PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBACA RESPICLICK™

salbutamol inhalation powder

97 mcg salbutamol (as salbutamol sulphate) per actuation

200 actuations

For oral inhalation

Bronchodilator
(beta$_2$-adrenergic agonist)

Distributed by:
Teva Canada Limited
Toronto, Ontario M1B 2K9

Date of Revision:
November 1, 2017

Manufactured for:
Teva Canada Innovation
Montreal, Quebec H2Z 1S8

Submission Control No: 189577

Table of Contents

[Pr]BACA RESPICLICK™
salbutamol inhalation powder

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral inhalation	Salbutamol (as salbutamol sulphate) inhalation powder 97 mcg per actuation	Lactose monohydrate (which contains milk protein).

INDICATIONS AND CLINICAL USE

Adults and Children (4 years and older)
BACA RESPICLICK™ (salbutamol) inhalation powder is indicated for

- the treatment and/ or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.
- the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Geriatrics (> 65 years of age):
There are limited data available on the use of BACA RESPICLICK in patients over 65 years old.

Pediatrics (< 4 years of age):
The efficacy and safety of BACA RESPICLICK in children below the age of 4 years has not been established.

CONTRAINDICATIONS

- Patients with known hypersensitivity to salbutamol or to any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with severe hypersensitivity to milk protein.
- As a tocolytic in patients at risk of premature labour or threatened abortion.

WARNINGS AND PRECAUTIONS

General
Patients should always carry their BACA RESPICLICK (salbutamol) inhalation powder to use immediately if an episode of asthma is experienced. If therapy does not produce a significant improvement or if the patient's condition worsens, medical advice must be sought to determine a new plan of treatment. In the case of acute or rapidly worsening dyspnea, healthcare professionals should be consulted immediately.

Excessive Use and Use with other Sympathomimetic
Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

DO NOT EXCEED RECOMMENDED DOSE.

Concomitant use of BACA RESPICLICK with other sympathomimetic agents is not recommended since the combined use may lead to deleterious cardiovascular effects. If concomitant use is necessary, this should take place only under strict medical supervision.

Use of Anti-Inflammatory Agents
The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

Cardiovascular
Like other beta-adrenergic agonists, BACA RESPICLICK can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with beta agonists. Care should be taken with patients suffering from cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.

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. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T-wave, prolongation of the QTc interval, and ST-segment depression. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin. Cardiac arrest was noticed in several instances.

Endocrine and Metabolism
As with other beta-agonists, BACA RESPICLICK may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation. Particular caution is advised in acute severe asthma since hypokalemia may be potentiated by concomitant treatment with xanthine derivatives, steroids and diuretics and 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.

BACA RESPICLICK, like all sympathomimetic amines, should be used with caution in patients with hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous salbutamol have been reported to aggravate preexisting diabetes mellitus and lead to the development of ketoacidosis. Concurrent administration of corticosteroids can exaggerate this effect.

Hypersensitivity Reactions
Immediate hypersensitivity reactions may occur after administration of salbutamol sulphate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

BACA RESPICLICK contains small amounts of lactose, which may contain trace levels of milk proteins. Hypersensitivity reactions including anaphylaxis, angioedema, pruritus, and rash have been reported with the use of therapies containing lactose. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving BACA RESPICLICK.

Neurologic
Care should be taken with patients with convulsive disorders.

Respiratory

Deterioration of Asthma
Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of BACA RESPICLICK than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Paradoxical Bronchospasm
As with other inhaled medications, paradoxical bronchospasm may occur that may be life threatening. If paradoxical bronchospasm occurs, characterized by an immediate increase in wheezing after dosing, BACA RESPICLICK should be discontinued immediately and alternative therapy instituted e.g. a different fast-acting inhaled bronchodilator to relieve acute asthmatic symptoms.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of BACA RESPICLICK or salbutamol sulphate in pregnant women. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity (see Toxicology, Teratogenicity studies). Seven patients became pregnant during clinical trials, including 5 patients treated with drug and 2 patients treated with placebo. One patient treated with placebo had a miscarriage.

Post-Marketing Experience in Pregnant Women: Human data are available from voluntary safety reporting during worldwide marketing experience. However, because these reactions are reported voluntarily from a population of unknown size; it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

During post marketing experience, various structural abnormalities, including cleft palate and limb defects, have been reported in the offspring of patients treated with salbutamol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of structural abnormalities can be discerned, and no relationship between salbutamol use and congenital anomalies has been established.

Since the data are insufficient to determine if there is any added risk to the fetus from salbutamol, BACA RESPICLICK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor or Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of BACA RESPICLICK for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

BACA RESPICLICK is contraindicated for the management of pre-term labour. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labour with $beta_2$-agonists, including salbutamol.

Nursing Women: It is not known whether salbutamol sulphate is excreted in human milk. There are no available data to assess the presence or absence of salbutamol in human milk, effects on the breast-fed child, or the effect of salbutamol on milk production. Because of the potential for tumorigenicity shown for salbutamol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drugs taking into account the benefit of the drug to the mother. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for salbutamol and any potential adverse effects on the breastfed child from salbutamol or from the underlying maternal condition.

Pediatrics (< 4 years of age):
The safety and effectiveness of BACA RESPICLICK in pediatric patients below the age of 4 years have not been established.

Geriatrics (> 65 years of age):
Clinical studies of BACA RESPICLICK did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. As with other $beta_2$-agonists, special caution should be observed when using BACA Respiclick in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug (see WARNINGS and PRECAUTIONS, CARDIOVASCULAR).

All $beta_2$-adrenergic agonists, including salbutamol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Monitoring and Laboratory Tests

Monitoring Control of Asthma
Failure to respond for at least three hours to a previously effective dose of BACA Respiclick indicates a deterioration of the condition and the physician should be contacted promptly. Patients should be warned not to exceed the recommended dose.

