PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrTEVA-IPRATROPIUM STERINEBS

Ipratropium bromide inhalation solution

Solution for inhalation, 250 mcg/mL (0.025%), for oral inhalation use

Bronchodilator (Anticholinergic)

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	02/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-IPRATROPIUM STERINEBS (ipratropium bromide) solution administered either alone or with an adrenergic stimulant solution is indicated:

- As a bronchodilator for the maintenance treatment of bronchospasm associated with acute exacerbations of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in adults.
- As a bronchodilator for the treatment of acute exacerbations of COPD in adults.
- When used concomitantly with an inhaled $beta_2$-adrenergic agonist, such as salbutamol, for the treatment of acute bronchospasm due to asthma in patients 5 years and older.

1.1 Pediatrics:

Pediatrics (less than 5 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TEVA-IPRATROPIUM STERINEBS in pediatric patients younger than 5 years has not been established; therefore, Health Canada has not authorized an indication for use in patients younger than 5 years.

1.2 Geriatrics:

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

TEVA-IPRATROPIUM STERINEBS is contraindicated in patients who are hypersensitive to ipratropium bromide or atropine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General

The dose of TEVA-IPRATROPIUM STERINEBS should be determined individually and patients should be kept under supervision by a healthcare professional during treatment.

Patients should be instructed to consult a healthcare professional immediately in the case of acute or rapidy worsening dyspnea.

COPD

Counselling by healthcare professionals on smoking cessation should be the first step in treating patients with chronic obstructive pulmonary disease (COPD), who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema.

Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.

Asthma
TEVA-IPRATROPIUM STERINEBS when administered to patients with acute severe asthma, should only be used with a concomitant β_2-adrenergic agonist.

Only specialists in respiratory medicine should initiate and clinically manage use of nebulisers and associated nebulised medicines at home for acute treatment of asthma in children and adolescents.

Urgent medical assistance should be sought if worsening asthma symptoms are not relieved by rescue medicines, even if there is short-term recovery following use of nebulised medication.

4.2 Recommended Dose and Dosage Adjustment

Adults and children 12 years of age and older
The recommended single dose of TEVA-IPRATROPIUM STERINEBS solution is 250-500 mcg (1 or 2 vials of 250 mcg/1 mL or 1 vial of 500 mcg/2 mL).

For the maintenance treatment of bronchospasm associated with COPD, the recommended dose is 500 mcg of TEVA-IPRATROPIUM STERINEBS given 3-4 times per day.

The maximum recommended daily dose is 2 mg per day in patients 12 years and older.

Daily doses exceeding 2 mg in adults should only be given under medical supervision.

Children 5 to 12 years of age
The recommended single dose of TEVA-IPRATROPIUM STERINEBS is 125-250 mcg.

Treatment with TEVA-IPRATROPIUM STERINEBS may be repeated every 4-6 hours as necessary.

The maximum recommended daily dose in children is 1 mg per day.

4.4 Administration

TEVA-IPRATROPIUM STERINEBS is for oral inhalation only with suitable nebulizing devices and must not be taken orally or administered parenterally.

Patients should be instructed in the proper use of the nebulizer. Patients should be cautioned against accidental release of the solution into the eyes.

TEVA-IPRATROPIUM STERINEBS is to be administered by compressed air or oxygen driven nebulizers. Nebulization should take place using a gas flow (oxygen or compressed air) of 6-10 L/minute and the solution nebulized to dryness over a 10-15 minute period. The Hudson Updraft™, Bennett Twin Jet®, DeVilbiss, Pari Compressors and Inspiron Mini-Neb® nebulizers, with facemask or mouthpiece have been used. The manufacturers' instructions concerning cleaning and maintenance of the nebulizer should be strictly followed.

Ipratropium bromide may be combined with a short-acting beta2-agonist (such as salbutamol) in the same nebuliser chamber, for simultaneous administration. The solution should be used as soon as possible after mixing and any unused solution should be discarded.

In most cases, dilution of the dose with sterile preservative-free saline is not necessary.

4.5 Missed Dose

If a dose is missed, the next scheduled dose should be taken. An extra dose must not be taken.

5 OVERDOSAGE

Doses of ipratropium bromide solution up to 1.2 mg (60 puffs) have been administered by inhalation without the appearance of serious systemic anticholinergic effects. Minor systemic manifestations of anticholinergic action, including dry mouth, visual accomodation disturbances and increased heart rate may occur.

Should signs of serious anticholinergic toxicity appear, cholinesterase inhibitors may be considered.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Inhalation	Solution, 250 mcg/mL	Normal Saline (9 mg/mL (0.9%) sodium chloride solution), hydrochloric acid
Inhalation	Solution, 500 mcg/2mL	Normal Saline (9 mg/mL (0.9%) sodium chloride solution), hydrochloric acid

TEVA-IPRATROPIUM STERINEBS is available as unit dose vials (UDV) containing ipratropium bromide 0.025% in Normal Saline (9 mg/mL (0.9%) sodium chloride solution). Also contains hydrochloric acid. The unit dose vials do not contain preservatives.

