▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ATECTURA® BREEZHALER® (INDACATEROL/MOMETASONE FUROATE) POWDER FOR INHALATION IN HARD CAPSULE

1 NAME OF THE MEDICINE

Indacaterol/mometasone furoate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atectura Breezhaler 125/62.5 micrograms, inhalation powder, hard capsules

Atectura Breezhaler hard capsules are for oral inhalation only. They are also supplied with an Atectura Breezhaler inhalation device to permit oral inhalation of the contents of the capsule shell.

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

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

Atectura Breezhaler 125/127.5 micrograms, inhalation powder, hard capsules

Atectura Breezhaler hard capsules are for oral inhalation only. They are also supplied with an Atectura Breezhaler inhalation device to permit oral inhalation of the contents of the capsule shell.

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

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

Atectura Breezhaler 125/260 micrograms, inhalation powder, hard capsules

Atectura Breezhaler hard capsules are for oral inhalation only. They are also supplied with an Atectura Breezhaler inhalation device to permit oral inhalation of the contents of the capsule shell.

Each capsule contains 173 micrograms of indacaterol acetate equivalent to 150 micrograms of indacaterol and 320 micrograms of mometasone furoate.

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

Excipients with known effect

Each capsule contains approximately 25 mg lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule

Atectura Breezhaler 125/62.5 micrograms, inhalation powder, hard capsules

Capsules with natural transparent cap and uncoloured transparent body containing a white to practically white powder, with the product code “IM150-80” printed in blue above one blue bar on the body and with a logo printed in blue and surrounded by two blue bars on the cap.

Atectura Breezhaler 125/127.5 micrograms, inhalation powder, hard capsules

Capsules with natural transparent cap and uncoloured transparent body containing a white to practically white powder, with the product code “IM150-160” printed in grey on the body and with a logo printed in grey on the cap.

Atectura Breezhaler 125/260 micrograms, inhalation powder, hard capsules

Capsules with natural transparent cap and uncoloured transparent body containing a white to practically white powder, with the product code “IM150-320” printed in black above two black bars on the body and with a logo printed in black and surrounded by two black bars on the cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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 beta2-agonist and inhaled corticosteroid is appropriate:
- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists or
-patients not adequately controlled with long-acting beta2-agonists and low dose of inhaled corticosteroids and "as needed" inhaled short-acting beta2-agonists.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults and adolescents 12 years of age and older

Inhalation of the content of one capsule of Atectura Breezhaler 125/62.5 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 125/127.5 micrograms or 125/260 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 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 125/260 micrograms once daily.

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 5 PHARMACOLOGICAL PROPERTIES).

Renal impairment

No dose adjustment is required in patients with renal impairment.

Elderly patients

No dose adjustment is required in elderly patients 65 years of age or older (see section 5 PHARMACOLOGICAL PROPERTIES).

Paediatric patients

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

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 6.4 SPECIAL PRECAUTIONS FOR STORAGE).

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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 beta2 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 being treated with medicinal products affecting the QT interval.

Hypokalaemia with beta agonists

Beta$_2$-adrenergic agonists may produce significant hypokalaemia 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, hypokalaemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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

Hyperglycaemia

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.

Use in hepatic impairment

Enerzair Breezhaler can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment, therefore caution should be observed in these patients (see section 5.2).

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.

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

Use in the elderly

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hypokalaemic treatment

Concomitant treatment with methylxanthine derivatives, steroids or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise 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 the 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 section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 4.9 OVERDOSE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on the effect on fertility have been conducted with indacaterol and mometasone furoate in combination. No adverse effects on fertility were observed in male and female rats given indacaterol by subcutaneous injection at doses up to 2 mg/kg/day, yielding systemic exposure hundreds of times higher than in patients. As with other corticosteroids, at exposure levels associated with marked signs of systemic corticosteroid toxicity, mometasone furoate had progestogenic effects on the female reproductive tract and mammary glands. However, fertility was unimpaired in a reproductive toxicity study carried out in rats.

Use in pregnancy – Pregnancy Category B3

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 foetal malformations and decreased foetal survival and growth.