The increasing use of fast-acting, short duration inhaled $beta_2$-adrenergic agonists to control symptoms indicates deterioration of asthma control and the patient's therapy plan should be reassessed. In worsening asthma it is inadequate to increase $beta_2$-agonist use only, especially over an extended period of time. In the case of acute or rapidly worsening dyspnea, a doctor should be consulted immediately. Sudden or progressive deterioration in asthma control is potentially life threatening; the treatment plan must be re-evaluated, and consideration be given to corticosteroid therapy (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

As with other bronchodilator inhalation therapy, the potential for paradoxical bronchospasm should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Potentially serious hypokalemia may result from $beta_2$-agonist therapy primarily from parenteral and nebulised routes of administration (see WARNINGS and PRECAUTIONS, Endocrine and Metabolism).

Peripheral vasodilation and a compensatory small increase in heart rate may occur in some patients. Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported usually in susceptible patients.

Other adverse reactions associated with salbutamol are nervousness and tremor. In some patients inhaled salbutamol may cause a fine tremor of skeletal muscle, particularly in the hands. This effect is common to all $beta_2$-adrenergic stimulants. Adaptation occurs during the first few days of dosing and the tremor usually disappears as treatment continues.

In addition, salbutamol, like other sympathomimetic agents, can cause adverse effects such as drowsiness, flushing, restlessness, irritability, chest discomfort, difficulty in micturition, hypertension, angina, vomiting, vertigo, central nervous system stimulation, hyperactivity in children, unusual taste and drying or irritation of the oropharynx, headache, palpitations, transient muscle cramps, insomnia, nausea, weakness and dizziness.

Rarely, in children, hyperactivity occurs and occasionally, sleep disturbances, hallucination or atypical psychosis have been reported.

A total of 1289 subjects were treated with BACA RESPICLICK (salbutamol) during the clinical development program. The most common adverse reactions (≥1%) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection.

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.

Adults and Adolescents 12 years of Age and Older:

A total of 1456 adult and adolescents patients were included in the clinical program of whom 1120 received treatment with salbutamol.

The safety data described below for BACA RESPICLICK in adults and adolescents 12 years of age and older is derived from the 12-week double blind placebo-controlled trials which compared BACA RESPICLICK 194 mcg administered four times daily with a double-blinded matched placebo in 653 asthmatic patients 12 to 76 years of age. Table 1 displays the adverse reactions with an incidence ≥ 1% in BACA RESPICLICK treated patients and greater than placebo-treated patients.

Table 1: Adverse Reactions Experienced by ≥1.0% of Adult and Adolescent Patients in the BACA RESPICLICK Group and Greater Than Placebo in three 12-Week Clinical Trials*

Preferred Term	Number (%) of patients	
	BACA RESPICLICK 194 mcg QID N=321	Placebo QID N=333
Back pain	6 (2%)	4 (1%)
Pain	5 (2%)	2 (<1%)
Gastroenteritis viral	4 (1%)	3 (<1%)
Sinus headache	4 (1%)	3 (<1%)
Urinary tract infection	4 (1%)	3 (<1%)

*All adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of greater than or equal to 1.0% in the BACA RESPICLICK group and greater than placebo.

In a long-term study of 168 patients treated with BACA RESPICLICK for up to 52 weeks (including a 12-week double-blind period), the most commonly reported adverse events greater than or equal to 5% were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia.

In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.

Pediatric Patients Aged 4 to 11 Years:

The safety data for BACA RESPICLICK in pediatric patients 4 to 11 years of age is derived from the double-blind placebo controlled trial of 3 weeks which compared BACA RESPICLICK 194 mcg administered 4 times daily with a double blinded matched placebo in 185 asthmatic patients.

Table 2: Adverse Reactions Experienced by ≥2.0% of Patients 4 to 11 Years of Age in the BACA RESPICLICK Group and Greater Than Placebo in the 3 Week Trial

Preferred Term	Number (%) of patients	
	BACA RESPICLICK 194 mcg QID N=93	Placebo N=92
Nasopharyngitis	2 (2.2%)	1 (1.1%)
Oropharyngeal pain	2 (2.2%)	1 (1.1%)
Vomiting	3 (3.2%)	1 (1.1%)

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

Cardiac disorders: Palpitations

Gastrointestinal disorders: Dry mouth

General disorders and administration site conditions: Feeling jittery

Nervous system disorders: Headache, migraine and tremor

Respiratory, thoracic, and mediastinal disorders: Dysphonia and oropharyngeal pain.

Post-Market Adverse Drug Reactions

The following adverse events have been reported during postapproval use of salbutamol products: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles), rare cases of aggravated bronchospasm, muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In addition, salbutamol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 3 - Established or Potential Drug-Drug Interactions

Drug type	Ref	Effect	Clinical comment
Monoamine Oxidase Inhibitors or Tricyclic Antidepressants	CS	May potentiate action of salbutamol on cardiovascular system	Salbutamol 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 cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.
Other sympathomimetic bronchodilators or epinephrine	CS	May lead to deleterious cardiovascular effects.	Other sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol. 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.
Beta Blockers	CS	May antagonize the action of salbutamol and may produce severe bronchospasm in asthmatic patients	Beta-adrenergic blocking drugs especially the non cardioselective ones should not be prescribed with BACA RESPICLICK. BACA
Diuretics	CS	May lead to ECG changes and/or hypokalemia, although the clinical significance of these effect is not known	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. Caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.
Digoxin	CS	May lead to a decrease in serum digoxin levels. The clinical significance of these findings for patients with obstructive airway disease who are receiving salbutamol and digoxin on a chronic basis is unclear.	Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. It would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and BACA RESPICLICK.

Legend: C = Case Study

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
BACA RESPICLICK (salbutamol) inhalation powder is not recommended for children under 4 years of age.

The dosage for BACA RESPICLICK should be individualized and the patient's response should be monitored by a prescribing physician on an ongoing basis.

Increasing demand for inhaled salbutamol in bronchial asthma is usually a sign of poorly controlled or worsening asthma and indicates that the patient should be reevaluated and the treatment plan should be reviewed. If inhaled salbutamol treatment alone is not adequate to control asthma, concomitant anti-inflammatory therapy should be part of the treatment regimen (e.g., corticosteroids).