500 mcg /2 mL
TEVA-IPRATROPIUM STERINEBS 500 mcg /2 mL is provided as 2 mL of clear, colourless solution containing 0.025% ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 500 mcg of ipratropium bromide. Available in cartons of 10 vials.

250 mcg/mL
TEVA-IPRATROPIUM STERINEBS 250 mcg /mL is provided as 1 mL of clear, colourless solution containing 0.025% ipratropium bromide in isotonic solution, presented in a plastic single use vial. Each vial contains a total of 250 mcg of ipratropium bromide. Available in cartons of 20 vials.

7 WARNINGS AND PRECAUTIONS

General

TEVA-IPRATROPIUM STERINEBS should not be used alone for the abatement of an acute asthmatic attack since the drug has a slower onset of effect than that of a β_2-adrenergic agonist.

If a reduced response to TEVA-IPRATROPIUM STERINEBS becomes apparent, the patient should seek medical advice.

Excessive Use and Use with other Muscarinic Antagonists:
TEVA-IPRATROPIUM STERINEBS should not be used more frequently or at higher doses than recommended.

TEVA-IPRATROPIUM STERINEBS should not be administered concomitantly with other medications that contain a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium or umeclidinium)

Anticholinergic Effects
Like other anticholinergic drugs, TEVA-IPRATROPIUM STERINEBS should be used with caution in patients with narrow-angle glaucoma (see Ophthalmologic) or urinary retention (see Renal).

Cardiovascular
Cardiovascular effects, such as cardiac arrhythmias (e.g. atrial fibrillation and tachycardia), may be seen after the administration of muscarinic receptor antagonists.

Gastrointestinal
Patients with cystic fibrosis may be more prone to gastro-intestinal motility disturbances, therefore, ipratropium bromide should be used with caution in these patients.

Immune
Hypersensitivity:
Immediate hypersensitivity reactions may occur after administration of TEVA-IPRATROPIUM STERINEBS, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema and anaphylaxis.

Ophthalmologic

Worsening of narrow-angle glaucoma:
Like other anticholinergic drugs, TEVA-IPRATROPIUM 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 does not escape into the eyes. In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of an ipratropium solution or a combined ipratropium/β_2-agonist solution should be avoided unless measures (e.g. use of swimming goggles or use of a nebulizer with a mouth piece) are taken to ensure that nebulized solution does not reach the eye.

There have been isolated reports of ocular complications (i.e., mydriasis, increased intraocular pressure, angle closure glaucoma) when nebulized ipratropium bromide either alone or in combination with an β_2-adrenergic agonist solution has escaped into the eyes.

Eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal edema may be signs or acute narrow-angle glaucoma. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition. Miotic drops alone are not considered to be effective treatment.

Renal

Worsening of urinary retention:
TEVA-IPRATROPIUM STERINEBS should be used with caution in patients with urinary retention, prostatic hyperplasia or bladder neck obstruction. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Patients should be instructed to consult a health professional immediately should any of these signs or symptoms develop.

Respiratory

Paradoxical bronchospasm:
As with other inhalation therapy, inhalation induced bronchoconstriction may occur with an immediate increase in wheezing after dosing. This should be treated straight away with a fast acting inhaled bronchodilator. Ipratropium bromide should be discontinued immediately, the patient assessed and, if necessary, alternative treatment instituted.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of TEVA-IPRATROPIUM STERINEBS in pregnancy has not been established. The benefits of using ipratropium bromide during confirmed or suspected must be weighed against possible harms to the fetus. Studies in rats, mice and rabbits showed no embryotoxic nor teratogenic effects (See 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

No specific studies have been conducted on excretion of ipratropium bromide in breast milk. It is not known whether ipratropium bromide is excreted into human breast milk. TEVA-IPRATROPIUM STERINEBS should be used during breastfeeding only if the potential benefit outweighs the potential risks to the infant.

7.1.3 Pediatrics

The efficacy and safety of TEVA-IPRATROPIUM STERINEBS in children younger than 5 years have not been established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Side effects observed with inhaled ipratroprium bromide solution are consistent with other inhalation therapies and include cough, local irritation and inhalation induced bronchospasm, and in very rare instances exacerbation of symptoms has been observed.

The most frequent non-respiratory adverse events reported in clinical trials were headache, gastro-intestinal motility disturbances (constipation, diarrhea and vomiting), dizziness and dryness of the mouth/throat.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

The adverse event profile was examined in a total of 214 patients receiving ipratropium bromide solution and 94 patients receiving ipratropium bromide plus a β_2-adrenergic agonist. Furthermore the frequency of adverse reactions reported as possibly related to ipratropium bromide treatment was studied in a 12-week controlled clinical trial in 219 COPD patients.

