrenergic agonist drugs, including salbutamol, are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

As suggested from the results of experiments in isolated animal tissues, salbutamol has been shown to produce a substantial bronchodilator effect in the intact animal. In the anaesthetized guinea pig, salbutamol completely prevents acetylcholine-induced bronchospasm at the dose of 100 μg/kg intravenously. Administration of salbutamol aerosol at a dose of 250 μg/mL for one minute to guinea pigs prevented acetylcholine-induced bronchospasm without any chronotropic effect. A prolonged bronchodilator effect of salbutamol (in terms of mean times to dyspnea following acetylcholine challenge) was observed following oral administration to conscious guinea pigs. The protective action persisted for up to six hours.

In anaesthetized cats and dogs, salbutamol prevented the bronchospasm elicited by vagal stimulation without any significant effect on heart rate and blood pressure. Tests in isolated dog papillary muscle, guinea pig atrial muscle and

human heart muscle have shown that the effect of salbutamol on beta1-adrenergic receptors in the heart is minimal.

In a number of studies using guinea pig atrium, it was found that on a weight-to-weight basis, salbutamol was from 2,000 to 2,500 times less active in terms of inotropic effect and 500 times less active in terms of chronotropic effect than isoprenaline. Compared to orciprenaline, salbutamol was about 40 times less active in terms of inotropic effect and four times less potent in terms of chronotropic effect. Salbutamol has been shown to be one-fifth as potent a vasodilator in skeletal muscle as isoprenaline, as measured by effects on hind limb blood flow in the anaesthetized dog. In the perfused rabbit ear, salbutamol was shown to possess only one-tenth the activity of isoprenaline in terms of vasodilating effect. In dogs, salbutamol was shown to increase coronary blood flow, which was subsequently shown to be the result of a direct coronary vasodilating effect of salbutamol.

In six dogs with right-sided cardiac by-pass, salbutamol, given at the dose of 25 μg/kg, improved left ventricular efficiency and increased coronary blood flow.

Studies in minipigs, rodents and dogs recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

Animal studies show that salbutamol does not pass the blood brain barrier.

TOXICOLOGY

Ipratropium Bromide /Salbutamol Sulphate Inhalation Solution

Single Dose Studies

The toxicity of ipratropium bromide and salbutamol sulphate inhalation solution after single inhalation administration was tested in rats and dogs. Up to the highest technically feasible dose (rat: 887/5397 μg/kg ipratropium bromide/salbutamol, dog: 164/861 μg/kg ipratropium bromide/salbutamol) there were no indications of systemic toxic effects, the combination was locally well tolerated. The approximate LD_{50} after intravenous administration was calculated for the individual substances to be between 12 and 20 mg/kg for ipratropium bromide and between 60 and 73 mg/kg for salbutamol sulphate depending on the species tested (mouse, rat, and dog).

Multiple Dose Studies

Inhalation *(Nasal):*

In rats, inhalation of the ipratropium bromide/salbutamol sulphate combination for 2 weeks, up to average maximum doses of 298/1876 μg/kg/day, produced no evidence of toxicity. The increased heart weights in high-dose males, in the absence of any histopathologic findings, was suggestive of an adaptive response to the known cardiac stimulatory actions of sympathomimetic drugs, including salbutamol sulphate.

Inhalation (Oral):

In a 14 day inhalation study in dogs with up to a maximum ipratropium bromide and salbutamol sulphate combination dose of 110/575 μg/kg/day resulted in sinus tachycardia and exaggerated T-waves changes (secondary to tachycardia) in all treated groups. These effects, noted on the first day of dosing, were either not present or greatly diminished in incidence and magnitude by the end of the second week of treatment. Five of six dogs in the mid-dose group (55/287 μg/kg) had interstitial fibrosis of the papillary muscle of the left ventricle of the heart; this was not noted at the low or high doses. Hepatic glycogen accumulation was found at each dose level, but was of doubtful toxicological significance.

In another multiple dose inhalation study, beagle dogs were exposed for 14 days with up to 56/348 μg/kg of the ipratropium bromide and salbutamol sulphate combination to examine the cardiotoxicity of the combination versus the individual components. In this study no evidence of an interactive effect of ipratropium bromide and salbutamol sulphate was noted. The cardiac changes in this study (increased heart rate and changes in electrocardiographic patterns) were virtually identical in the groups treated with the ipratropium bromide salbutamol combination and those treated with the same dose of salbutamol sulphate alone.