If a previously effective dose fails to provide the usual relief or the effects of a dose last for less than three hours, patients should seek prompt medical advice since this is usually a sign of worsening asthma.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice. However, if a more severe attack has not been relieved by the usual dose, additional doses may be required. In these cases, patients should immediately consult their doctors or the nearest hospital.

Recommended Dose and Dosage Adjustment

Bronchospasm:
For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the recommended dosage for adults and children 4 years of age or older is 2 inhalations (2 x 97 mcg) repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation (97 mcg) every 4 hours may be sufficient.
Maximum daily dose: 776 mcg, equivalent to 8 inhalations.

Exercise-Induced Bronchospasm:
For prevention of exercise-induced bronchospasm, the recommended dosage for adults and children 4 years of age or older is 2 inhalations (2 x 97 mcg) 15 to 30 minutes before exercise.
Maximum daily dose: 776 mcg, equivalent to 8 inhalations.

Missed Dose
If a single dose is missed, instruct the patient to take the next dose when it is due or if they become wheezy.

Administration

BACA RESPICLICK should be administered by the orally inhaled route only in patients aged 4 years and older.

The healthcare professional should instruct the patient as per the following points:

- BACA RESPICLICK does **not** require priming.
- Do not use BACA RESPICLICK with a spacer or volume holding chamber.
- **Do not open your BACA RESPICLICK cap unless you are taking your medication**. Repeated opening and closing the green cap without taking medication will waste medication and may damage the inhaler.
- **Immediately replace inhaler if mouthpiece cover is damaged or broken.**

- **Counter:** The BACA RESPICLICK inhaler has a counter.
  - When the patient receives the inhaler, the number 200 will be displayed. The counter will count down each time the mouthpiece is opened and closed. When the counter reaches 20, the color of the numbers will change to red to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the counter reaches 0, the background will change to solid red. Patients should never try to alter the numbers for the counter.
  - Instruct the patient to discard BACA RESPICLICK 13 months after opening the foil pouch, when the counter displays 0 or after the expiration date on the product, whichever comes first. See Part III: PATIENT MEDICATION INFORMATION and illustrated instructions for proper use.

- **Cleaning:**
  - Keep the inhaler clean and dry at all times. Never wash or put any part of your inhaler in water.
  - Gently wipe the mouthpiece with a dry cloth or tissue once a week.

OVERDOSAGE

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

Symptoms and Signs

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g. seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of BACA RESPICLICK.

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.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma (See Warnings and Precautions).

Treatment
Discontinue BACA RESPICLICK treatment and consider administration of appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of BACA RESPICLICK.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Salbutamol is a beta$_2$-adrenergic agonist. It acts as a functional antagonist to relax the smooth muscle of all airways, from the trachea to the terminal bronchioles, irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges.

The pharmacologic effects of salbutamol are attributable to activation of beta$_2$-adrenergic receptors on airway smooth muscle. Activation of beta$_2$-adrenergic receptors leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3',5' adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta$_2$-adrenergic receptors. The precise function of these receptors has not been established, but their presence raises the possibility that even selective beta$_2$-agonists may have cardiac effects.

Salbutamol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than the non-selective β_1-β_2–agonist isoproterenol at comparable doses while producing fewer cardiovascular effects. However, 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 electrocardiographic changes.

Pharmacodynamics

Primary Pharmacodynamics: Following 97 or 194 mcg single-dose inhalation, the bronchodilatory effect of BACA RESPICLICK was significantly greater than placebo in patients 12 years of age and older (N=71) and pediatric patients 4 to 11 years of age (N=61) with persistent asthma.

Secondary Pharmacodynamics: As with other beta$_2$-adrenergic agonists, BACA RESPICLICK prolonged QT intervals following a 1552 mcg cumulative dose.

Pharmacokinetics

Absorption: Salbutamol was rapidly absorbed into the systemic circulation with peak plasma concentrations occurring at half an hour following single- or multiple-dose oral inhalation(s) of BACA RESPICLICK.

Distribution: The volume of distribution has not been determined for BACA RESPICLICK. Published literature suggests that salbutamol exhibits low *in vitro* plasma protein binding (10%).

Metabolism: Information available in the published literature suggests that the primary enzyme responsible for the metabolism of salbutamol in humans is SULTIA3 (sulfotransferase). When racemic salbutamol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S)-salbutamol enantiomers, with (S)-salbutamol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-salbutamol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.
Elimination: The accumulation ratio (~1.6 fold) was observed following one week QID dosing. The corresponding effective half-life was approximately 5 hours, which was consistent with the elimination half-life following both single- or multiple-dose administration.

Excretion**:** The primary route of elimination of salbutamol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic salbutamol, between 25% and 46% of the (R)-salbutamol fraction of the dose was excreted as unchanged (R)-salbutamol in the urine.

Special Populations and Conditions

Age: No pharmacokinetic studies for BACA RESPICLICK have been conducted in neonates or elderly subjects. The systemic exposure in children 6 to 11 years of age is similar to that of adults following 194 mcg single dose inhalation of BACA RESPICLICK.

Sex: The influence of sex on the pharmacokinetics of BACA RESPICLICK has not been studied.

Race: The influence of race on the pharmacokinetics of BACA RESPICLICK has not been studied.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of BACA RESPICLICK has not been evaluated.

Renal Insufficiency: The effect of renal impairment on the pharmacokinetics of salbutamol was evaluated in 5 subjects with creatinine clearance of 7 to 53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in salbutamol clearance. Caution should be used when administering high doses of BACA RESPICLICK to patients with renal impairment.

STORAGE AND STABILITY

Store at room temperature between 15° and 30°C. Avoid exposure to extreme heat, cold, or humidity.

Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BACA RESPICLICK is an inhalation driven dry powder inhaler for oral inhalation that contains a formulation of salbutamol sulphate and lactose monohydrate. Each inhaler contains 0.65 g of the formulation and provides 200 actuations.

Each actuation provides 117 mcg of salbutamol sulphate (equivalent to 97 mcg of salbutamol base) delivered ex valve, equal to 108 mcg of salbutamol sulphate (90 mcg of salbutamol base) delivered from the mouthpiece.