ACUTE ADMINISTRATION

The frequency of adverse reactions (≥1%) recorded in 214 patients receiving ipratropium bromide solution was as follows:

Table 2 -

ADVERSE REACTION	% OF PATIENTS
Dry mouth or throat	9.3
Bad taste	5.1
Tremor	4.2
Exacerbation of symptoms	4.2

The adverse reaction judged to be most severe was exacerbation of bronchospasm. This occurred in 8 patients treated with ipratropium bromide solution alone, 6 of whom withdrew from the clinical studies.

Bronchospasm occurred in 3 patients with acute severe asthma who received ipratropium bromide solution alone. In two patients, this was reversed after therapy with a β_2 sympathomimetic solution. The third patient received no other therapy.

The following table compares the incidence of adverse reactions (≥1%) of the combination of ipratropium bromide and a β_2-adrenergic agonist (fenoterol or salbutamol) solution with that of the β_2–adrenergic agonist alone.

Table 3-

ADVERSE REACTION	IPRATROPIUM BROMIDE + β_2 AGONIST (% of 94 patients)	β_2 AGONIST (% of 96 patients)
Tremor	31.9	26.0
Dry Mouth	16.0	28.1
Bad Taste	16.0	13.5
Vomiting	2.1	2.1
Palpitations	2.1	1.0
Headache	1.1	2.1
Cough	1.1	0.0
Flushing	1.1	0.0

CHRONIC ADMINISTRATION

The frequency of adverse reactions reported as possibly related to ipratropium treatment in 219 COPD patients participating in 12-week controlled clinical trials was as follows:

Table 4-

ADVERSE REACTION	% OF PATIENTS
Dry mouth	2.7
Coughing	1.8
Dyspnea	1.8
Headache	1.8
Urinary retention	1.4
Tremor	0.9
Nausea	0.9
Palpitation	0.9
Eye pain	0.9

Observed adverse events occurring in at least 1% of subjects include rhinitis (0.9) and sputum increase (0.9%).

The following other adverse reactions were reported in one patient each: bronchospasm, tachycardia and urticaria.

In addition, the following adverse events were observed in one patient each: bronchitis, chest pain, depression, fatigue, flu-symptoms, hypoaesthesia, increased saliva, insomnia, nervousness, pain, paraesthesia, pharyngitis, somnolence.

The frequency of adverse reactions reported as possibly related to drug treatment in greater than 1% of COPD patients participating in long-term (12-week) controlled clinical trials that compared the efficacy and safety of ipratropium bromide solution + β_2 agonists (metaproterenol or salbutamol) versus the β_2 agonist alone, was as follows:

Table 5-

ADVERSE EFFECT	% OF PATIENTS	
	IPRATROPIUM BROMIDE + β_2 AGONIST (n =208)	β_2 AGONIST (n =417)
Headache	4.3	1.7
Tremor	3.8	3.4
Nervousness	3.8	1.9
Dyspnea	2.4	3.4
Dry mouth	2.4	1.0
Bronchitis	2.9	2.9
Dizziness	1.4	1.9
Coughing	1.4	1.0
Taste perversion	1.9	1.2
Insomnia	1.9	0.2
Dysuria	1.0	0.2
Nausea	1.0	1.7
Abnormal vision	0.5	1.2
Chest pain	1.4	0.7
Constipation	1.4	0.0
Dysphoria	1.0	0.2
Dyspepsia	1.0	0.0
Bronchospasm aggravated	1.0	0.7
Micturition frequency	1.0	0.2

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

In the acute administration trial in 214 patients treated with ipratropium bromide solution the following less common adverse reactions were reported: burning eyes, cough, headache, nausea, palpitations and sweating.

There have been isolated reports of ocular effects such as mydriasis, increased intraocular pressure, and acute glaucoma associated with the escape of nebulized ipratropium bromide, alone or in combination with a β_2 agonist solution into the eyes.

Side effects such as tachycardia and palpitations, supraventricular tachycardia and atrial fibrillation, ocular accommodation disturbances, nausea and urinary retention have been reversible, although the risk of urinary retention may be increased in patients with pre-existing outflow tract obstruction.

Ocular side effects have been reported (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

8.5 Post-Market Adverse Reactions

World-wide safety data, which includes post-marketing data, spontaneous reports and literature reports indicates that the most frequent non-respiratory side effects of ipratropium bromide are headache and dryness of mouth/throat.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide. Allergic type reactions such as skin rash, pruritus, angioedema of the tongue, lips and face, urticaria (including giant uritcaria), laryngospasm, oropharyngeal edema, bronchospasm, and anaphylactic reactions, may occur.

Dizziness has been reported.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The chronic co-administration of ipratropium bromide inhalation with other anticholinergic drugs has not been studied. There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, TEVA-IPRATROPIUM STERINEBS should not be administered concomitantly with other medications that contain a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium) as this may lead to an increase in anticholinergic adverse effects (see 7 WARNINGS AND PRECAUTIONS).