Two 13-week inhalation toxicity studies in rats and dogs have been performed with the combination of ipratropium bromide and salbutamol sulphate. In these studies, the heart proved to be the target organ. In the rat at dosages of 34/197 to 354.5/2604 μg/kg/day ipratropium bromide/salbutamol sulphate, a non dose dependent increase in heart weights was present, however without any histopathological correlate. In the dog at doses of 32/198 to 129/790 μg/kg/day ipratropium bromide/salbutamol sulphate, slightly increased heart rates and, at higher dosages, histopathologically detectable scars and/or fibrosis in the papillary muscle of the left ventricle, sometimes accompanied with mineralisation, were observed.

The cardiovascular findings obtained in the above mentioned studies must be regarded as well-known effects of ß-adrenergics such as salbutamol. The toxicological profile of ipratropium bromide is also well known for many years and characterized by typical anticholinergic effects as dryness of the mucosal membranes of the head, mydriasis, keratoconjunctivitis sicca (dry eye) in dogs only, reduction in tone and inhibition of motility in the gastrointestinal tract (rat).

Genotoxicity

Ipratropium bromide and salbutamol sulphate inhalation solution did not show genotoxic activity in *vitro* assays.

Immunotoxicity

No evidence was found of any immunotoxicological effect caused by ipratropium bromide and salbutamol sulphate inhalation solution or its individual active ingredients.

IPRATROPIUM BROMIDE

Single Dose Studies

LD_{50} VALUES FOR IPRATROPIUM			
Species	**Sex**	**Route**	**LD_{50} (mg/kg)**
Mouse		i.v.	13.5
Mouse	M	i.v.	12.3
Mouse	F	i.v.	15.0
Mouse		s.c.	322
Mouse		s.c.	300
Mouse		oral	2010
Mouse		oral	1038
Rat		i.v.	15.8
Rat		s.c.	1500
Rat		oral	>4000
Rat		oral	1722

The signs of toxicity were apathy, reduced motility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after i.v. and 8 days after oral administration.

Single dose tolerance studies were performed in dogs. No deaths occurred at doses of up to 400 mg/kg oral or 50 mg/kg s.c. Signs of toxicity were mydriasis, dryness of oral, nasal and optic mucosa, vomiting, ataxia, increased heart rate, decreased body temperature and death from respiratory failure.

A single dose inhalation toxicity study of ipratropium bromide administered as a 4% and 8% solution to guinea pigs was performed. No toxic signs were observed with the 4% solution and death occurred after 5 hours of administration of the 8% solution (approximately 200 mg/kg).

Anaesthetized normal and hypoventilated dogs tolerated doses up to 200 puffs (4 mg) of ipratropium bromide without ECG changes or heart failure. Reductions in heart rate were observed. Similar findings were seen in dogs given i.v. infusions (10 mg/kg/min) up to 1550 mg/kg or 1000 mg/kg plus 200 puffs from a placebo inhaler. Blood pressure reductions were also seen in these experiments.

A single dose inhalation, dose tolerance study in rats using doses up to 160 puffs (3.2 mg) from an ipratropium bromide inhaler was performed. No deaths occurred.

Multiple Dose Studies

Oral:
A multiple dose toxicity study of nine weeks duration in rats, utilizing doses of 10, 100 and 500 mg/kg, revealed no pathologic findings apart from a dose related decrease in food consumption and growth rate.

A four week study in dogs using doses of 3, 30 and 150 mg/kg (for three weeks) increased to 300 mg/kg, showed mydriasis, inhibition of lacrimal and salivary secretion, tracheal and ocular inflammation, decreased food intake and weight loss at the medium and high doses. Three of six dogs died when the dose was increased from 150 to 300 mg/kg.

A supplementary study of 13 weeks using doses of 1.5, 3.0 and 15 mg/kg revealed no pathologic changes apart from a dose related inhibition of lacrimal secretion and associated keratoconjunctivitis and dryness of the mouth.

Subcutaneous:
Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg group from paralytic ileus. Inflammatory changes were noted at the injection site.