Each inhaler has a red cap and is packaged individually in a foil pouch in a carton. The inhaler has a counter.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

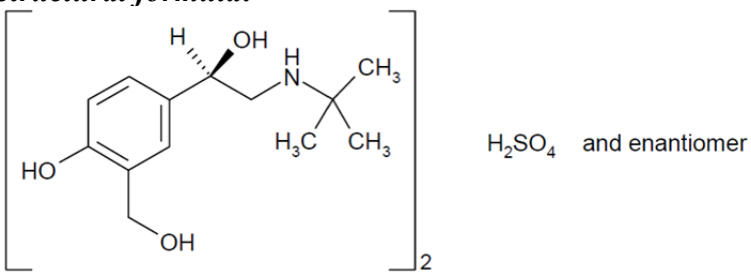
Drug Substance

Proper name: Salbutamol Sulphate

Chemical name: Bis[1RS]-2-[1,1-dimethylethyl)amino]-1-[4-hydroxy-3-(hydroxymethyl)phenyl]ethanol]sulphate
or
1,3-benzenedimethanol, α1-[[1,1-dimethylethyl)amino]methyl]-4-hydroxy-, sulphate (2:1) salt
or
α1-[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulphate (2:1) salt
[Module 3, Section 3.2.S.1.1 Nomenclature]

Molecular formula and molecular mass: $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ / 576.7 g/mol

Structural formula:



Physicochemical properties: A white or almost white crystalline powder. Freely soluble in water, practically insoluble or very slightly soluble in Methylene Chloride and Alcohol, slightly soluble in Chloroform and Ether. Does not show optical activity, as it is a racemic drug substance.

CLINICAL TRIALS

Bronchospasm Associated with Asthma

Adult and Adolescent Patients 12 Years of Age and Older

Patient Demographics and Trial design

The efficacy and safety of BACA RESPICLICK have been evaluated in two 12-week, randomized, double-blind, placebo-controlled studies of identical design (Study 1 and Study 2). BACA RESPICLICK (153 patients) was compared to a matched placebo dry powder inhaler (163 patients) in asthmatic patients 12 to 76 years of age at a dose of 194 mcg salbutamol four times daily (Table 4). Patients were maintained on inhaled corticosteroid treatment.

Table 4 - Summary of the Design and Patient Demographics of Studies 1 and 2 in Adults and Adolescents Patients with Bronchospasm (FAS)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender %M/F
Study 1	Phase 3, multicenter randomized, double blind placebo controlled, parallel group study in patients 12 years of age and older with persistent asthma	Salbutamol MDPI 194 mcg x 4 times daily Oral inhalation	n=78	37.26 (12-67)	45/55
		Placebo MDPI 4 times daily Oral inhalation	n=79	40.32 (12-70)	41/59
		12 weeks duration			
Study 2	Phase 3, multicenter randomized, double blind placebo controlled, parallel group study in patients 12 years of age and older with persistent asthma	Salbutamol MDPI 194 mcg x 4 times daily Oral inhalation	n=75	39.97 (12-74)	52/48
		Placebo MDPI 4 times daily Oral inhalation	n=84	36.52 (12-68)	46/54
		12 weeks duration			

Study results:

The primary efficacy variable was the baseline-adjusted FEV_1 $AUC_{0\text{-}6hr}$ over the 12-week treatment period. In both studies, there was a statistically significant difference from placebo (See Tables 5 and 6).

Table 5: Phase 3 Studies 1 and 2: Baseline-Adjusted FEV_1 $AUC_{0\text{-}6hr}$ (L*Hour) over the 12-Week Treatment Period (FAS)

Statistic	Study 1		Study 2	
	Placebo MDPI QID (N=79)	SB MDPI 194 mcg QID (N=78)	Placebo MDPI QID (N=84)	SB MDPI 194 mcg QID (N=75)
n	79	78	84	75
Estimated mean	0.28	1.11	0.38	1.30
Standard error	0.09	0.09	0.11	0.12
95% confidence interval	0.10, 0.46	0.92, 1.29	0.16, 0.61	1.06, 1.54

FEV_1 $AUC_{0\text{-}6hr}$=baseline-adjusted area under the FEV_1 (forced expiratory volume in 1 second) curve over 6 hours; FAS=Full analysis set; SB MDPI=Salbutamol Multidose Dry Powder Inhaler; QID=4 times a day; N=number of patients included in the FAS; n=number of patients included in the analysis.

Table 6: Phase 3 Studies 1 and 2: FEV_1 $AUC_{0\text{-}6hr}$ (L*Hour) Difference between Salbutamol MDPI versus Placebo Over the 12-Week Treatment Period (FAS)

Statistic	Salbutamol MDPI minus Placebo MDPI	
	Study 1	Study 2
Difference	0.83	0.92
Standard error	0.13	0.16
95% confidence interval	0.57, 1.08	0.59, 1.24
p-value	<0.0001	<0.0001

FEV_1 $AUC_{0\text{-}6hr}$=baseline-adjusted area under the FEV_1 (forced expiratory volume in 1 second) curve over 6 hours; FAS=Full analysis set; MDPI=Multidose Dry Powder Inhaler; QID=4 times a day.

Serial FEV_1 measurements, as shown in Figures 1 and 2, demonstrated that two inhalations of BACA RESPICLICK produced significantly greater improvement in FEV_1 $AUC_{0\text{-}6hr}$ over the pre-treatment value than placebo in Study 1. Consistent results were observed in Study 2.