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

Clinical Considerations

Disease-associated maternal and/or embryo/foetal 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.

Labour and Delivery

Like other medicinal products containing beta$_2$-adrenergic agonists, indacaterol may inhibit labour 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

Indacaterol was not teratogenic at subcutaneous doses up to 1 mg/kg/day in rats and 3 mg/kg/day in rabbits (yielding more than 150-and 920-times, respectively, the AUC in humans at 150 µg/day). An increase in the incidence of a rib skeletal variation and retarded ossification were observed in the rabbit at 3 mg/kg/day, possibly secondary to maternal toxicity; embryofoetal development was unaffected in the species at 1 mg/kg/day (relative exposure, 365). Impaired learning and decreased fertility were observed in the pups of rats given indacaterol at a subcutaneous dose of 1 mg/kg/day during pregnancy and lactation (relative exposure, approximately 140; unaffected at 0.3 mg/kg/day, associated with a relative exposure level of 55). The potential risk for humans is unknown.

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 foetal growth (lower foetal body weight and/or delayed ossification) in rats, rabbits and mice, and reduced offspring survival in mice. In rats, subcutaneous mometasone furoate at 15 micrograms/kg prolonged gestation and difficult labour occurred with a reduction in offspring survival and body weight.

Use in lactation

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. Reduced body weight gain, impaired learning and decreased fertility were observed in pups of rats treated with indacaterol during pregnancy and lactation.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 125/62.5, 125/127.5 or 125/260 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 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 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]
	125/127.5 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=437	125/260 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
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

Adverse drug reactions	Atectura Breezhaler		Mometasone furoate		Frequency category [based on the higher frequency between the two arms]
	125/127.5 micrograms once daily Medium dose Rate (%) [number of events] (95% CI) N=437	125/260 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	
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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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, hypokalaemia, hyperglycaemia, 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 hospitalised.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 catalyses 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 favourable 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

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 125/62.5, 125/127.5, 125/260 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 characterised by rapid onset of action within 5 minutes after dosing (see section 5.1 Clinical trials) 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.

Clinical trials

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 125/127.5 micrograms once daily (N=439) and 125/260 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 baseline % predicted FEV1, mean ACQ-7 score and proportion of patients with at least one exacerbations 12 months prior to start of the study was 67.3%, 2.3 and 30.6%, respectively. A total of 107 adolescents were randomized.

The primary objective of the study was to demonstrate superiority of either Atectura Breezhaler 125/127.5 micrograms once daily to MF 400 micrograms once daily or Atectura Breezhaler 125/260 micrograms once daily to MF 400 micrograms twice daily in terms of trough FEV_1 at week 26.

Mometasone furoate (MF) 127.5 (medium dose) and 260 (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 125/127.5 and 125/260 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 2). Findings at week 52 were consistent with week 26.

Atectura Breezhaler 125/127.5 and 125/260 micrograms once daily both demonstrated a clinically meaningful reduction in the annual rate of moderate or severe exacerbations, compared to MF 400 micrograms once and twice daily (see Table 2).

Results for the most clinically relevant endpoints are described in Table 2.

Lung function, symptoms and exacerbations

Table 2 Results of primary and secondary endpoints

Endpoint	**Time point/ Duration**	**Atectura Breezhaler[1] vs MF[2]**	
		Medium dose vs medium dose	High dose vs high dose
Lung function			
Trough FEV_1[3]			
Treatment difference P value (95% CI)	Week 26 (primary endpoint)	211 ml <0.001 (167, 255)	132 ml <0.001 (88, 176)
	Week 52	209 ml <0.001 (163, 255)	136 ml <0.001 (90, 183)
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)
	Week 52	-0.266 (-0.354, -0.177)	-0.141 (-0.229, -0.053)
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%
Odds ratio (95% CI)	Week 26	1.73 (1.26, 2.37)	1.31 (0.95, 1.81)
Percentage	Week 52	82% vs 69%	78% vs 74%
Odds ratio (95% CI)	Week 52	2.24 (1.58, 3.17)	1.34 (0.96, 1.87)

Annualised rate of asthma exacerbations*			
Moderate or severe exacerbations			
AR	Week 52	0.27 vs 0.56	0.25 vs 0.39
RR (95% CI)	Week 52	0.47 (0.35, 0.64)	0.65 (0.48, 0.89)
Severe exacerbations			
AR	Week 52	0.13 vs 0.29	0.13 vs 0.18
RR (95% CI)	Week 52	0.46 (0.31, 0.67)	0.71 (0.47, 1.08)

* RR <1.00 favours indacaterol/mometasone furoate.

