NOVARTIS

Tradename(s)

ATECTURA® BREEZHALER® (indacaterol/mometasone furoate) 150/80 micrograms inhalation powder, hard capsules

ATECTURA® BREEZHALER® (indacaterol/mometasone furoate) 150/160 micrograms inhalation powder, hard capsules

ATECTURA® BREEZHALER® (indacaterol/mometasone furoate) 150/320 micrograms inhalation powder, hard capsules

1 Description and composition

Pharmaceutical form(s)

Indacaterol/mometasone furoate 150/80 micrograms, inhalation powder, hard capsules.
Capsules with natural transparent (uncolored) cap and body containing a white to practically white powder, with the product code "IM150-80" printed in blue on the body and the "◈" printed in blue on the cap.

Indacaterol/mometasone furoate 150/160 micrograms, inhalation powder, hard capsules.
Capsules with natural transparent (uncolored) cap and body containing a white to practically white powder, with the product code "M150-160" printed in grey on the body and the "◈" printed in grey on the cap.

Indacaterol/mometasone furoate 150/320 micrograms, inhalation powder, hard capsules.
Capsules with natural transparent (uncolored) cap and body containing a white to practically white powder, with the product code "IM150-320" printed in black on the body and the "◈" printed in black on the cap.

Active substance(s)

Each capsule of Atectura Breezhaler 150/80 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 80 micrograms of mometasone furoate.

Each capsule of Atectura Breezhaler 150/160 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 160 micrograms of mometasone furoate.

Each capsule of Atectura Breezhaler 150/320 micrograms, contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 320 micrograms of mometasone furoate

The delivered dose of Atectura Breezhaler 150/80 micrograms (the dose that leaves the mouthpiece of the inhaler) is equivalent to 125 micrograms indacaterol, and 62.5 micrograms mometasone furoate.

The delivered dose of Atectura Breezhaler 150/160 micrograms (the dose that leaves the mouthpiece of the inhaler) is equivalent to 125 micrograms indacaterol, and 127.5 micrograms mometasone furoate.

The delivered dose of Atectura Breezhaler 150/320 micrograms (the dose that leaves the mouthpiece of the inhaler) is equivalent to 125 micrograms indacaterol, and 260 micrograms mometasone furoate.

Excipients

Capsule fill: Lactose (as monohydrate).

Capsule shell components: Gelatin.

2 Indications

Atectura Breezhaler is indicated as a once-daily maintenance treatment of asthma in adults and adolescents 12 years of age and older where use of a combination of long-acting beta$_2$-agonist and inhaled corticosteroid is appropriate.

3 Dosage regimen and administration

Dosage regimen

General target population

Inhalation of the content of one capsule of Atectura Breezhaler 150/80 micrograms once daily is recommended in patients who require a combination of a long-acting beta$_2$-agonist and a low dose of inhaled corticosteroid.

Inhalation of the content of one capsule of Atectura Breezhaler 150/160 micrograms or 150/320 micrograms once-daily is recommended in patients who require a combination of a long-acting beta$_2$-agonist and a medium or high dose of inhaled corticosteroid.

Patients usually experience an improvement in lung function within 5 minutes of inhaling Atectura Breezhaler. However, the patient should be informed that regular daily use is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

The maximum recommended dose is Atectura Breezhaler 150/320 micrograms once daily.

Special populations

Renal impairment

No dose adjustment is required in patients with renal impairment.

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for Atectura Breezhaler in subjects with severe hepatic impairment, therefore Atectura Breezhaler should be used in these patients only if the expected benefit outweighs the potential risk (see section 11 Clinical pharmacology).

Pediatric patients (below 12 years)

Atectura Breezhaler may be used in pediatric patients (12 years of age and older) at the same posology as in adults. The safety and efficacy of Atectura Breezhaler in pediatric patients below 12 years of age have not been established.

Geriatric patients (65 years or above)

No dose adjustment is required in elderly patients 65 years of age or older (see section 11 Clinical pharmacology).

Method of administration

For inhalation use only. Atectura Breezhaler capsules must not be swallowed.

Patients should be instructed on how to administer the medicinal product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the capsule rather than inhaling it.

The capsules must be administered only using the Atectura Breezhaler inhaler. The inhaler provided with each new prescription should be used.

Atectura Breezhaler should be administered at the same time of the day each day. It can be administered irrespective of the time of the day.

The capsules must always be stored in the blister to protect from moisture and light, and only removed immediately before use (see section 14 Pharmaceutical information).

After inhalation, patients should rinse their mouth with water without swallowing.

If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day.

4 Contraindications

Atectura Breezhaler is contraindicated in patients with hypersensitivity to any of the active substances or excipients.

5 Warnings and precautions

Deterioration of disease

Atectura Breezhaler should not be used to treat acute asthma symptoms including acute episodes of bronchospasm, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop Atectura Breezhaler treatment without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with Atectura Breezhaler. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with Atectura Breezhaler.

Hypersensitivity

Immediate hypersensitivity reactions have been observed after administration of Atectura Breezhaler. If signs suggesting allergic reactions occur, in particular angioedema (including difficulties in breathing or swallowing, swelling of the tongue, lips, and face), urticaria, or skin rash, Atectura Breezhaler should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

As with other inhalation therapy, administration of Atectura Breezhaler may result in paradoxical bronchospasm which can be life-threatening. If paradoxical bronchospasm occurs, Atectura Breezhaler should be discontinued immediately and alternative therapy instituted.

Cardiovascular effects of beta agonists

Like other medicinal products containing beta$_2$-adrenergic agonists, Atectura Breezhaler may produce a clinically significant cardiovascular effect in some patients as measured by increases in

pulse rate, blood pressure, and/or symptoms. If such effects occur, treatment may need to be discontinued.

Atectura Breezhaler should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

While beta$_2$-adrenergic agonists have been reported to produce electrocardiographic (ECG) changes, such as flattening of the T wave, prolongation of QT interval, and ST segment depression, the clinical significance of these findings is unknown.

Therefore, long-acting beta$_2$-adrenergic agonists (LABA) or LABA containing combination products such as Atectura Breezhaler should be used with caution in patients with known or suspected prolongation of the QT interval or who are treated with medicinal products affecting the QT interval.