Figure 1. Mean Day 1 Change from Baseline FEV_1 by Treatment and Time point (Study 1-Full Analysis Set)

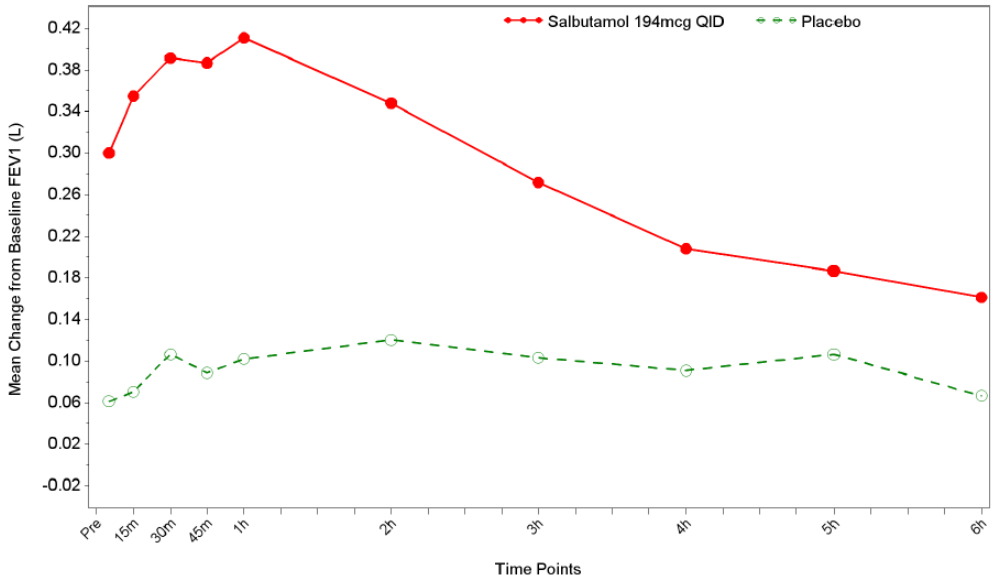
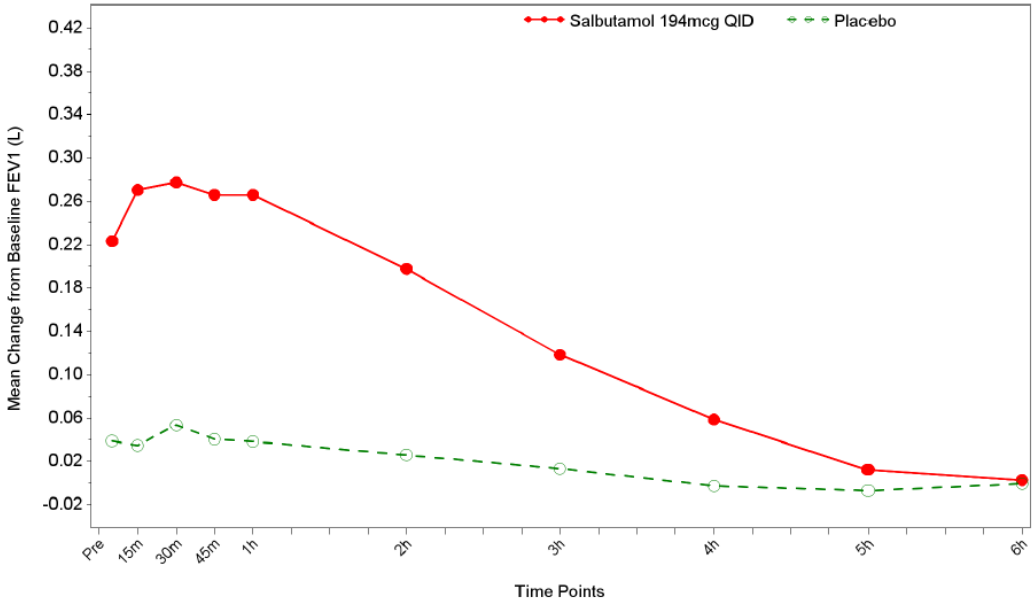


Figure 2: Mean Day 85 Change from Baseline FEV_1 by Treatment and Time point (Study 1-Full Analysis Set)



In Study 1, 44 of 78 patients treated with BACA RESPICLICK achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.7 minutes, and median duration of effect as measured by a 15% increase was approximately 2 hours. Consistent results were observed in Study 2.

The secondary endpoints in Study 1 and 2 were FEV_1 $AUC_{0\text{-}6hr}$ on days 1, 8 and 85 demonstrated the bronchodilatory effect of BACA RESPICLICK was largely maintained during the 12 week treatment period.

Pediatric Patients 4 to 11 Years of Age
In a 3-week, randomized, double-blind, placebo-controlled trial, BACA RESPICLICK (92 patients) was compared to a matched placebo (92 patients) in asthmatic children 4 to 11 years of age at a dose of 194 mcg salbutamol four times daily. Serial FEV_1 measurements, expressed as the baseline-adjusted percent-predicted FEV_1 $AUC_{0\text{-}6h}$ over the 3-week treatment period, demonstrated that 2 inhalations of BACA RESPICLICK produced significantly greater improvement in FEV_1 over the pre-treatment value than the matched placebo.

In this study, 48 of 92 patients treated with BACA RESPICLICK achieved a 15% increase in FEV_1 within 30 minutes post-dose on Day 1. The median time to onset was 5.9 minutes, and the median duration of effect as measured by a 15% increase was approximately 1 hour.

Exercise-Induced Bronchospasm
In a randomized, single-dose, crossover study in 38 adult and adolescent patients with exercise-induced bronchospasm (EIB), two inhalations of BACA RESPICLICK taken 30 minutes before exercise prevented EIB for the hour following exercise (defined as the maintenance of FEV_1 within 80% of post-dose, pre-exercise baseline values) in 97% (37 of 38) of patients as compared to 42% (16 of 38) of patients when they received placebo.

Patients who participated in these clinical trials were allowed to use concomitant steroid therapy.

DETAILED PHARMACOLOGY

Intravenous studies in rats with salbutamol sulphate have demonstrated that salbutamol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), salbutamol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings is unknown.

TOXICOLOGY

Acute Toxicity

Species (n)	Oral LD_{50}	Intravenous LD_{50}
Mouse (10)	> 2000 mg/kg	72 mg/kg
Rat (10)	> 2000 mg/kg	60 mg/kg

Rat (n)	Intraperitoneal LD_{50}
Newborn (155)	216 mg/kg
Weanling (100)	524 mg/kg
2 week old (90)	437 mg/kg

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.

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 1000 mcg 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 mesovarian leiomyomas. No similar tumors were seen in mice.