There is evidence that the administration of ipratropium bromide with beta-adrenergic drugs and xanthine preparations may produce an additive bronchodilatory effect.

The risk of acute glaucoma in patients with a history of narrow-angle glaucoma may be increased when nebulised ipratropium bromide and $beta_2$-adrenergic agonists are administered simultaneously (See 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ipratropium bromide, a quaternary ammonium derivative of atropine, is an anticholinergic drug having bronchodilator 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. Bronchodilation is still evident 8 hours after inhalation.

10.2 Pharmacodynamics

Large, single inhaled doses of ipratropium bromide have been given to man without any signs of toxicity. After the administration of 400 mcg by inhaler (10 times the recommended single dose) to 10 normal subjects, no changes were detected in pulse rate, blood pressure, intraocular pressure, salivary secretion, visual accommodation or electrocardiograms. Likewise, in another study, no changes in pulse rate or salivary secretion were seen when cumulative doses up to 1.2 mg were administered by inhaler to 12 normal volunteers.

Special studies utilizing normal therapeutic doses in asthmatic and chronic bronchitic patients again have not revealed any systemic anticholinergic effects. In one study, 14 patients were treated for 45 days with either ipratropium bromide inhaler 40 mcg q.i.d. or ipratropium bromide inhaler 40 mcg q.i.d. plus oral fenoterol hydrobromide 5 mg q.i.d. No changes in visual acuity intraocular 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 inhaler 40 mcg t.i.d. administered for 3 days.

Deterioration in pulmonary function in patients treated in all clinical trials with therapeutic doses of ipratropium bromide solution was examined. The following table shows the number of patients who showed a 15% or greater fall in FEV_1 at any time within 2 hours following the administration of the drug. Also shown are the figures for comparative agents used.

Table 6-

Treatment	Incidence	
Normal saline	15/90	(16.7%)
Ipratropium Bromide Solution	14/214	(6.5%)
Ipratropium Bromide Inhaler	4/78	(5.1%)

Dose titration studies in stable asthmatic patients with ipratropium bromide solution have indicated that maximal improvement in pulmonary function occurs at approximately 250 mcg for adults and 125 mcg for children over 5 years.

A clinical pharmacology study comparing single doses of ipratropium bromide inhaler (80 mcg) and ipratropium bromide solution (250 mcg) in 16 stable adult asthmatics was performed. No difference between the regimens was found, based on an improvement in pulmonary function over a 2 hour period.

A wide variety of challenge studies have been conducted utilizing 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 little or no effect against histamine or serotonin.

Antigen challenge studies have demonstrated that ipratropium bromide offers some protection against the “early” allergic asthma response, but has no effect on the “late” response.

Non-clinical pharmacology
Ipratropium bromide was shown to abolish acetylcholine-induced bronchospasm in the guinea pig and dog after intravenous (i.v) administration at an ED_{50} of 0.15-0.40 mcg /kg with a transient effect on blood pressure. By inhalation, approximately 25 mcg of ipratropium bromide produced 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 i.v. administration.

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 subcutaneous dose of about 0.011 mg/kg, equipotent to atropine, but the equi-effective oral dose of ipratropium was 58 times greater. When given by inhalation, no increase in heart rate or pathological changes in ECG pattern were recorded at doses up to 8 mg. Salivary secretion in rat, mouse and dog was effectively inhibited by low parenteral doses of ipratropium bromide (0.001 to 0.032 mg/kg) but when given by the oral route, the effective dose increased over 100-fold. Aerosol administration in dogs of about 65 puffs (0.04 mg/puff) produced a 50% inhibition of 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 subcutaneous (s.c.) doses but were 10-20 times less after oral administration. Tests of doses of ipratropium bromide up to 100 mg/kg in the rabbit showed no effect on the central nervous system.

Ipratropium bromide administered by inhalation in combination with a β_2 sympathomimetic agent (fenoterol hydrobromide) showed additive effects in antagonizing acetylcholine induced bronchospasm in the dog and guinea pig. In the dog, 50 mcg of fenoterol by inhalation produced an 8% increase in heart rate and a 16% increase in left ventricular dp/dt. When 20 mcg ipratropium was added the corresponding increases were 8% and 9%.

10.3 Pharmacokinetics

Absorption:
Ipratropium bromide is absorbed quickly after oral inhalation of a nominal dose of 40 mcg 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 systemic bioavailability after inhalation of 2 mg ipratropium bromide, via an ultrasonic Mizer inhaler, over 20 minutes is estimated to be 7% of the dose. The bioavailability of the swallowed portion of the dose is approximately 2%.

Distribution:
Intravenous administration of 1.0 mg showed a rapid distribution into tissues (half-life of an alpha phase approximately 5 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).