Hypokalemia with beta agonists

Beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. In patients with severe condition, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias (see section 8 Interactions).

Clinically relevant hypokalemia has not been observed in clinical studies of Atectura Breezhaler at the recommended therapeutic dose.

Hyperglycemia

Inhalation of high doses of beta$_2$-adrenergic agonists and corticosteroids may produce increases in plasma glucose. Upon initiation of treatment with Atectura Breezhaler, plasma glucose should be monitored more closely in diabetic patients.

Prevention of oropharyngeal infections

In order to reduce the risk of oropharyngeal candida infection, patients should be advised to rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling the prescribed dose.

Systemic effects of corticosteroids

Systemic effects may occur with inhaled corticosteroids, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations.

Possible systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataracts, glaucoma, and, more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is therefore important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control of asthma is maintained.

Visual disturbance may be reported with systemic and topical (including intranasal, inhaled and intraocular) corticosteroid use. Patients presenting with symptoms such as blurred vision or other visual disturbances should be considered for referral to an ophthalmologist for evaluation of possible causes of visual disturbances, which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Atectura Breezhaler should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

6 Adverse drug reactions

Summary of the safety profile

The safety profile of Atectura Breezhaler was based on safety data from three phase 3 studies with a total of 2497 adult or adolescent patients with asthma treated with Atectura Breezhaler 150/80, 150/160 or 150/320 micrograms once daily for up to 52 weeks.

The most common adverse drug reaction related to Atectura Breezhaler was headache.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions are listed by MedDRA system organ class. The frequency of the ADRs are based on the 52-week clinical study PALLADIUM (Table 7-1). Similar adverse event profile was observed in a 12-week clinical study (QUARTZ) except that no events of angioedema, myalgia, rash or tachycardia were observed. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 6-1 Estimated cumulative incidence (%) of adverse drug reactions in study PALLADIUM at 52 weeks

Adverse drug reactions	Atectura Breezhaler		Mometasone furoate		Frequency category [based on the higher frequency between the two arms]
	150/160 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=437	150/320 micrograms once daily High dose Rate (%) [number of events] (95% CI) N=443	400 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=443	400 micrograms twice daily High dose Rate (%) [number of events] (95% CI) N=440	
Infections and infestations					
Candidiasis*[1]	0.48 [2] (0.10, 1.63)	0.25 [1] (0.02, 1.34)	1.25 [5] (0.48, 2.75)	0.71 [5] (0.20, 1.94)	Uncommon
Immune system disorders					
Hypersensitivity*[2]	1.20 [6] (0.46, 2.64)	1.88 [8] (0.89, 3.53)	2.26 [10] (1.12, 4.10)	0 [0]	Common
Angioedema*[3]	0.47 [2] (0.10, 1.58)	0 [0]	0.48 [2] (0.10, 1.62)	0.48 [2] (0.10, 1.62)	Uncommon
Metabolism and nutrition disorders					
Hyperglycaemia*[4]	0.98 [4] (0.33, 2.36)	0.97 [5] (0.33, 2.33)	1.52 [6] (0.63, 3.13)	0.23 [1] (0.02, 1.21)	Uncommon
Nervous system disorders					
Headache*[5]	5.29 [25] (3.42, 7.73)	6.22 [39] (4.18, 8.82)	5.84 [33] (3.85, 8.40)	5.75 [37] (3.79, 8.27)	Common

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Cardiac disorders					
Tachycardia*[6]	0.23 [1] (0.02, 1.25)	0.73 [3] (0.21, 2.00)	0.25 [1] (0.02, 1.31)	0.25 [1] (0.02, 1.32)	Uncommon
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal Pain*[7]	1.92 [9] (0.91, 3.60)	3.11 [14] (1.74, 5.10)	2.87 [14] (1.57, 4.81)	2.41 [10] (1.24, 4.24)	Common
Dysphonia	1.64 [7] (0.73, 3.22)	1.86 [9] (0.88, 3.49)	0.69 [3] (0.19, 1.88)	0.68 [4] (0.19, 1.88)	Common
Skin and subcutaneous tissue disorders					
Rash*[8]	0 [0]	0.93 [4] (0.31, 2.23)	0.51 [2] (0.10, 1.71)	0 [0]	Uncommon
Pruritus*[9]	0.25 [1] (0.02, 1.32)	0.48 [2] (0.10, 1.62)	0.71 [3] (0.20, 1.96)	0 [0]	Uncommon
Musculoskeletal and connective tissue disorders					
Musculoskeletal Pain*[10]	4.53 [24] (2.83, 6.83)	2.65 [11] (1.41, 4.54)	2.16 [9] (1.07, 3.91)	2.62 [17] (1.39, 4.50)	Common
Muscle Spasms	0.47 [2] (0.10, 1.58)	0.47 [2] (0.10, 1.57)	0 [0]	0.72 [3] (0.20, 1.96)	Uncommon

* Indicates grouping of preferred terms (PTs) observed in the three Phase 3 studies.

[1] oral candidiasis, oropharyngeal candidiasis.

[2] drug eruption, drug hypersensitivity, hypersensitivity, rash, rash erythematous, rash pruritic, urticaria.

[3] allergic oedema, angioedema, periorbital swelling, swelling of eyelid.

[4] blood glucose increased, hyperglycaemia.

[5] headache, tension headache.

[6] heart rate increased, tachycardia, sinus tachycardia, supraventricular tachycardia.

[7] oral pain, oropharyngeal discomfort, oropharyngeal pain, throat irritation, odynophagia.

[8] drug eruption, rash, rash erythematous, rash pruritic.

[9] anal pruritus, eye pruritus, nasal pruritus, pruritus, pruritus genital.

[10] back pain, musculoskeletal pain, myalgia, neck pain, musculoskeletal chest pain.

7 Interactions

Interactions linked to Atectura Breezhaler

No specific interaction studies were conducted with Atectura Breezhaler. Information on the potential for interactions is based on the potential for each of the monotherapy components.

Clinically significant pharmacokinetic drug interactions mediated by Atectura Breezhaler at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Concomitant administration of orally inhaled indacaterol and mometasone furoate under steady-state conditions did not affect the pharmacokinetics of either active substances.