Mutagenicity
In vitro tests involving four micro-organisms revealed no mutagenic activity.

Carcinogenicity
In a two-year study in the rat, salbutamol sulphate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at doses corresponding to 111, 555, and

2,800 times the maximum human inhalation dose. In another study, the effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity.

Teratogenicity
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.

A reproduction study in CD-1 mice given salbutamol at doses of 0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 1.4, 14, and 140 times the maximum human aerosol dose respectively, showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. No cleft palates were observed at a dose of 0.025 mg/kg salbutamol. Cleft palate occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoprenaline (positive control).

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 human inhalation dose, cranioschisis was observed in 7 of 19 (37%) fetuses.

A reproduction study in New Zealand White rabbits using salbutamol sulfate/HFA-134a formulation, revealed enlargement of the frontal portion of the fontanelles in 6 of 95 (6%) and 15 of 107 (14%) fetuses at 28 and 149 mcg/kg, respectively (approximately 2/5 and 2 times, respectively, the maximum recommended human daily dose on a mg/m^2 basis), giving plasma levels of approximately 12 and 60 ng/mL, respectively.

REFERENCES

1. Libretto SE. A review of the toxicology of salbutamol (albuterol). Arch Toxicol. 1994; 68(4):213-6

2. Salbutamol: A review. Drugs 1971; 4:274-302.

3. Walle et al. Steroselective metabolism of RS-Albuterol in Humans. Clinical Reviews in Allergy and Immunology. 1996; (14): 101-113.

4. US-FDA Prescribing Information ProAir Respiclick dated September 2016.

5. Health Canada Product Monograph NOVO-SALBUTAMOL HFA dated 22 September 2016.

6. Albuterol multidose dry powder inhaler and albuterol hydrofluoroalkane versus placebo in children with persistent asthma. Qaqundah PY, Taveras H, Iverson H, Shore P. Allergy Asthma Proc. 2016 Sep;37(5):350-8. doi: 10.2500/aap.2016.37.3986.

7. Pharmacokinetics and pharmacodynamics of albuterol multidose dry powder inhaler and albuterol hydrofluoroalkane in children with asthma. Ratnayake A, Taveras H, Iverson H, Shore P. Allergy Asthma Proc. 2016 Sep;37(5):370-5. doi: 10.2500/aap.2016.37.3985. Epub 2016 Aug 12.

8. Novel albuterol multidose dry powder inhaler in patients with exercise-induced bronchoconstriction: A single-dose, double-blind, randomized, 2-way crossover study. Ostrom NK, Taveras H, Iverson H, Pearlman DS. Respir Med. 2015 Nov;109(11):1410-5. doi: 10.1016/j.rmed.2015.09.004. Epub 2015 Sep 8.

9. Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of Albuterol (Salbuterol) Multi-dose Dry-Powder Inhaler and ProAir(®) Hydrofluoroalkane for the Treatment of Persistent Asthma: Results of Two Randomized Double-Blind Studies. Kerwin EM, Taveras H, Iverson H, Wayne D, Shah T, Lepore MS, Miller DS. Clin Drug Investig. 2016 Jan;36(1):55-65. doi: 10.1007/s40261-015-0346-y.

10. Twelve- and 52-week safety of albuterol multidose dry powder inhaler in patients with persistent asthma. Raphael G, Taveras H, Iverson H, O'Brien C, Miller D. J Asthma. 2016;53(2):187-93. doi: 10.3109/02770903.2015.1070862. Epub 2015 Sep 15.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

BACA RESPICLICK
(salbutamol inhalation powder)

Read this carefully before you start taking **BACA RESPICLICK** or start administering it to a child. 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 **BACA RESPICLICK.**

What is BACA RESPICLICK used for?
BACA RESPICLICK is used in adults and children of 4 years and older to:

- treat and/or prevent bronchospasm in patients who have narrowing of the airways and,
- prevent exercise-induced bronchospasm.

Bronchospasm is a sudden worsening of shortness of breath and wheezing.

The safety and efficacy of BACA RESPICLICK in children under 4 years of age has not been established.

How does BACA RESPICLICK work?
Salbutamol is one of a group of medicines called bronchodilators. Salbutamol relaxes the muscles in the walls of the small air passages in the lungs. This helps to open up the airways and relieve chest tightness, wheezing and cough so that you can breathe more easily.

What are the ingredients in BACA RESPICLICK?
Medicinal ingredients: salbutamol (as salbutamol sulphate).
Non-medicinal ingredients: lactose monohydrate (which contains milk proteins).

BACA RESPICLICK comes in the following dosage forms:

- Inhalation powder.
- Each actuation contains 97 mcg salbutamol base (equivalent to 117 mcg of salbutamol sulphate).
- Each inhaler has a red cap, contains a minimum of 200 actuations (inhalations) and has a counter which displays the number of actuations (inhalations) remaining.

Do not use BACA RESPICLICK if:

- You are allergic to salbutamol sulphate, lactose or milk protein, or any component of the container.
- You are having preterm labour or are at risk for a miscarriage. BACA RESPICLICK has the potential to affect the way the uterus contracts.

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

- have ever had to stop taking other medicines for your condition because you were allergic to them or they caused problems.
- have a heart problem, irregular heart beat or high blood pressure (hypertension).
- have convulsions (seizures).
- have been told that you are allergic to lactose or milk protein.
- have thyroid problems.
- have kidney problems.
- have high blood sugar (diabetes).
- have low potassium levels in your blood, especially if you are taking:
    - drugs known as xanthine derivatives (such as theophylline)
    - steroids to treat asthma
    - water pills (diuretics)
- have any other medical conditions.
- are pregnant or plan to become pregnant. Taking BACA RESPICLICK may cause harm to your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if BACA RESPICLICK passes into your breast milk and whether it may harm your baby. Talk to your doctor about the best way to feed your baby if you are using BACA RESPICLICK.