Parameters describing the disposition of ipratropium bromide were calculated from the plasma concentrations after i.v. administration. A rapid biphasic decline in plasma is noted for ipratropium. The half-life of the terminal elimination phase is about 1.6 hours. The total clearance of the active ingredient is 2.3 L/min. Approximately 40% of the clearance is renal (0.9 L /min) and

60% non-renal i.e. mainly hepato-metabolic. The volume of distribution is 338 L (corresponding to approximately 4.6 L /kg).

Radio-labelled technetium was administered with ipratropium bromide solution in an adult dose finding study. The following table outlines the doses reaching the patient.

Dose Available (μg)	Amount Reaching Patient (μg)	Lung dose (μg)
500	53	17.0
250	27	8.5
125	13	4.3

The drug is minimally (less than 20%) bound to plasma proteins. The ipratropium ion does not cross the blood-brain barrier, consistent with the quaternary amine structure of the molecule.

Metabolism:
Up to 8 metabolites of ipratropium bromide have been detected in man, rat and dog. However, the main metabolites bind poorly to the muscarinic receptor.

Excretion:
In man, about 70% of the ^{14}C labelled drug is excreted unchanged after i.v. administration and only one metabolite exceeds 10% of the total radioactivity. The elimination of ipratropium and its metabolites occurs primarily via the kidney with less than 10% of the total intravenous dose excreted via the biliary or fecal route. After oral or inhaled doses, however, up to 90% of the radiolabelled dose is detectable in the feces, suggesting relatively low lung deposition and poor absorption of the swallowed portion.

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. Depending on the formulation and inhalation technique, renal excretion may increase up to 13% of the dose (40 or 80 μg dose), reflecting a higher deposition in the airways and a higher bioavailability.

Special Populations and Conditions

Pediatrics: The efficacy and safety of ipratropium bromide in children younger than 5 years have not been established.

11 STORAGE, STABILITY AND DISPOSAL

1 mL or 2 mL Unit Dose Vials:
Unopened unit dose vials of TEVA-IPRATROPIUM STERINEBS should be stored at controlled room temperature (15°C – 30°C) and protected from light. If required, the solution should be diluted with a preservative free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

The solution is physically compatible with orciprenaline sulfate, or salbutamol sulfate (6 mg/mL) solutions. If such mixtures are prepared, they should be diluted with preservative free 0.9% sterile sodium chloride solution and used immediately. Any unused portion of such combined solutions must be discarded.

12 SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required for this product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

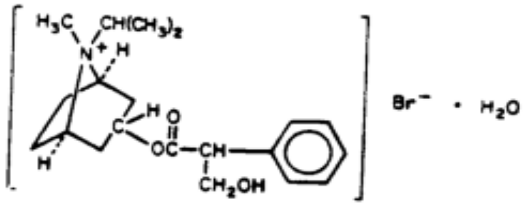
Proper Name: ipratropium bromide

Chemical Name: 8-azoniabicyclo [3.2.1] octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1- methylethyl)-,bromide, monohydrate(endo,syn)-,(±)-.

Molecular Formula: $C_{20}H_{30}BrNO_3 \bullet H_2O$

Molecular Weight: 430.4

Structural Formula:



Description: 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.

pH: Between 5.0 to 7.5 of 1% solution in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Chronic Obstructive Pulmonary Disease (COPD)

In controlled 12-week studies in patients with bronchospasm associated with COPD (chronic bronchitis and emphysema), treatment with ipratropium bromide solution resulted in significant improvements in pulmonary function (FEV_1 and $FEF_{25-75\%}$ increases of 15% or more) occurred within 15 minutes, and reached a peak in 1 - 2 hours. The improvements persisted for periods of 4 - 5 hours in the majority of patients, with 25 to 38% of the patients demonstrating increases of at least 15% at 7 - 8 hours. Continued effectiveness of ipratropium bromide solution was demonstrated throughout the 12-week period. In addition, significant changes in forced vital capacity (FVC) have been demonstrated.

Asthma

Controlled 12-week studies were conducted to evaluate the safety and efficacy of ipratropium bromide solution administered concomitantly with bronchodilator solutions of orciprenaline or salbutamol, compared with the administration of each of the $beta_2$-adrenergic agonists alone in patients with asthma.

Combined therapy produced significant additional responses in FEV_1, FVC and $FEF_{25-75\%}$. On combined therapy, the median duration of 15% improvement in FEV_1 was 5 - 7 hours, compared with 3 - 4 hours in patients receiving a beta agonist alone.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute

Acute toxicity has been investigated with observation periods of 14 days in several rodent and non-rodent species.

Table 7-

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 mobility, ataxia, paralysis of skeletal muscle, clonic convulsions and death from respiratory failure. Toxic signs persisted for 3 hours after intravenous (i.v.) and 8 days after oral administration.