Medicinal products known to prolong the QTc interval

Atectura Breezhaler, like other medicinal products containing beta$_2$-adrenergic agonists, should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants or medicinal products known to prolong the QT interval, as any effect of these on the QT interval may be potentiated. Medicinal products known to prolong the QT interval may increase the risk of ventricular arrhythmia (see section 6 Warnings and precautions).

Hypokalemic treatment

Concomitant treatment with methylxanthine derivatives, steroids or non-potassium-sparing diuretics may potentiate the possible hypokalemic effect of beta$_2$-adrenergic agonists (see section 6 Warnings and precautions).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonize the effect of beta$_2$-adrenergic agonists. Therefore, Atectura Breezhaler should not be given together with beta-adrenergic blockers unless there are compelling reasons for their use. Where required, cardioselective beta-adrenergic blockers should be preferred, although they should be administered with caution.

Interaction with CYP3A4 and P-glycoprotein inhibitors

Inhibition of CYP3A4 and P-glycoprotein (P-gp) has no impact on safety of therapeutic doses of Atectura Breezhaler.

Inhibition of the key contributors of indacaterol clearance (CYP3A4 and P-gp) or mometasone furoate clearance (CYP3A4) raises the systemic exposure of indacaterol or mometasone furoate up to two-fold.

The magnitude of exposure increases for indacaterol due to interactions does not raise any safety concerns given the safety experience of treatment with indacaterol in clinical studies of up to one year at doses of 600 micrograms.

Due to the very low plasma concentration achieved after inhaled dosing, clinically significant drug interactions with mometasone furoate are unlikely. However, there may be a potential for increased systemic exposure to mometasone furoate when strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, nelfinavir, ritonavir, cobicistat) are co-administered.

Other long acting beta$_2$-adrenergic agonists

The co-administration of Atectura Breezhaler with other medicinal products containing long-acting beta$_2$-adrenergic agonists has not been studied and is not recommended as it may potentiate adverse reactions (see sections 7 Adverse drug reactions and 10 Overdosage).

8 Pregnancy, lactation, females and males of reproductive potential

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of Atectura Breezhaler or its individual components (indacaterol and mometasone furoate) in pregnant women to inform a drug-associated risk.

Indacaterol was not teratogenic in rats or rabbits following subcutaneous administration (see Animal data). In animal reproduction studies with pregnant mice, rats and rabbits, mometasone furoate caused increased fetal malformations and decreased fetal survival and growth.

Atectura Breezhaler should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control.

Labor and Delivery

Like other medicinal products containing beta$_2$-adrenergic agonists, indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle.

Animal data

The combination of indacaterol and mometasone furoate has not been studied in pregnant animals.

Indacaterol

Following subcutaneous administration in a rabbit study, adverse effects of indacaterol with respect to pregnancy and embryonal/fetal development could only be demonstrated at doses more than 500-fold than achieved following the daily inhalation of 150 micrograms in humans (based on $AUC_{0\text{-}24h}$). Although indacaterol did not affect general reproductive performance in a rat fertility study, a decrease in the number of pregnant F1 offspring was observed in the peri- and post-natal developmental rat study.

Mometasone furoate

Like other glucocorticoids, mometasone furoate is a teratogen in rodents and rabbits. Effects noted were umbilical hernia in rats, cleft palate in mice and gallbladder agenesis, umbilical hernia and flexed front paws in rabbits. There were also reductions in maternal body weight gains, effects on fetal growth (lower fetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice. In studies of reproductive function, subcutaneous mometasone furoate at 15 micrograms/kg prolonged gestation and difficult labor occurred with a reduction in offspring survival and body weight.

8.2 Lactation

Risk summary

There is no information available on the presence of indacaterol or mometasone furoate in human milk, on the effects on a breastfed child, or on the effects on milk production. Other inhaled corticosteroids, similar to mometasone furoate, are transferred into human milk. Indacaterol (including its metabolites) and mometasone furoate have been detected in the milk of lactating rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Atectura Breezhaler and any potential adverse effects on the breast-fed child from Atectura Breezhaler or from the underlying maternal condition

8.3 Females and males of reproductive potential

Infertility

Reproduction studies and other data in animals did not indicate a concern regarding fertility in either males or females.

9 Overdosage

There is limited experience with overdose in clinical studies with Atectura Breezhaler. General supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

An overdose will likely produce signs, symptoms or adverse effects associated with the pharmacological actions of the individual components (e.g. tachycardia, tremor, palpitations, headache, nausea, vomiting, drowsiness, ventricular arrhythmias, metabolic acidosis, hypokalemia, hyperglycemia, suppression of hypothalamic pituitary adrenal axis function). Use of cardioselective beta blockers may be considered for treating $beta_2$-adrenergic effects, but only under the supervision of a physician and with extreme caution since the use of beta-adrenergic blockers may provoke bronchospasm. In serious cases, patients should be hospitalized.

10 Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Long-acting inhaled therapy (beta-agonists and glucocorticosteroids)

Mechanism of action (MOA)

Atectura Breezhaler is a combination of indacaterol, a long-acting $beta_2$-adrenergic agonist (LABA), and mometasone furoate, an inhaled synthetic corticosteroid (ICS). Following oral inhalation, indacaterol acts locally on airways to produce bronchodilation and mometasone furoate reduces pulmonary inflammation.

Indacaterol

Indacaterol is a long-acting $beta_2$-adrenergic agonist for once-daily administration. The pharmacological effects of $beta_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle. *In vitro* studies have shown that indacaterol is a weak partial agonist at $beta_1$-receptors with a potency more than 24-fold greater at $beta_2$-receptors compared to $beta_1$-receptors and is a full agonist at $beta_3$-receptors with a potency 20-fold greater at $beta_2$-receptors compared to $beta_3$-receptors.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a nearly full agonist at the human $beta_2$-adrenergic receptor with nanomolar potency. In isolated human bronchus, indacaterol has a rapid onset of action and a long duration of action.

Although $beta_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the human heart, there are also $beta_2$-adrenergic receptors in the human heart comprising 10% to 50% of the total adrenergic receptors. The precise function of $beta_2$-adrenergic receptors in the heart is not known, but their presence raises the possibility that even highly selective $beta_2$-adrenergic agonists may have cardiac effects.