A 4 week study in dogs using doses of 10, 20 and 30 mg/kg (increased to 40 mg/kg on the last five days) was conducted. Dryness of oral and nasal mucosal membranes and mydriasis were noted along with conjunctivitis and keratitis associated with decreased lacrimal secretions. A decrease in food intake and

body weight also occurred. One dog died in the high dose group. Signs of liver damage were noted in two of the high dose dogs. Low testicular weights, which have not been observed in other subsequent studies, were also observed.

Inhalation:
Twelve rats were exposed to aerosolized ipratropium bromide at a concentration of 11.5 μg/L for
1 hour, 4 times per day for 7 days. No drug toxicity was found.

In another study, administration of ipratropium bromide at concentrations of 128, 256 and 384 μg per rat per day for 30 days showed no signs of toxicity apart from low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2 of 9 females in the high dose group.
This finding has not been observed in subsequent studies.

Four rhesus monkeys inhaled 500 μg of ipratropium bromide twice a day (total dose 1 mg/day) for seven days without the appearance of any drug induced toxicity.

In another rhesus monkey study, the animals were given ipratropium bromide at doses of 200, 400 and 800 μg/day by inhalation, for six weeks. Included in the tests were measurements of mucociliary transport rate and ciliary beat frequency. No signs of drug toxicity were found.

Oral:
A 6 month and 1 year study in rats using doses of 6, 30 and 150 mg/kg were performed. The high dose was increased to 200 mg/kg after 14 weeks. Reductions in food consumption and growth rates were observed in the highest dose group. A dose dependent constipation which caused severe coprostasis and dilatation of the intestines was observed in the highest dose group. A toxic hepatosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs at doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year.
A decrease in body weight development was seen in the highest dose group and food consumption was reduced in the dogs receiving 3 mg/kg and above. Emesis was seen in all treated groups. A dose dependent decrease (3 mg/kg and above) in nasal, oral and lacrimal secretions, the latter leading to keratoconjunctivitis, was observed. Increases in SGPT and SGOT (15 and 75 mg/kg) and alkaline phosphatase (75 mg/kg) were noted. Localized gastric necrosis was found in two

dogs at the highest dose and a non-dose-dependent fatty degeneration of the liver which varied from animal to animal, was also seen.

Inhalation:

A 6 month study in rats was performed using doses of 128, 256 and 384 μg per rat per day. Measurements included ciliary beat frequency, lung mechanics and blood gas. The only finding was a dose related decrease in growth rate of the male animals.

A 6 month inhalation toxicity study was performed in rhesus monkeys utilizing daily doses of 20, 800 and 1,600 μg. All findings were negative including measurements of lung mechanics, ciliary beat frequency and blood gases.

Mutagenicity

Three Ames tests, a micronucleus test in mice, a cytogenic study in Chinese hamsters, and a dominant lethal test were performed to assess the mutagenic potential of ipratropium bromide. Two positive tests (one Ames and the micronucleus study) were apparently spurious as they could not be reproduced with subsequent exhaustive experimentation. In the cytogenic study, a dose-related increase in the number of chromatid gaps, but not of other aberrations, was seen. The significance of this finding is not known. All other test results were negative.

Carcinogenicity

Ipratropium bromide was tested individually for neoplastic properties in several carcinogenicity studies. Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. Ipratropium bromide revealed no carcinogenic potential when tested orally in mice and rats.

Genotoxicity

Ipratropium bromide was tested in numerous *in-vivo* and *in-vitro* genotoxicity tests and showed no evidence of mutagenic properties.

Reproductive Studies

Three teratology studies, one in mice using oral doses of 2 and 10 mg/kg and two in rats have been conducted. The first rat study used the same dosages while the

second employed 10 and 20 mg/kg. None of these studies revealed any drug induced fetal abnormalities.

A similar oral study in rabbits utilizing doses of 2 and 10 mg/kg again demonstrated no teratogenic or embryotoxic effects of ipratropium bromide.

An inhalation teratology study in rabbits using doses of 0.3, 0.9 and 1.8 mg/kg demonstrated no effects on litter parameters and no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 10 and 500 mg/kg given 60 days prior to and during early gestation was performed. Fertility was delayed in eight of 20 couples at the 500 mg/kg dose and spurious pregnancy in five of 20 females occurred at this dose. In addition, the conception rate was decreased in 75% of females at this dose. No embryotoxic or teratogenic effects were observed.

Apart from these findings, the studies performed with salbutamol sulphate and with ipratropium bromide revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity.