Other warnings you should know about:

- You should always carry your inhaler with you. You may need to use it immediately in case you experience a sudden worsening of shortness of breath and wheezing.
- See your doctor as soon as possible if your condition does not improve or if it worsens while you are taking BACA RESPICLICK. Get medical help right away if your shortness of breath gets really bad very quickly.
- **Excessive use**: Some patients have died when using an excessive amount of their inhalers that are of a specific type like salbutamol. The exact cause of death is unknown. Be sure to only take BACA RESPICLICK as recommended by your doctor. Your doctor will monitor you if you need to take a drug that is similar to BACA RESPICLICK at the same time you are taking BACA RESPICLICK.
- You may also need to take anti-inflammatory medicines while you take BACA RESPICLICK to better help control your asthma.
- **Severe wheezing (paradoxical bronchospasm):** as with other inhaled medicines, you may develop severe wheezing after taking BACA RESPICLICK. This could be life-threatening. If this happens, stop taking BACA RESPICLICK right away and seek medical help. You will need to use a different medication to help relieve your symptoms. Severe wheezing frequently happens with the first use of a new inhaler.
- **Elderly patients:** if you are elderly, your doctor may adjust your dose and/or monitor your kidneys while you are taking BACA RESPICLICK.

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

Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

You and your healthcare provider will discuss whether it is appropriate for you to continue to receive your medications, or change your treatment plan.

The following may interact with BACA RESPICLICK:

- other inhaled medicines or asthma medicines
- epinephrine
- beta blocker medicines used to lower blood pressure (propranolol, metoprolol, etc.)
- diuretics ("water pills")
- digoxin, a heart medication
- anti-depressants

How to USE BACA RESPICLICK:

- BACA RESPICLICK is for oral inhalation only.
- Use BACA RESPICLICK exactly as your doctor tells you to use it.
- Do not use a spacer or volume holding chamber with BACA RESPICLICK.
- BACA RESPICLICK **does not** need priming.
- If your child needs to use BACA RESPICLICK, watch them closely to make sure they use the inhaler correctly. Your doctor will show you how your child should use BACA RESPICLICK.
- Get medical help right away if:
    - the effects of one dose last less than 3 hours;
    - you notice a sudden worsening of your shortness of breath;
    - your symptoms gets worse;
    - your usual dose does not provide relief of wheezing or chest tightness;
    - you need to use BACA RESPICLICK more often than before;

  These may be signs that your asthma or chest condition is getting worse. Your doctor may want to reassess your treatment plan.

- Do not increase the dose or the number of times you use your medicine without asking your doctor, as this may make you feel worse.
- **Do not** use other inhaled rescue and asthma medicines unless your doctor tells you to do so.

Usual dose:
Adults and Children 4 years of age and older

- Each dose is equal to 2 actuations (inhalations).
    - **To relieve bronchospasm:** 2 actuations (inhalations) as needed. If you have a more severe attack, you can repeat the dose every 4 to 6 hours, and immediately consult your doctor or the nearest hospital.

- **To prevent bronchospasm:** 2 actuations (inhalations) repeated every 4 to 6 hours as needed up to a maximum three or four times a day, as prescribed by your doctor.

- **To prevent bronchospasm caused by exercise:** 2 actuations (inhalations) 15 to 30 minutes before exercise.

- **Maximum daily dose:** 8 actuations (inhalations) per day.

Instructions for Use:

About the inhaler:
When you are ready to use BACA RESPICLICK for the first time, remove the inhaler from the foil pouch.

There are 2 main parts of the inhaler including (see Figure A):
- the white inhaler with the mouthpiece.
- the red dust cap that covers the mouthpiece of the inhaler.

There is a counter in the back of the inhaler with a viewing window that shows you how many actuations of medicine you have left.

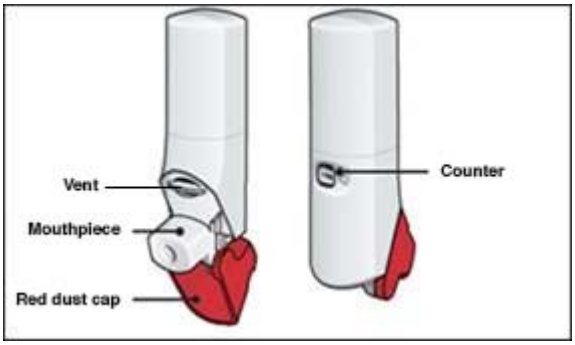


Figure A

About the counter:
- The inhaler contains '200' actuations (inhalations) (see Figure B).
- The counter on the back of your inhaler shows how many actuations (inhalations) you have remaining.
- When there are 20 actuations (inhalations) left, the counter will change to red and you should refill your prescription or ask your doctor for another prescription.
- Bring your inhaler to your pharmacy for safe disposal:
  - 13 months after removing it from the foil pouch for the first time OR
  - when the dose counter displays '0' OR
  - after the expiration date on the package, whichever comes first.

Figure B

IMPORTANT POINTS TO REMEMBER ABOUT USING YOUR INHALER:

- Always close the cap after each actuation (inhalation) so your inhaler will be ready for you to take your next dose.
- Do not open the cap unless you are ready for your next dose. Opening and closing the cap a lot without inhaling will waste the medicine and may damage your inhaler.
- BACA RESPICLICK does not have an activation button or medicine canister. When you open the cap, the inhaler will be ready to deliver the medicine.
- You will hear a "click" sound when the cap is opened fully. If you do not hear the "click" sound the inhaler may not deliver the medicine.
- In general, children will take BACA RESPICLICK in a similar way as for adults. Supervise your child when they use BACA RESPICLICK.
- Your BACA RESPICLICK inhaler contains dry powder so it is important that you do not blow or breathe into it.

Step-by-step instructions

Important: Make sure the cap is closed before you start.

Step 1: Open

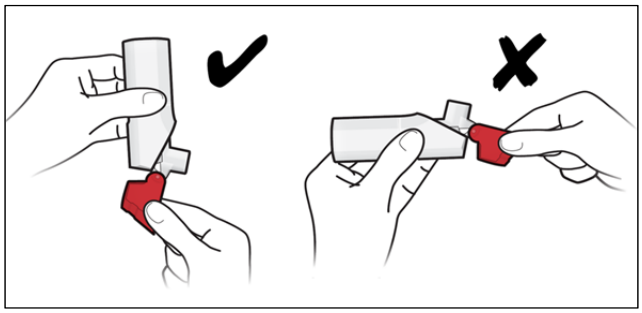


Figure C

Hold the inhaler upright as you open the red cap.