Mometasone furoate

Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and local anti-inflammatory properties. Studies in asthmatic patients have demonstrated that inhaled mometasone furoate provides a favorable ratio of pulmonary to systemic activity. It is likely that much of the mechanism for the effects of mometasone furoate lies in its ability to inhibit the release of mediators of the inflammatory cascade. *In vitro,* mometasone furoate inhibits the release of leukotrienes (LT) from leukocytes of allergic patients. In cell culture, mometasone furoate demonstrated high potency in inhibition of synthesis and release of IL-1, IL-5, IL-6 and TNF-alpha.

It is also a potent inhibitor of LT production and an extremely potent inhibitor of the production of the Th2 cytokines, IL-4 and IL-5, from human CD4+ T-cells.

Pharmacodynamics (PD)

The primary pharmacodynamics of Atectura Breezhaler in obstructive airway disease reflects the complementary mechanisms of action of the individual components of Atectura Breezhaler.

Clinical data confirmed the hypothesis that bronchodilation with indacaterol coupled with the anti-inflammatory action of mometasone furoate results in improved lung function and asthma control. The Atectura Breezhaler clinical program showed consistently superior lung function when Atectura Breezhaler 150/80, 150/160, 150/320 micrograms once daily were compared to mometasone furoate (MF) 200, 400 micrograms once daily and 400 micrograms twice daily, and placebo.

The pharmacodynamic response profile of Atectura Breezhaler is characterized by rapid onset of action within 5 minutes after dosing (see section 12 Clinical studies) and sustained effect over the 24 h dosing interval as evidenced by improvements in trough forced expiratory volume in the first second (FEV_1) versus comparators, 24 hours after dosing.

No tachyphylaxis to the lung function benefits of Atectura Breezhaler were observed over time.

Effects on the QTc interval

The effect of Atectura Breezhaler on the QTc interval has not been evaluated in a thorough QT (TQT) study.

For mometasone furoate, no QTc prolonging properties are known.

Pharmacokinetics (PK)

Absorption

Following inhalation of Atectura Breezhaler, the median time to reach peak plasma concentrations of indacaterol and mometasone furoate was approximately 15 minutes and 1 hour, respectively.

Based on the *in vitro* performance data, the dose of each of the monotherapy components delivered to the lung is expected to be similar for Atectura Breezhaler and the monotherapy products. Steady-state plasma exposure to indacaterol and mometasone furoate after Atectura Breezhaler inhalation was similar to the systemic exposure after inhalation of indacaterol maleate or mometasone furoate as monotherapy products.

Following inhalation of Atectura Breezhaler, the absolute bioavailability was estimated to be about 45% for indacaterol and less than 10% for mometasone furoate.

Indacaterol

Indacaterol concentrations increased with repeated once-daily administration. Steady state was achieved within 12 to 14 days. The mean accumulation ratio of indacaterol, i.e. AUC over the 24-hour dosing interval on Day 14 compared to Day 1, was in the range of 2.9 to 3.8 for once-daily inhaled doses between 75 and 600 micrograms. Systemic exposure results from a composite of pulmonary and gastrointestinal absorption; about 75% of systemic exposure was from pulmonary absorption and about 25% from gastrointestinal absorption.

Mometasone furoate

Mometasone furoate concentrations increased with repeated once-daily administration via the Breezhaler device. Steady state was achieved after 12 days. The mean accumulation ratio of

mometasone furoate, i.e. $AUC_{0\text{-}24hr}$ on Day 14 compared to Day 1, was in the range of 1.61 to 1.71 for once-daily inhaled doses of between 80 and 320 micrograms as part of Atectura Breezhaler.

Following oral administration of mometasone furoate, the absolute oral systemic bioavailability of mometasone furoate was estimated to be very low (<2%).

Distribution

Indacaterol

After intravenous infusion the volume of distribution (V_z) of indacaterol was 2,361 to 2,557L indicating an extensive distribution. The *in vitro* human serum and plasma protein binding were 94.1 to 95.3% and 95.1 to 96.2%, respectively.

Mometasone furoate

After intravenous bolus administration, the V_d is 332L. The *in vitro* protein binding for mometasone furoate is high, 98 % to 99 % in concentration range of 5 to 500 ng/ml.

Biotransformation/metabolism

Indacaterol

After oral administration of radiolabelled indacaterol in a human absorption, distribution, metabolism, excretion (ADME) study, unchanged indacaterol was the main component in serum, accounting for about one third of total drug-related AUC over 24 hours. A hydroxylated derivative was the most prominent metabolite in serum. Phenolic O-glucuronides of indacaterol and hydroxylated indacaterol were further prominent metabolites. A diastereomer of the hydroxylated derivative, an N-glucuronide of indacaterol, and C- and N-dealkylated products were further metabolites identified.

In vitro investigations indicated that UGT1A1 was the only UGT isoform that metabolized indacaterol to the phenolic O-glucuronide. The oxidative metabolites were found in incubations with recombinant CYP1A1, CYP2D6, and CYP3A4. CYP3A4 is concluded to be the predominant isoenzyme responsible for hydroxylation of indacaterol. *In vitro* investigations further indicated that indacaterol is a low affinity substrate for the efflux pump P-gp.

In vitro the UGT1A1 isoform is a major contributor to the metabolic clearance of indacaterol. However, as shown in a clinical study in populations with different UGT1A1 genotypes, systemic exposure to indacaterol is not significantly affected by the UGT1A1-genotype.

Mometasone furoate

The portion of an inhaled mometasone furoate dose that is swallowed and absorbed in the gastrointestinal tract undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. In human liver microsomes, mometasone furoate is metabolized by CYP3A4.

Elimination

Indacaterol

In clinical studies which included urine collection, the amount of indacaterol excreted unchanged *via* urine was generally lower than 2% of the dose. Renal clearance of indacaterol was, on average, between 0.46 and 1.20 L/h. When compared with the serum clearance of indacaterol of 18.8 to 23.3 L/h, it is evident that renal clearance plays a minor role (about 2 to 6% of systemic clearance) in the elimination of systemically available indacaterol.