SALBUTAMOL

Single Dose Studies

SPECIES	**(n)**	**ORAL LD_{50}**	**SPECIES**	**(n)**	**INTRAVENOUS LD_{50}**
Mouse	(10)	> 2000 mg/kg	Mouse	(10)	72 mg/kg
Rat	(10)	> 2000 mg/kg	Rat	(10)	60 mg/kg

	(n)	INTRA PERITONEAL LD_{50} IN RAT
Newborn	(155)	216 mg/kg
Weanling	(100)	524 mg/kg
2-week old	(90)	437 mg/kg
Key: (n) – Number of Animals		

The rate of respiration in test animals initially increased, but subsequently became abnormally slow and deep. Death, preceded by convulsions and cyanosis, usually occurred within four hours after drug administration.

Rabbits, cats and dogs survived a single dose of 50 mg/kg salbutamol.

Multiple Dose Studies

Intermediate (Four Months) Toxicity

Rats received salbutamol twice daily, in oral doses from 0.5 to 25 mg/kg, on an increasing scale.
The only significant hematological changes were a small increase in hemoglobin and packed cell volume. BUN and SGOT values were elevated while blood glucose and plasma protein levels remained unchanged. Pituitaries had increased amount of PAS-positive material in the cleft at the higher dose levels.

Salbutamol was given to dogs twice daily, in oral doses from 0.05 to 12.5 mg/kg, on an increasing scale. The rate of increase of hemoglobin and packed cell volume was depressed, particularly at higher doses. Leukocyte count decreased after sixteen weeks of treatment at each dose level. Platelet count was increased after eight weeks at the highest dose. No significant biochemical effects were observed. The only significant histological change was the appearance of corpora amylacea in the stomach which was attributed to altered mucus secretion. Inhalation of 1,000 μg of salbutamol aerosol twice daily for three months did not produce any morphological changes in the lungs, trachea, lymph nodes, liver or heart.

Long-Term Toxicity

Fifty female, Charles River CD Albino rats received salbutamol orally at 2, 10 and 50 mg/kg/day for one hundred and four weeks; fifty female Charles River CD Sprague-Dawley-derived rats received 20 mg/kg/day salbutamol orally for fifty weeks, and fifty female Charles River Long-Evans rats received 20 mg/kg/day salbutamol orally for ninety-six weeks. These rat studies demonstrated a dose-related incidence of mesovaria leiomyoma. No similar tumours were seen in mice.

Mutagenicity

In vitro tests involving four microorganisms revealed no mutagenic activity.

Carcinogenicity

Salbutamol sulphate and ipratropium bromide were tested individually for neoplastic properties in several carcinogenicity studies. After oral administration of salbutamol sulphate in rats, but not in mice, hamsters and dogs, an increased incidence of leiomyomas of the mesovarium was observed at dosages about ≥ 20-fold higher than inhalation MRHDD. The development of the leiomyomas was found to be preventable by simultaneous administration of beta-blockers. These findings were

assessed to be species specific and therefore without clinical relevance, consequently not leading to any restriction of the clinical use of salbutamol sulphate.

Reproductive Studies

Salbutamol has been shown to be teratogenic in mice when given in doses corresponding to 14 times the human aerosol dose; when given subcutaneously in doses corresponding to 0.2 times the maximum human (child weighing 21 kg) oral dose; and when given subcutaneously in doses corresponding to 0.4 times the maximum human oral dose.

Salbutamol sulphate caused cleft palates at high subcutaneous dosages in mice starting at dosages in the range of the inhalation MRHDD (based on mg/m2). However this phenomenon is well known and occurs also after the administration of other beta-adrenergic compounds. Today it is assumed that this effect is caused by an increase in the maternal corticosterone level and might be regarded as a result of general stress not relevant for other species. Apart from these findings, the studies performed with salbutamol sulphate revealed only marginal effects, if any, on embryos, foetuses and pups and these only in the range of maternal toxicity.

In rats, salbutamol treatment given orally at 0.5, 2.32, 10.75 and 50 mg/kg/day throughout pregnancy resulted in no significant fetal abnormalities. However, at the highest dose level there was an increase in neonatal mortality. Reproduction studies in rats revealed no evidence of impaired fertility.