[1] Atectura Breezhaler medium dose: 125 mcg/127.5 mcg od; high dose: 125 mcg/260 mcg od.

[2] MF: mometasone furoate medium dose: 400 mcg od; high dose: 400 mcg bid (content doses).
Mometasone furoate 127.5 mcg od and 260 mcg od in Atectura Breezhaler are comparable to mometasone furoate 400 mcg od and 800 mcg per day (given as 400 mcg bid).

[3] Trough FEV_1: the mean of the two FEV_1 values measured at 23 hours 15 min and 23 hours 45 min after the evening dose.

Primary endpoint (trough FEV_1 at week 26) and key secondary endpoint (ACQ-7 score at week 26) were part of confirmatory testing strategy and thus controlled for multiplicity. All other endpoints were not part of confirmatory testing strategy.
RR = rate ratio, AR = annualised rate
od = once daily, bid = twice daily

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 125/62.5 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 3.

Table 3 Results of primary and secondary endpoints in study QUARTZ at week 12

Endpoints	**Atectura Breezhaler low dose* vs MF low dose****
Lung function	
*Trough FEV_1 (primary endpoint)****	
Treatment difference P value (95% CI)	182 ml <0.001 (148, 217)
Symptoms	
ACQ-7 (key secondary endpoint)	
Treatment difference P value (95% CI)	-0.218 <0.001 (-0.293, -0.143)
* Atectura Breezhaler low dose: 125/62.5 mcg od. ** MF: mometasone furoate low dose: 200 mcg od (content dose). Mometasone furoate 62.5 mcg in Atectura Breezhaler od is comparable to mometasone furoate 200 mcg od (content dose). *** Trough FEV_1: the mean of the two FEV_1 values measured at 23 hours 15 min and 23 hours 45 min after the evening dose. od = once daily	

5.2 PHARMACOKINETIC PROPERTIES

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 i*n 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 60 and 480 micrograms (delivered dose). 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 $AUC_{0\text{-}24hr}$ on Day 1, was in the range of 1.61

to 1.71 for once-daily inhaled doses of between 62.5 and 260 micrograms (delivered dose) 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 (Vz) 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.

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 metabolised 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 metabolised by cytochrome P-450 3A4 (CYP3A4).

Excretion

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 faecal route of excretion was dominant over the urinary route. Indacaterol was excreted into human faeces 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 faeces (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 125/62.5 and 125/260 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 125/62.5 and 125/260 micrograms. Dose proportionality assessments were not performed for indacaterol as only one dose was used across all dose strengths of Atectura Breezhaler.

Specific 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.

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.

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Indacaterol

Indacaterol was not mutagenic or clastogenic in a battery of in vitro and in vivo assays including bacterial reverse mutation, chromosomal aberrations in Chinese hamster V79 cells and the rat bone marrow micronucleus test.

Mometasone furoate

Mometasone furoate is not considered to be genotoxic. There was no evidence of mutagenicity in in vitro tests which included tests for reverse mutation in Salmonella typhimurium and Escherichia coli and forward gene mutation in a mouse lymphoma cell line. Limited evidence of clastogenicity was obtained in Chinese Hamster ovary cells, although this finding was not confirmed in a second assay in Chinese Hamster lung cells in vitro, nor in vivo assays including a chromosomal aberration assay in mouse spermatogonia, a mouse micronucleus assay or in a rat bone marrow clastogenicity assay. Mometasone furoate did not cause DNA damage in rat liver cells.

Carcinogenicity

No carcinogenicity studies have been conducted with indacaterol and mometasone furoate in combination.