Table 8-IPRATROPIUM BROMIDE + FENOTEROL HYDROBROMIDE (RATIO 1:2.5)

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	M	i.v.	23.6
Mouse	F	i.v.	26.2
Mouse	M	oral	630
Mouse	F	oral	650
Rat	M	i.v.	32.5
Rat	F	i.v.	32.5
Rat	M	oral	3200
Rat	F	oral	2450

The signs of toxicity were spasmodic breathing, tonic, clonic and saltatory convulsions, sedation, ataxia, spasms, exophthalmus, chromolacryorrhoea, reduced motility, tremor and positive sliding test. Late mortality occurred only after oral administration.

Acute dose tolerance studies were performed in dogs. No deaths occurred up to doses of 400 mg/kg oral or 50 mg/kg subcutaneous (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.

An acute inhalation toxicity study of ipratropium bromide administered as 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 with the 8% solution (approximately 200 mg/kg).

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

No deaths occurred in an acute inhalation dose tolerance study in rats using doses up to 160 puffs (3.2 mg) from an ipratropium bromide inhaler was performed or with a combination of ipratropium bromide (up to 3.2 mg/kg) and fenoterol hydrobromide (up to 8 mg/kg) administered by inhalation (up to 320 puffs) to rats.

SUBACUTE
Oral:

A study of 9 weeks duration in rats utilizing doses of 10, 100 and 500 mg/kg revealed no pathological findings apart from a dose related decrease in food consumption and growth rate.

A 4 week study in dogs using doses of 3, 30 and 150 (for 3 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 6 dogs died when the dose was increased from 150 to 300 mg/kg.

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

Intravenous:

A 32 day study in rats was conducted with the combination of ipratropium bromide and fenoterol hydrobromide at doses of 1.32 + 3.32 μg/kg (Group 1) 8 + 20 μg /kg (Group 2) and 24 + 60 μg /kg (Group 3), respectively. Fenoterol 60 μg /kg (Group 4) and ipratropium 24 μg /kg (Group 5) were also administered. Increases in heart rate (dose related in all treated animals) and dry mouth and nose (Groups 3 and 5) were seen. Increases in LDH (Groups 3 and 4), creatine kinase (all treated Groups), potassium (Groups 2, 3 and 4) and cholesterol (Groups 3 and 4) were observed. Myocardial scars were seen in one animal in Group 3 and fatty changes in the liver were noted in one animal in Group 4.

Subcutaneous:

Rats were treated with subcutaneous injections of 1, 10 and 100 mg/kg. One death occurred in the 10 mg/kg dose 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 5 days) was conducted. Dryness of the oral and nasal mucous 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 2 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 in a concentration of 11.5 mcg /L for 1 hour, 4 times per day for 7 days. No drug toxicity was found.

Aerosolized ipratropium bromide of 11.5 mcg/L for 1 hour 4 times daily for 7 days administered to rats demonstrated no toxicity. Administration of ipratropium bromide in doses of 128, 256 and 384 mcg per rat per day for 30 days showed no signs of toxicity apart from a low grade inflammatory response and areas of fibrosis and hemorrhage in the parametrium of 2/9 females in the high dose group. This finding has not been observed in subsequent studies.

No signs of toxicity were observed in rhesus monkeys following inhalation of 500 mcg iptratropium twice daily for 7 days or following inhaled doses of 200, 400 and 800 mcg/day for 6 weeks.

No changes apart from a reduction in food consumption were observed in rats following inhalation exposure to a combination of ipratropium bromide and fenoterol.

A 28 day study in dogs was conducted using fenoterol and ipratropium in the following doses respectively: 350 + 140 μg (Group 3); 1050 + 420 μg (Group 4); 3150 + 1260 μg (Group 5). Vasodilation occurred in Groups 4 and 5 and heart rate was increased in the treated animals. Potassium levels were raised in Group 5. Liver glycogen content was raised in 4 (of 6) animals in Group 5 and 2 in Group 4.

A further 13 week combination study was done in dogs using doses of 23 + 9 μg (Group 1), 160 + 64 μg (Group 2) and 1100 + 440 (Group 3) fenoterol + ipratropium bromide respectively. Peripheral hyperaemia and dry mucous membranes were observed in all treated animals. Increases in heart rate were seen in Groups 1 to 3, and 5 of 6 dogs in Group 3 had disturbances of impulse formation and conduction. Slight increases in GPT in Groups 2 and 3, as well as increases in AP in individual animals of Groups 1 to 3 were noted. Histological findings consisted of a scar in the papillary muscle of the left ventricle of one dog in Group 3 as well as centrolobular fatty infiltration of hepatocytes in dogs of Groups 2 and 3.

CHRONIC
Oral:

A 6 month and a 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 groups. A toxic hepatosis was observed in some animals of the highest dose group.

Ipratropium bromide was administered to dogs in doses of 1.5, 3.0, 15.0 and 75.0 mg/kg for 1 year. A decrease in body weight 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 2 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:

In a 6 month study in rats using inhaled doses of 128, 256 and 384 mcg per rat per day the only finding was a dose related decrease in growth rate of the male animals.