Salbutamol had no adverse effect when given orally to Stride Dutch rabbits, at doses of 0.5, 2.32 and 10.75 mg/kg/day throughout pregnancy. At a dose of 50 mg/kg/day, which represents 2800 times the maximum inhalational dose, cranioschisis was observed in 7 of 19 (37%) fetuses.

Genotoxicity

Salbutamol sulphate was tested in numerous *in-vivo* and *in-vitro* genotoxicity tests and showed no evidence of mutagenic properties.

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10. Product Monograph ^{Pr}COMBIVENT® UDV, manufactured by Boehringer Ingelheim (Canada) Limited, date of revision: November 25, 2015, control number 186512.

PART III: CONSUMER INFORMATION

PrTEVA-COMBO STERINEBS®
Ipratropium Bromide (as Monohydrate) and Salbutamol (as Salbutamol Sulphate) Nebulizer Solution

Read this carefully before you start taking TEVA-COMBO Sterinebs® and each time you get a refill. This leaflet is a summary and will not tell you everything about TEVA-COMBO Sterinebs®. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about TEVA-COMBO Sterinebs®.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-COMBO Sterinebs® is used to treat the wheezing or shortness of breath caused by COPD (chronic obstructive pulmonary disease which includes chronic bronchitis and emphysema).

What it does:
TEVA-COMBO Sterinebs® is a combination of two drugs that are bronchodilators: ipratropium bromide (an anticholinergic) and salbutamol (a beta-agonists). TEVA-COMBO Sterinebs® works by relaxing the muscle surrounding the bronchi (airways in the lungs) and therefore helps to ease breathing problems.

You may already be familiar with one or both of these bronchodilators, since they are also available separately, with a prescription as Teva-Ipratropium (Ipratropium bromide) and Teva-Salbutamol (salbutamol).

When it should not be used:
Do not take TEVA-COMBO Sterinebs®

- if you are allergic to ipratropium bromide or other drugs which are anticholinergic (contain atropine or its derivatives), salbutamol sulphate, or to any component of TEVA-COMBO Sterinebs® (see "**What the non-medicinal ingredients are**");
- if you have a fast or irregular heart beat or have a thickened heart muscle due to various conditions;
- if you are under 18 years of age.

What the medicinal ingredients are:
Ipratropium bromide monohydrate and salbutamol sulphate.

What the non-medicinal ingredients are:
Ssodium chloride and hydrochloric acid.

What dosage forms it comes in:

TEVA-COMBO Sterinebs® (Salbutamol Sulphate and Ipratropium Bromide inhalation solution) is supplied in plastic single dose units in strips of 5 with a foil overwrap, each containing 0.5 mg ipratropium bromide (as monohydrate) and 2.5 mg salbutamol (as salbutamol sulphate) in a 2.5 mL isotonic preservative-free solution for inhalation by ventilator or compressor-driven nebulizer. There are 4 strips per carton for a carton size of 20 unit dose vials

WARNINGS AND PRECAUTIONS

The solution is intended for inhalation only. Do not inject or drink.

Do not let the nebulized mist get into your eyes as this may cause blindness known as acute angle glaucoma. This may present as eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes. If any combination of these symptoms occurs, seek immediate medical attention. Patients with glaucoma should use swimming goggles or a nebulizer with a mouthpiece to prevent nebulized solution getting into the eyes.

BEFORE you use TEVA-COMBO Sterinebs® talk to your doctor or pharmacist if you:

- are pregnant or intend to become pregnant;
- are breast feeding;
- are having treatment for a thyroid or adrenal gland condition;
- are having treatment for high blood pressure, angina or a heart problem;
- have diabetes;
- have low levels of potassium in your blood (hypokalemia), especially if you are taking:
  - drugs known as xanthine derivatives (such as theophylline)
  - steroids to treat asthma
  - water pills (diuretics)
- have eye problems, such as glaucoma, or eye pain;

- are taking any other medications including eye drops or any medications you can buy without a prescription;
- have difficulty in urination;
- have enlarged prostate;
- have any allergies or reactions to foods or drugs;
- have a history of convulsions (uncontrolled shaking or seizures);
- have liver or kidney disease.

Contact your doctor immediately if:

- you require more than one dose to relieve your breathing problems;
- your shortness of breath becomes worse;
- you don't get the same benefit from your medicine as you did before;
- you have breathing difficulties and chest pain;
- you experience difficulty with urination.