In a human ADME study where indacaterol was given orally, the fecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human feces primarily as unchanged

parent substance (54% of the dose) and, to a lesser extent, hydroxylated indacaterol metabolites (23% of the dose). Mass balance was complete with ≥90% of the dose recovered in the excreta.

Indacaterol serum concentrations declined in a multi-phasic manner with an average terminal half-life ranging from 45.5 to 126 hours. The effective half-life, calculated from the accumulation of indacaterol after repeated dosing, ranged from 40 to 52 hours which is consistent with the observed time to steady state of approximately 12 to 14 days.

Mometasone furoate

After intravenous bolus administration, mometasone furoate has a terminal elimination $T_{1/2}$ of approximately 4.5 hours. A radiolabelled, orally inhaled dose is excreted mainly in the feces (74 %) and to a lesser extent in the urine (8 %)

Linearity/non-linearity

Systemic exposure of mometasone furoate increased in a dose proportional manner following single and multiple doses of Atectura Breezhaler 150/80 and 150/320 micrograms in healthy subjects. A less than proportional increase in steady state systemic exposure was noted in patients with asthma over the dose range of 150/80 to 150/320 micrograms. Dose proportionality assessments were not performed for indacaterol as only one dose was used across all dose strengths of Atectura Breezhaler.

Special populations

A population PK analysis in patients with asthma after inhalation of Atectura Breezhaler indicated no significant effect of age, gender, body weight, smoking status, baseline estimated glomerular filtration rate (eGFR) and FEV_1 at baseline on the systemic exposure to indacaterol and mometasone furoate.

Race/Ethnicity

There were no major differences in total systemic exposure (AUC) for both compounds between Japanese and Caucasian subjects. Insufficient pharmacokinetic data is available for other ethnicities or races.

Pediatric patients (below 12 years)

Atectura Breezhaler may be used in pediatric patients (12 years of age and older) at the same posology as in adults. The safety and efficacy of Atectura Breezhaler in pediatric patients below 12 years of age have not been established.

Renal impairment

Due to the very low contribution of the urinary pathway to total body elimination of indacaterol and mometasone furoate, the effects of renal impairment on their systemic exposure have not been investigated.

Hepatic impairment

The effect of indacaterol/mometasone furoate has not been evaluated in subjects with hepatic impairment. However, studies have been conducted with the mono-components.

***Indacaterol*:** Patients with mild or moderate hepatic impairment showed no relevant changes in C_{max} or AUC of indacaterol, nor did protein binding differ between mild and moderate hepatic impaired subjects and their healthy controls. No data are available for subjects with severe hepatic impairment.

Mometasone furoate: A study evaluating the administration of a single inhaled dose of 400 micrograms mometasone furoate by dry powder inhaler to subjects with mild (n=4), moderate (n=4), and severe (n=4) hepatic impairment resulted in only 1 or 2 subjects in each group having detectable peak plasma concentrations of mometasone furoate (ranging from 50 to 105 pcg/mL). The observed peak plasma concentrations appear to increase with severity of hepatic impairment; however, the numbers of detectable levels (assay Lower Limit of Quantification was 50pcg/mL) were few.

11 Clinical studies

Two phase III randomized, double-blind studies (PALLADIUM and QUARTZ) of different durations evaluated the safety and efficacy of Atectura Breezhaler in adults and adolescent patients with asthma.

Study PALLADIUM was a 52-week pivotal study evaluating Atectura Breezhaler 150/160 micrograms once daily (N=439) and 150/320 micrograms once-daily (N=445) via Breezhaler over mometasone furoate (MF) 400 micrograms once daily (N=444) and 800 micrograms per day given as 400 micrograms twice daily (N=442), respectively. A third active control arm included subjects treated with salmeterol xinafoate /fluticasone propionate (SAL/FP) 50/500 micrograms twice daily (N=446). All subjects were required to be asthma symptomatic and on asthma maintenance therapy using an inhaled corticosteroid (ICS) with or without LABA for at least 3 months prior to study entry. At screening, 30% of patients had a history of exacerbation in the previous year. At study entry, the most common asthma medications reported were medium and high dose of ICS (27%) or LABA and low dose of ICS (69%).

The primary objective of the study was to demonstrate superiority of either Atectura Breezhaler 150/160 micrograms once daily to MF 400 micrograms once daily or Atectura Breezhaler 150/320 micrograms once daily to MF 400 micrograms twice daily in terms of trough FEV_1 at week 26.

Mometasone furoate (MF) 160 (medium dose) and 320 (high dose) micrograms in Atectura Breezhaler once daily are comparable to MF 400 micrograms once daily (medium dose) and 800 micrograms (given as 400 micrograms twice daily, high dose) using multi-dose dry powder inhaler, respectively.

Atectura Breezhaler 150/160 and 150/320 micrograms once daily both demonstrated statistically significant improvements in trough FEV_1 at week 26 and Asthma Control Questionnaire (ACQ-7) score compared to MF 400 micrograms once or twice daily, respectively (see Table 12-1). A greater percentage of subjects were ACQ responders (defined as achieving minimal clinical important difference (MCID) from baseline with ACQ $\geq$ 0.5) for both doses of Atectura Breezhaler compared to MF 400 micrograms once or twice daily, respectively (see Table 12-1). Findings at week 52 were consistent with week 26.

Atectura Breezhaler 150/160 and 150/320 micrograms once daily both demonstrated a clinically meaningful reduction in the annual rate of moderate or severe exacerbations, 53% and 35% respectively, compared to MF 400 micrograms once and twice daily (see Table 12-3).

For information on other endpoints see Table 12-1 and 12-3.