No findings were observed in a 6 month inhalation toxicity study in rhesus monkeys administered daily doses of 20, 800 and 1600 mcg.

MUTAGENICITY:

Three Ames tests, a micronucleus test in mice, a cytogenetic study in Chinese hamsters, and a dominant lethal test in mice 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 cytogenetic 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:

Carcinogenicity studies in mice (107 weeks duration) and rats (114 weeks duration) utilizing oral doses of up to 6 mg/kg were performed. No tumorigenic or carcinogenic effects were observed.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Three teratological studies, one in mice using oral doses of 2 and 10 mg/kg, and two in rats (oral doses of 2 and 10 mg/kg and 10 and 20 mg/kg), were performed. No drug induced fetal abnormalities were observed.

An oral study in rabbits utilizing doses of 2 and 10 mg/kg again showed 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 effect on litter parameters, and no embryotoxic or teratogenic effects.

Two inhalation teratology studies with the combination of fenoterol and ipratropium in rats (doses up to 8 x 25 minute exposures of 7.5 mg fenoterol + 3.0 mg ipratropium per day) and rabbits (doses up to 3.0 mg fenoterol + 1.2 mg ipratropium) revealed no embryotoxic or teratogenic effects.

A fertility study in rats with oral doses of 5, 50 and 500 mg/kg being given 60 days prior to and during early gestation was performed. Fertility was delayed in 8 of 20 couples at 500 mg/kg and spurious pregnancy in 5 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTEVA-IPRATROPIUM STERINEBS
ipratropium bromide inhalation solution

Read this carefully before you start taking **TEVA-IPRATROPIUM STERINEBS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-IPRATROPIUM STERINEBS**.

What is TEVA-IPRATROPIUM STERINEBS used for:
TEVA-IPRATROPIUM STERINEBS is used:

- in adults for the maintenance treatment of chronic obstructive pulmonary disease (COPD) This includes chronic bronchitis and emphysema.
- in adults for the treatment of sudden breathlessness (bronchospasm) in COPD.
- in adults and children 5 years of age and older together with an inhaled beta2-adrenergic agonist, such as salbutamol, for the treatment of sudden breathlessness (bronchospasm) due to asthma.

If you have COPD and you are a smoker, it is important to quit smoking. This will help decrease the symptoms of COPD and potentially increase your lifespan.

How does TEVA-IPRATROPIUM STERINEBS work?
TEVA-IPRATROPIUM STERINEBS belongs to a group of medicines known as “bronchodilators”. They make breathing easier by opening your narrowed airways. This makes it easier for air to get in and out of the lungs.

What are the ingredients in TEVA-IPRATROPIUM STERINEBS?

Medicinal ingredients: ipratropium bromide
Non-medicinal ingredients: normal saline (9 mg/mL sodium chloride solution), hydrochloric acid

TEVA-IPRATROPIUM STERINEBS comes in the following dosage forms:
Inhalation solution; 250 mcg / mL, 500 mcg / 2 mL

Do not use TEVA-IPRATROPIUM STERINEBS if:

- you are allergic (hypersensitive) to ipratropium bromide, atropine or to any of the non-medicinal ingredients, or component of the container (see **What are the ingredients in TEVA-IPRATROPIUM STERINEBS?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-IPRATROPIUM STERINEBS. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning to become pregnant
- are breastfeeding. It is not known if ipratropium bromide passes into breastmilk.
- are taking other medications to treat your breathing problems, such as ipratropium, tiotropium, glycopyrronium, aclidinium or umeclidinium
- have trouble passing urine or painful urination
- have an enlarged prostate
- have eye problems, such as glaucoma (increased pressure in your eye) or eye pain

- have the lung disease cystic fibrosis (CF)

Other warnings you should know about:

Worsening of your COPD or Asthma Symptoms: While you are taking TEVA-IPRATROPUM STERINEBS, get immediate medical help if:

- you have sudden or worsening shortness of breath, increased wheezing or tightness in the chest or difficulty in breathing.
- your asthma symptoms have gotten worse and are not relieved by your rescue medicine, even if there is short-term relief after using TEVA-IPRATROPIUM STERINEBS.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TEVA-IPRATROPIUM STERINEBS:

- other medicines to treat breathing problems, such as ipratropium, tiotropium, glycopyrronium, aclidinium, umeclidinium

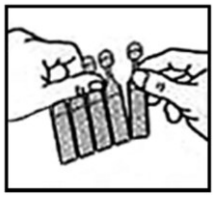
How to take TEVA-IPRATROPIUM STERINEBS:

- TEVA-IPRATROPIUM STERINEBS is for oral inhalation only.
- Take TEVA-IPRATROPIUM STERINEBS exactly how your healthcare professional has told you to.
- DO NOT use a higher dose than you have been prescribed or change the frequency of your treatments without talking to your healthcare professional.
- Before you start to use TEVA-IPRATROPIUM STERINEBS, read the Instructions for Use carefully. It is important that you are completely familiar with the use and proper care of your nebulizer.
- You must ensure that the nebulizer mask fits the face properly and that the nebulized solution does not escape into the eyes. If you have glaucoma you should use swimming goggles or a nebulizer with a mouthpiece to prevent the nebulized solution from getting into your eyes
- If you have any questions about using the nebulizer, talk to your healthcare professional.