TEVA-COMBO Sterinebs® may cause dizziness, difficulty in focusing the eye, dilated pupils, and blurred vision. You should not drive or operate machinery if this occurs.

The use of TEVA-COMBO Sterinebs® may test positive for performance enhancement (doping) in athletic competition.

INTERACTIONS WITH THIS MEDICATION

Do not mix TEVA-COMBO STERINEB with other drugs in the same nebulizer.

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with TEVA-COMBO Sterinebs®:

- digitalis;
- other anticholinergic drugs, such as ipratropium bromide and other beta$_2$-adrenergic agents such as salbutamol, the individual ingredients of TEVA-COMBO Sterinebs®;
- beta blockers, such as propranolol;
- xanthine derivatives such as theophylline;
- monoamine oxidase inhibitors such as isocarboxazid
- tricyclic antidepressants such as amitriptyline;
- epinephrine;
- certain diuretics or "water pills" such as furosemide, hydrochlorothiazide.

PROPER USE OF THIS MEDICATION

TEVA-COMBO Sterinebs® **should only be inhaled** from a nebulizer. It must not be injected or swallowed.

Do not let the TEVA-COMBO Sterinebs® or the mist produced by the nebulizer, get in your eyes.

Use your nebulizer in a well ventilated room. Some of the mist will be released into the air and may be breathed in by others.

Use TEVA-COMBO Sterinebs® only as directed by your doctor. During administration your doctor may want to monitor your blood.

Treatment with TEVA-COMBO Sterinebs® is to be initiated and administered under medical supervision (e.g. in the hospital setting). Home based treatment can be recommended in exceptional cases (severe symptoms or experienced patients requiring higher doses) when a low dose rapid acting beta-agonist bronchodilator has been insufficient in providing relief after consultation with an experienced physician. Administration should be stopped when sufficient symptom relief is achieved.

TEVA-COMBO Sterinebs® has been prescribed to treat your current condition. DO NOT give it to other people. Always use TEVA-COMBO Sterinebs® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

TEVA-COMBO Sterinebs® should be used only in a properly functioning and regularly maintained nebulizer or an intermittent positive pressure ventilator. Before starting treatment, be certain that you are completely familiar with the use and proper care of your nebulizer. The content of the

unit dose vials does not need to be diluted for nebulization.

Not recommended for use in children and adolescents under 18 years of age.

Usual Adult dose:

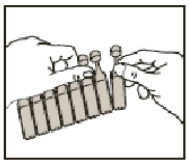
The recommended dosage is 1 unit dose vial (0.50 mg
ipratropium bromide (as ipratropium bromide monohydrate) and 2.5 mg salbutamol (as salbutamol sulfate) in 2.5 mL) three or four times daily.

If one unit dose vial does not improve your breathing difficulties, you may need another unit dose vial. If this is the case, you should contact your doctor or the nearest hospital.

Your doctor or pharmacist will tell you how to prepare your
TEVA-COMBO Sterinebs® solution for inhalation. Your doctor or pharmacist might instruct you to use sterile sodium chloride solution (0.9%) to dilute the TEVA-COMBO Sterinebs®. If you are told to dilute TEVA-COMBO Sterinebs® solution, you must do so immediately before you plan to use the solution. If necessary, doses may be diluted to a total nebulization volume of 3-5 mL with preservative free 0.9% sterile sodium chloride solution and used immediately. Discard any unused solution. Nebulize over 10-15 minutes at gas flow of 6-10L/min. Repeat every six hours as necessary.

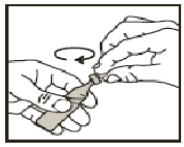
Please read and carefully follow these instructions:

1.



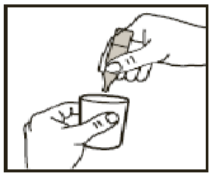
Open the pouch foil and detach one plastic vial by pulling it firmly from the strip.

2.



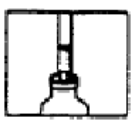
Open the vial by twisting off the top. It is important that you use the contents of the vial as soon as possible after opening it.

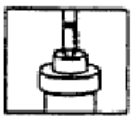
3.



Squeeze the contents of the plastic vial into your nebulizer chamber. If your doctor has instructed you to use less than one complete vial, use a syringe to withdraw the prescribed dose. Any solution left in the plastic vial must be thrown away.

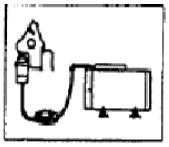
4.