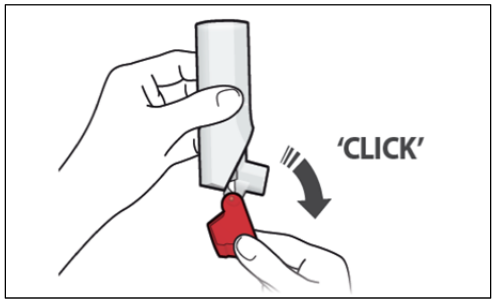


Figure D

- Open the red cap all the way back until you feel and hear a "click".
- Every time the red cap is opened and it clicks, **one actuation is ready**.
- Do not open the red cap unless you are ready to use the inhaler.

Step 2: Inhale

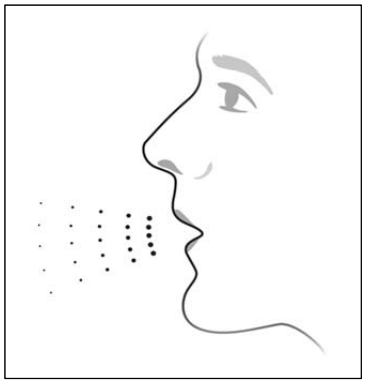


Figure E

- Breathe out fully away from the inhaler before inhaling. **Never breathe out into the inhaler mouthpiece.**

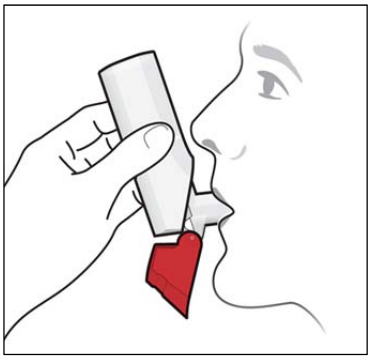


Figure F

- **Place the mouthpiece in your mouth and close your lips around it so you form a good seal.**
- **Do not block the vent above the mouthpiece with your lips or fingers.**
- **Breathe in quickly and deeply through your mouth,** until your lungs feel completely full of air.
- Remove the inhaler from your mouth.
- Hold your breath for about 10 seconds or for as long as you comfortably can.
- Your BACA RESPICLICK inhaler delivers your medicine as a very fine powder that you may or may not taste or feel. **Do not** take an extra actuation from the inhaler even if you do not taste or feel the medicine.

Step 3: Close

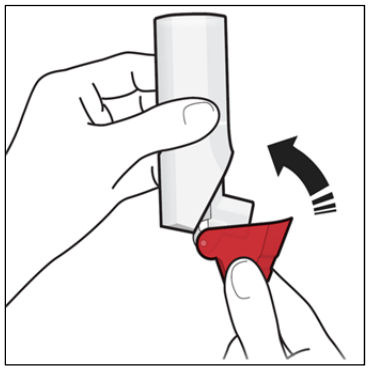


Figure G

- Close the red cap after inhaling to reload your next actuation.
- If you need another actuation, repeat steps 1-3.

- If you do not need another actuation, keep the cap closed until it is time to take your next dose.

Cleaning your BACA RESPICLICK Inhaler

- **Do not wash or put any part of your BACA RESPICLICK inhaler in water.**
- BACA RESPICLICK contains a powder and must be kept clean and dry at all times.
- Once a week, gently wipe with a dry cloth or tissue.

Overdose:

If you think you have taken too much BACA RESPICLICK contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take the next dose when it is due or if you become wheezy.

What are possible side effects from using BACA RESPICLICK?

These are not all the possible side effects you may feel when taking BACA RESPICLICK.

The most common side effects of BACA RESPICLICK include:

Effects on heart

- High blood pressure

Effects on nervous system

- Sinus headache
- Feeling restless
- Feeling irritable
- Feeling tired or weak
- Trouble sleeping (insomnia)
- Shakiness
- Nervousness
- Hyperactivity in children
- Dizziness
- Drowsiness

Effects on muscles and joints

- Back pain, body aches and pain

Other Effects

- Chest pain
- Runny nose
- Unusual taste in the mouth
- Dry or irritated throat
- Difficulty urinating
- Upset stomach, including feeling nauseous and vomiting
- Urinary tract infection

Rarely, children treated with salbutamol were hyperactive, and they sometimes had trouble sleeping, or had hallucinations.

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all of the possible side effects of BACA RESPICLICK. For more information, ask your doctor or pharmacist.

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	
UNCOMMON			
Irregular heart beat: (palpitations).		√	
Faster heart beat than usual.		√	
VERY RARE			
Paradoxical Bronchospasm: worsening of shortness of breath, coughing and wheezing shortly after using BACA RESPICLICK.			√
Allergic Reactions: sudden wheeziness and chest pain or tightness; or swelling of eyelids, face, lips, tongue or throat.			√
Irregular Heart Beat: (atrial fibrillation, supraventricular tachycardia, extrasystoles).		√	
RARE			
Low Blood Potassium (hypokalemia): muscle weakness and muscle spasms.		√	
Hallucinations in Children: see or hear things that are not there.		√	

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

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting: (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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:

- Store BACA RESPICLICK at room temperature between 15ºC and 30ºC.
- Avoid exposure to extreme heat, cold, or humidity.
- Keep the red cap on the inhaler closed during storage.
- Keep your BACA RESPICLICK inhaler dry and clean at all times.
- **Keep out of reach and sight of children.**

If you want more information about BACA RESPICLICK:

- 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/drug-product-database.html); Teva Canada Innovation site at http://www.tevacanadainnovation.ca
- or by contacting the sponsor, Teva Canada Innovation at: 1-855-514-8382.

This leaflet was prepared by Teva Canada Innovation.

BACA RESPICLICK™ is a trademark of Ivax International B.V., a member of the Teva Group; used under license.

Last Revised: November 1, 2017