Lung function and symptoms

Table 11-1 Results of primary and secondary endpoints

Endpoint	Time point/Duration	Atectura Breezhaler vs MF*		Atectura Breezhaler vs SAL/FP*
		Medium dose (150/160 od)	High dose	High dose

		versus medium dose (400 od)	(150/320 od) versus high dose (400 bid)	(150/320 od) versus high dose (50/500 bid)
Lung Function				
*Trough FEV_1***				
Treatment difference P value (95% CI)	Week 26 (Primary endpoint)	211 mL <0.001 (167, 255)	132 mL <0.001 (88, 176)	36 mL 0.101 (-7, 80)
	Week 52	209 mL <0.001 (163, 255)	136 mL <0.001 (90, 183)	48 mL 0.040 (2, 94)
Mean Morning Peak Expiratory Flow (PEF)				
Treatment difference P value (95% CI)	Week 1-26***	32.2 L/min <0.001 (26.4, 38.1)	29.6 L/min <0.001 (23.8, 35.4)	13.3 L/min <0.001 (7.5, 19.1)
	Week 1-52***	30.2 L/min <0.001 (24.2, 36.3)	28.7 L/min <0.001 (22.7, 34.8)	13.8 L/min <0.001 (7.7, 19.8)
Mean Evening Peak Expiratory Flow (PEF)				
Treatment difference P value (95% CI)	Week 1-26***	30.4 L/min <0.001 (24.8, 35.9)	24.8 L/min <0.001 (19.3, 30.3)	8.6 L/min 0.002 (3.1, 14.2)
	Week 1-52***	29.1 L/min <0.001 (23.3, 34.8)	23.7 L/min <0.001 (18.0, 29.5)	9.1 L/min 0.002 (3.3, 14.9)
Symptoms				
ACQ-7				
Treatment difference P value (95% CI)	Week 26 (key secondary endpoint)	-0.248 <0.001 (-0.334, -0.162)	-0.171 <0.001 (-0.257, -0.086)	-0.054 0.214 (-0.140, 0.031)
	Week 52	-0.266 <0.001 (-0.354, -0.177)	-0.141 0.002 (-0.229, -0.053)	0.010 0.824 (-0.078, 0.098)
ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥ 0.5)				
Percentage	Week 26	76% vs 67%	76% vs 72%	76% vs 76%
Odds Ratio P value (95% CI)	Week 26	1.73 <0.001 (1.26, 2.37)	1.31 0.094 (0.95, 1.81)	1.06 0.746 (0.76, 1.46)
Percentage	Week 52	82% vs 69%	78% vs 74%	78% vs 77%
Odds Ratio P value (95% CI)	Week 52	2.24 <0.001 (1.58, 3.17)	1.34 0.088 (0.96, 1.87)	1.05 0.771 (0.75, 1.49)
Mean number of daily puffs of rescue medication				
Treatment difference	Week 1-26***	-0.19 0.017	-0.31 <0.001	-0.09 0.290

P value (95% CI)		（-0.35, -0.03）	(-0.46, -0.15)	(-0.24, 0.07)
	Week 1-52***	-0.23 0.004 (-0.39,-0.07)	-0.28 <0.001 (-0.44,-0.12)	-0.09 0.245 (-0.25,0.06)
Percentage of rescue medication free days				
Treatment difference P value (95% CI)	Week 1-26***	8.3 <0.001 (4.3, 12.3)	10.1 <0.001 (6.2, 14.1)	4.1 0.045 (0.1, 8.0)
	Week 1-52***	8.6 <0.001 (4.7, 12.6)	9.6 <0.001 (5.7, 13.6)	4.3 0.034 (0.3, 8.3)
Percentage of days with no symptoms				
Treatment difference P value (95% CI)	Week 1-26***	7.8 <0.001 (3.7, 12.0)	6.6 0.002 (2.5, 10.7)	3.7 0.082 (-0.5, 7.9)
	Week 1-52***	9.1 <0.001 (4.6, 13.6)	5.8 0.012 (1.3, 10.2)	3.4 0.135 (-1.1, 7.9)
Percentage of nights with no night-time awakenings				
Treatment difference P value (95% CI)	Week 1-26***	4.1 0.013 (0.9, 7.4)	2.7 0.103 (-0.5, 5.9)	0.6 0.713 (-2.6, 3.9)
	Week 1-52***	3.9 0.024 (0.5, 7.3)	2.8 0.104 (-0.6, 6.2)	0.9 0.588 (-2.5, 4.3)
Quality of life as assessed by Asthma Quality of Life Questionnaire (S) (AQLQ-S+12)				
Treatment difference P value (95% CI)	Week 26	0.156 0.003 (0.053, 0.260)	0.127 0.016 (0.023, 0.230)	0.085 0.103 (-0.017, 0.188)
	Week 52	0.191 <0.001 (0.082, 0.299)	0.079 0.154 (-0.030, 0.187)	0.041 0.455 (-0.067, 0.148)

* MF: mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate;

** Trough FEV_1: the mean of the two FEV_1, values measured at 23 hour 15 min and 23 hour 45 min after the evening dose.

*** Mean value for the treatment duration.

Onset of action

In study PALLADIUM, Atectura Breezhaler demonstrated a rapid onset of bronchodilator effect within 5 minutes after administration (see Table 12-2).

Table 11-2 Onset of action on Day 1 based on treatment difference in FEV_1 by time points in study PALLADIUM

	Treatment difference Day 1
Atectura Breezhaler (medium dose) vs MF* (medium dose)	
5 min	152 mL**
15 min	174 mL**
30 min	185 mL**

Atectura Breezhaler (high dose) vs MF* (high dose)	
5 min	142 mL**
15 min	162 mL**
30 min	175 mL**
Atectura Breezhaler (high dose) vs SAL/FP* (high dose)	
5 min	55 mL**
15 min	44 mL**
30 min	27 mL (p=0.038)

* MF: mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate

** p-value <0.001

Exacerbations

Table 11-3 Analysis of Exacerbation endpoints

Endpoint	**Atectura Breezhaler vs MF***		**Atectura Breezhaler vs SAL/FP***
	Medium dose (150/160 od) versus medium dose (400 od)	High dose (150/320 od) versus high dose (400 bid)	High dose (150/320 od) versus high dose (50/500 bid)
Annualized rate of asthma exacerbations			
Moderate or severe exacerbations			
Annualized rate	0.27 vs 0.56	0.25 vs 0.39	0.25 vs 0.27
Rate Ratio (RR) p-value (95% CI)	0.47 <0.001 (0.35, 0.64)	0.65 0.008 (0.48, 0.89)	0.93 0.669 (0.67, 1.29)
Severe exacerbations			
Annualized rate	0.13 vs 0.29	0.13 vs 0.18	0.13 vs 0.14
Rate Ratio (RR) p-value (95% CI)	0.46 <0.001 (0.31, 0.67)	0.71 0.108 (0.47, 1.08)	0.89 0.597 (0.58, 1.37)
All exacerbations (mild, moderate or severe)			
Annualized rate	0.48 vs 1.05	0.49 vs 0.74	0.49 vs 0.52
Rate Ratio (RR) p-value (95% CI)	0.46 <0.001 (0.36, 0.59)	0.67 0.002 (0.52, 0.87)	0.95 0.681 (0.72, 1.23)