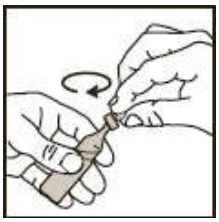
Instructions for Use:

- TEVA-IPRATROPIUM STERINEBS is to be used in a compressed air or oxygen driven nebulizer.
- Your healthcare professional will tell you how to prepare your TEVA-IPRATROPIUM STERINEBS solution for inhalation.
- If your dose of TEVA-IPRATROPIUM STERINEBS is less than 2 mL you might be told to dilute the TEVA-IPRATROPIUM STERINEBS solution with sterile saline before you use it to make 2 – 5 mL of solution to be nebulized.
- If you are told to dilute TEVA-IPRATROPIUM STREINEBS, you must do this immediately before using the solution.
- Only mix TEVA-IPRATROPIUM STERINEBS with other medicines in the nebulizer if your healthcare professional has told you to.

1. 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.

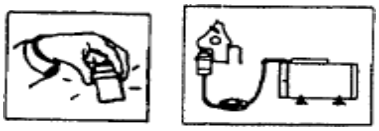


3. Squeeze the contents of the plastic vial into your nebulizer chamber. If your healthcare professional has told you to use less than one complete vial, use a syringe to withdraw the correct amount. Any solution left in the plastic vial must be thrown away.

4. If your healthcare professional has told you to use another inhalation solution in combination with TEVA-IPRATROPIUM STERINEBS, you should add the appropriate amount of that solution to the nebulizer chamber as well.

5. If your healthcare professional has told you to, add sodium chloride solution, use a syringe to add it to the nebulizer chamber as well.

6. 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.



7. 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.

8. Follow the instruction 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.

Usual dose:
Maintenance of COPD in Adults
The recommended dose is 500 mcg (2 vials of 250 mcg / mL or 1 vial of 500 mcg / 2mL) taken 3 -4 times per day.

Adults and children 12 years of age and older
The recommended single dose of TEVA-IPRATROPIUM STERINEBS is 250 mcg – 500 mcg (1 or 2 vials of 250 mcg / 1mL or 1 vial of 500 mcg / 2 mL).

Treatment may be repeated every 4 – 6 hours as needed.

The maximum recommended daily dose is 2 mg per day (8 vials of 250 mcg / mL or 4 vials of 500 mcg / 2 mL).

Children 5 to 12 years of age
The recommended single dose of TEVA-IPRATROPIUM STERINEBS is 125 mcg – 250 mcg (half a vial of 250 mcg / mL or 1 vial of 250 mcg / mL).

Treatment may be repeated every 4 – 6 hours as needed.

The maximum recommended daily dose is 1 mg per day (4 vials of 250 mcg / mL).

Overdose:

If you think you, or a person you are caring for, have taken too much **TEVA-IPRATROPIUM STERINEBS**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If a dose of this medication is missed, skip the missed dose and continue with the next scheduled dose. Do not take a double doses to make up for a missed dose.

What are possible side effects from using TEVA-IPRATROPIUM STERINEBS?
These are not all the possible side effects you may have when taking **TEVA-IPRATROPIUM STERINEBS**. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- dizziness
- constipation
- vomiting
- diarrhea
- nausea
- cough
- dry mouth
- irritation of mouth and/or throat
- hoarseness
- bad taste in the mouth
- tremor
- flushing
- skin rash
- trouble sleeping

If you experience a dry mouth or a bad taste, sucking on a sour candy or rinsing your mouth after taking TEVA-IPRATROPIUM STERINEBS may help.

Serious side effects and what to do about them			
Symptom /effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Sudden breathing problems (bronchospasm): increased wheezing or tightness in the chest, coughing, breathlessness			√
RARE			
Allergic reaction: rash, hives, swelling of the throat, tongue, lips or face, difficulty swallowing or breathing			√
Fast or irregular heart beat		√	
Eye problems: blurred vision, eye pain		√	
Difficult or painful urination		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected adverse reactions associated with the use of health products to health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

Keep out of reach and sight of children.

- Unopened unit dose vials of TEVA-IPRATROPIUM STERINEBS should be stored at room temperature (between 15°C and 30°C) and protected from light.
- Diluted solution should be used immediately.
- Any solution remaining in the vial must be discarded.

If you want more information about TEVA-IPRATROPIUM STERINEBS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html); the manufacturer's website www.tevacanada.com, or by calling 1-800-268-4127 ext. 5005.

This leaflet was prepared by: Teva Canada Limited, 30 Novopharm Court, Toronto, Ontario, Canada, M1B 2K9

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