Using a syringe, add sodium chloride solution to the chamber if you have been directed to do so by your pharmacist or physician.

5.



Gently shake the nebulizer chamber and connect it to the mouthpiece or face mask. Then connect the nebulizer tube to the air or oxygen pump and begin therapy.

6.

Breathe calmly and deeply through the mask or mouthpiece until no more mist is formed in the nebulizer chamber. This usually takes 10-15 minutes.

It is very important to adjust the face mask, if required, to prevent the mist from getting in your eyes.

7. Follow the instructions provided by the nebulizer and air pump manufacturers for the proper care and maintenance of the equipment. Keep the nebulizer, nebulizer tube and face mask clean to minimize microbial contamination.

Make sure you use the vial soon after opening and use a fresh vial each time to prevent

contamination (growth of harmful microorganisms). Partly used, opened or damaged unit dose vials should be discarded.

Do not mix TEVA-COMBO Sterinebs® with other drugs in the same nebulizer.

Overdose:

In case of an overdose, contact your doctor, or the Regional Poison Control Center, or go to the nearest hospital emergency department.

Missed dose:

If a dose is missed and no symptoms occur, the regular next dose according to the dosing schedule should be taken. If a dose is missed and respiratory symptoms are experienced, the missing dose should be taken and the dosing schedule according to the recommended dosage should be resumed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- wheezing after inhalation;
- headache, dizziness;
- nausea (feeling sick), digestive problems like constipation, diarrhoea and vomiting;
- muscle problems such as cramps weakness, pain, feeling weak, tremor (shaking);
- feeling nervous;
- mental disorder;
- impaired voice sounds;
- increased sweating;
- bronchitis and upper respiratory tract infection (a cold)
- throat irritation, cough, dry mouth or throat, bad taste-sucking on a sour candy or rinsing your mouth may help.

Check with your doctor if the dry mouth or bad taste persist or if you experience constipation for a prolonged period of time.

TEVA-COMBO Sterinebs® contains a beta-agonist, and taking additional doses in the form of other single agent, beta-agonists (fenoterol, salbutamol etc.) could cause harmful effects on the heart, lungs and circulatory system. Therefore do not take additional bronchodilators by inhalation with TEVA-COMBO Sterinebs® unless instructed to do so by your doctor or pharmacist.

Stop taking the medication and tell your doctor immediately if you notice any of the following:

- you are wheezy or have any other difficulties in breathing;
- you are having an allergic reaction - the signs may include skin rash, itching and nettle rash. In severe cases the signs include swelling of your tongue, lips and face, sudden difficulties in breathing and reduction of your blood pressure.

TEVA-COMBO Sterinebs® can cause abnormal blood test results for hypokalemia and/or ketoacidosis. Your doctor will decide when to perform blood tests and will interpret the results.

If you have any questions about TEVA-COMBO Sterinebs® or your nebulizer, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Uncommon	**Bronchospasm:** Increased wheezing or tightness in the chest, difficulty in breathing, coughing bouts			√
	Shortness of breath			√
	Hypotension or Hypertension, Changes in blood pressure: dizziness, fainting, lightheadedness			√
	Skin rash			√
Rare	**Allergic Reaction:** rash, hives, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, choking due to swelling of the muscles around the voice box			√
	Fast or irregular heart beat / chest pain			√
	Eye Disorders: new or worsened pressure in your eyes, eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes			√
	Urinary Retention: difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips			√
	Muscle pain, weakness or spasms; paralysis			√
	Myocardial Ischaemia: decreased blood flow to the heart leading to angina (chest pain), shortness of breath, or a heart attack			√
	Angina: Chest pain			√
	Decreased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell			√

This is not a complete list of side effects. For any unexpected effects while taking TEVA-COMBO Sterinebs®, contact your doctor or pharmacist.

HOW TO STORE IT

Unopened unit dose vials of TEVA-COMBO Sterinebs® should be stored at room temperature (15-25° C). The vials should be protected from heat and light. Do not use if solution is discoloured. Keep out of reach of children.

Partly used, opened or damaged unit dose vials should be discarded.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffet (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffet (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting
Teva Canada Limited
at: 1-800-268-4127 ext. 1255005 (English)
or 1-877-777-9117 (French)
or druginfo@tevacanada.com

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