* MF: mometasone furoate; SAL/FP: salmeterol xinafoate /fluticasone propionate

Atectura Breezhaler 150/160 and 150/320 micrograms once daily were also studied as active comparators in another Phase III study (IRIDIUM) in an asthma development program for indacaterol/glycopyrronium/mometasone furoate in adult patients with asthma. To enroll in this study, all subjects were required to be symptomatic on asthma maintenance therapy with a medium or high dose ICS and LABA combination therapy for at least 3 months prior to study entry. All subjects had

a history of asthma exacerbation requiring systemic corticosteroids in the past year. A pre-specified pooled analysis across both IRIDIUM and PALLADIUM studies was conducted to compare Atectura Breezhaler 150/320 micrograms once daily to salmeterol/fluticasone 50/500 micrograms twice daily for the endpoints of trough FEV_1 and ACQ-7 at week 26 and annualized rate of exacerbations. The pooled analysis demonstrated that Atectura Breezhaler improved trough FEV_1 by 43 mL (95% CI: 17, 69; p=0.001) and ACQ-7 score by -0.091 (95% CI: -0.153, -0.030; p=0.004) at week 26 versus salmeterol/fluticasone. The pooled analysis also demonstrated that Atectura Breezhaler reduced the annualized rate of moderate or severe asthma exacerbations by 22% (RR: 0.78; 95% CI: 0.66, 0.93; p=0.006) and of severe exacerbations by 26% (RR: 0.74; 95% CI: 0.61, 0.91; p=0.004) versus salmeterol/fluticasone.

Study QUARTZ was a 12-week study evaluating Atectura Breezhaler 150/80 micrograms once daily (N=398) via Breezhaler over MF 200 micrograms once daily (N=404). All subjects were required to be symptomatic and on asthma maintenance therapy using a low dose ICS (with or without LABA) for at least 1 month prior to study entry. At study entry, the most common asthma medications reported were low dose of ICS (43%) and LABA/low dose ICS (56%). The primary endpoint of the study was to demonstrate superiority of Atectura Breezhaler 150/80 micrograms once daily to MF 200 micrograms once daily in terms of trough FEV_1 at week 12.

MF 80 micrograms (low dose) in Atectura Breezhaler once daily is comparable to MF 200 micrograms once daily (low dose) using multi-dose dry powder inhaler.

Atectura Breezhaler 150/80 micrograms once daily demonstrated a statistically significant improvement in baseline trough FEV_1 at week 12 and Asthma Control Questionnaire (ACQ-7) score compared to MF 200 micrograms once daily. For additional details, see Table 12-4.

Table 11-4 Results of primary and secondary endpoints in study QUARTZ at week 12

Endpoints	**Atectura Breezhaler low dose (150/80 od) vs MF* low dose (200 od) P value (95% CI)**
Lung Function	
Trough FEV_1**	182 mL <0.001 (148, 217)
Mean Morning PEF	27.2 L/min <0.001 (22.1, 32.4)
Evening PEF	26.1 L/min <0.001 (21.0, 31.2)
Symptoms	
ACQ-7 (key secondary endpoint)	-0.218 <0.001 (-0.293, -0.143)
Percentage of patients achieving MCID from baseline with ACQ ≥ 0.5	75% vs 65% 1.69 0.001 (1.23, 2.33)
Mean number of daily puffs of rescue medication	-0.26

	<0.001 (-0.37, -0.14)
Percentage of rescue medication free days	8.1 <0.001 (4.3, 11.8)
Percentage of days with no symptoms	2.7 0.153 (-1.0, 6.4)
Percentage of nights with no night-time awakenings	4.8 0.002 (1.8, 7.7)
Quality of life as assessed by Asthma Quality of Life Questionnaire (S) (AQLQ-S+12)	0.149 <0.001 (0.064, 0.234)

* MF: mometasone furoate.

** Trough FEV_1: the mean of the two FEV_1, values measured at 23 hour 15 min and 23 hour 45 min after the evening dose.

12 Non-clinical safety data

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

The *in vivo* studies of each monotherapy and combination products are presented below.

Indacaterol and mometasone furoate combination

The findings during the 13-week inhalation toxicity studies were predominantly attributable to the mometasone furoate and were typical pharmacological effects of glucocorticoids. Increased heart rates associated with indacaterol were apparent in dogs after administration of indacaterol/mometasone furoate or indacaterol alone.

Indacaterol

Effects on the cardiovascular system attributable to the $beta_2$-agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritation of the nasal cavity and larynx were seen in rodents.

Genotoxicity studies did not reveal any mutagenic or clastogenic potential.

Carcinogenicity was assessed in a two-year rat study and a six-month transgenic mouse study. Increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in rats were consistent with similar findings reported for other $beta_2$-adrenergic agonists. No evidence of carcinogenicity was seen in mice.

All these findings occurred at exposures sufficiently in excess of those anticipated in humans.

Mometasone furoate

All observed effects are typical of the glucocorticoid class of compounds and are related to exaggerated pharmacologic effects of glucocorticoids. Mometasone furoate showed no genotoxic activity in a standard battery of *in vitro* and *in vivo* tests.

In carcinogenicity studies in mice and rats, inhaled mometasone furoate demonstrated no statistically significant increase in the incidence of tumours.

13 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.

Protect from moisture and light.

Keep this medicine out of the sight and reach of children.

Instructions for use and handling

For correct administration/use of the product, please refer to Section 4 Method of administration and the Instruction for use (IFU) below.

Instructions for use Atectura Breezhaler

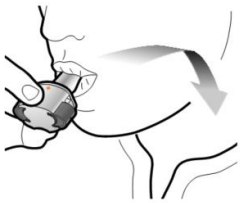
This part of the leaflet explains how to use and care for your Atectura Breezhaler inhaler. Please read carefully and follow these instructions.

If you have any questions, ask your doctor or pharmacist.

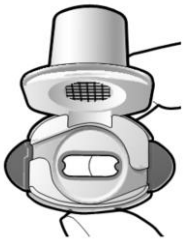
Please read the full **Instructions for Use** before using the Atectura Breezhaler.

Insert

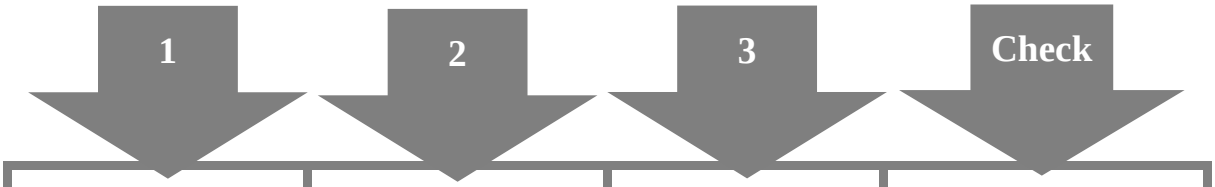
Pierce and release

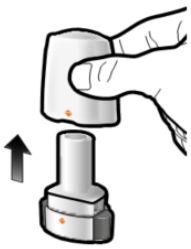


Inhale deeply

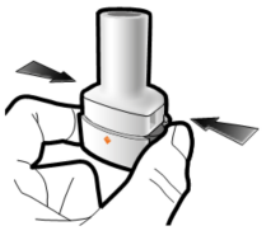


Check capsule is empty





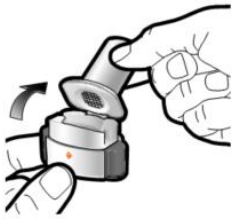
Step 1a:
Pull off cap



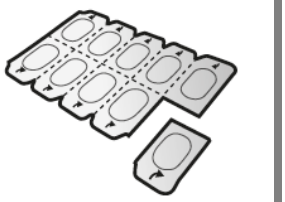
Step 2a:
Pierce capsule once
Hold the inhaler upright. Pierce capsule by firmly pressing both side buttons at the same time.

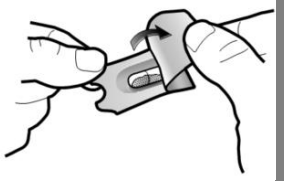
Step 3a:
Breathe out fully
Do not blow into the inhaler.

Check capsule is empty
Open the inhaler to see if any powder is left in the capsule.



Step 1b:
Open inhaler



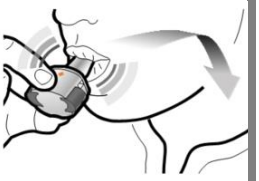


Step 1c:
Remove capsule
Separate one of the blisters from the blister card.

Peel open the blister and remove the capsule. <u>Do not push the capsule through the foil.</u>
<u>Do not swallow the capsule.</u>

You should hear a noise as the capsule is pierced. <u>Only pierce the capsule once.</u>

Step 2b:
Release side buttons



Step 3b:
Inhale medicine deeply
Hold the inhaler as shown in the picture.
Place the mouthpiece in your mouth and close your lips firmly around it.
<u>Do not press the side buttons</u>.

Breathe in quickly and as deeply as you can.
During inhalation you will hear a whirring noise.
You may taste the medicine as you inhale.

Step 3c:
Hold breath
Hold your breath for up to 5 seconds.

Step 3d :
Rinse mouth
Rinse your mouth with water after each dose and spit it out.

If there is powder left in the capsule:
- Close the inhaler.
- Repeat steps 3a to 3d.

Powder remaining **Empty**

Remove empty capsule
Put the empty capsule in your household waste.

Close the inhaler and replace the cap.

Step 1d:
Insert capsule
Never place a capsule directly into the mouthpiece.

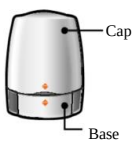
Step 1e:
Close inhaler

Important Information

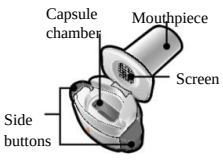
- Atectura Breezhaler capsules must always be stored in the blister card and only removed immediately before use.
- Do not push the capsule through the foil to remove it from the blister.
- Do not swallow the capsule.
- Do not use the Atectura Breezhaler capsules with any other inhaler.
- Do not use the Atectura Breezhaler inhaler to take any other capsule medicine.
- Never place the capsule into your mouth or the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Do not blow into the mouthpiece.
- Do not press the side buttons while inhaling through the mouthpiece.
- Do not handle capsules with wet hands.
- Never wash your inhaler with water.

Your Atectura Breezhaler Inhaler pack contains:

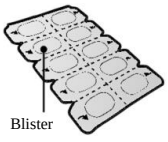
- One Atectura Breezhaler inhaler
- One or more blister cards each containing either 10 Atectura Breezhaler capsules to be used in the inhaler



Inhaler



Inhaler base



Blister card

Frequently Asked Questions

Why didn't the inhaler make a noise when I inhaled?

Cleaning the inhaler
Wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry. Never wash your inhaler with water.

	The capsule may be stuck in the capsule chamber. If this happens, carefully loosen the capsule by tapping the base of the inhaler. Inhale the medicine again by repeating steps 3a to 3d. **What should I do if there is powder left inside the capsule?** You have not received enough of your medicine. Close the inhaler and repeat steps 3a to 3d. **I coughed after inhaling – does this matter?** This may happen. As long as the capsule is empty you have received enough of your medicine. **I felt small pieces of the capsule on my tongue – does this matter?** This can happen. It is not harmful. The chances of the capsule breaking into small pieces will be increased if the capsule is pierced more than once.	**Disposing of the inhaler after use** Each inhaler should be disposed of after all capsules have been used. Ask your pharmacist how to dispose of medicines and inhalers that are no longer required.

Manufacturer

See folding box.

Presentation

Atectura Breezhaler 150/80, 150/160, 150/320 micrograms:

Single pack 10 capsules (1x10's) or 30 capsules (3x10's), together with one inhaler.

Not all pack sizes may be available locally.

Information issued: June 2020.SINv1

Novartis Pharma AG, Basel, Switzerland