Indacaterol

The carcinogenic potential of indacaterol has been evaluated in a 26-week oral gavage study in transgenic mice (CB6F1/TgrasH2) and a 2-year inhalation study in rats. No carcinogenicity was observed in mice at doses up to 600 mg/kg/day (approximately 180-times in males and almost 400-times in females the AUC in humans at the maximum recommended clinical dose of 150 μg/day). Lifetime treatment of rats at 2.1 mg/kg/day (relative exposure, 53) resulted in increased incidences of benign ovarian leiomyoma and focal hyperplasia of ovarian smooth muscle in females. Increases in leiomyomas of the rat female genital tract have been similarly demonstrated with other β_2-

adrenergic agonist drugs. Their development is consistent with proliferation in response to prolonged relaxation of the smooth muscle (pharmacologically mediated), and the finding is not considered to indicate a carcinogenic hazard to patients. Squamous metaplasia was observed in the upper respiratory tract tissues of mice, rats and dogs following inhalation administration of indacaterol. This finding is consistent with an adaptive response to irritation and occurred at large multiples of the human dose. It is not considered to indicate a carcinogenic hazard to humans with the therapeutic use of indacaterol. No data are available to determine whether exposure to tobacco smoke enhances the respiratory tract toxicity of indacaterol.

Mometasone furoate

Mometasone furoate demonstrated no statistically significant increase in the incidence of tumours with inhalational administration at doses up to 160 µg/kg/day in a 19-month study in mice and at up to 67 µg/kg/day in a 2-year study in rats. These doses are approximately 2 times that in patients at the maximum recommended clinical dose of 320 µg/day, adjusted for body surface area.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule fill: Lactose monohydrate.

Capsule shell components: Gelatin.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Protect from moisture and light.

The capsules must always be stored in the blister to protect from moisture and light, and only removed immediately before use

6.5 NATURE AND CONTENTS OF CONTAINER

Inhaler body and cap are made from acrylonitrile butadiene styrene, push buttons are made from methyl metacrylate acrylonitrile butadiene styrene. Needles and springs are made from stainless steel.

PA/Alu/PVC – Alu perforated unit-dose blister. Each blister contains 10 hard capsules.

Pack sizes:
Carton containing 10 ATECTURA capsules, together with 1 Breezhaler inhaler.
Carton containing 30 ATECTURA capsules, together with 1 Breezhaler inhaler.

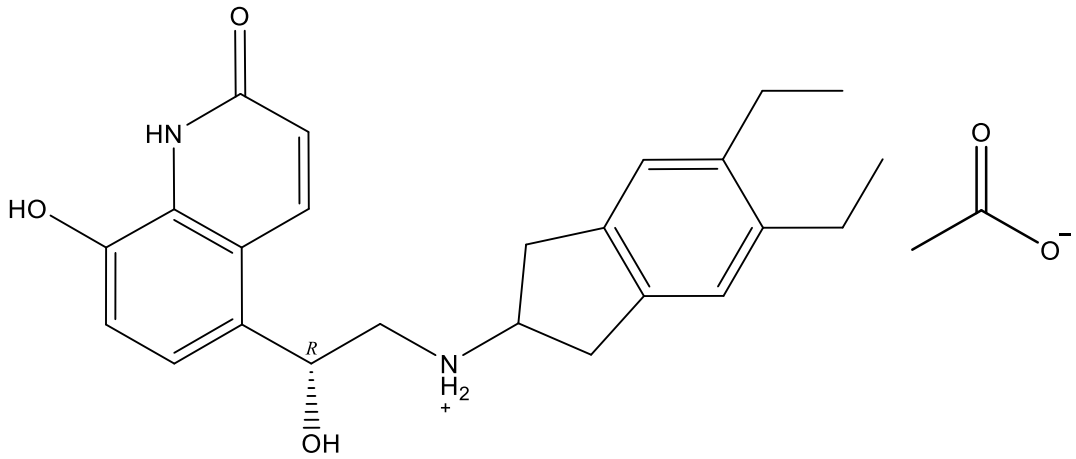
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

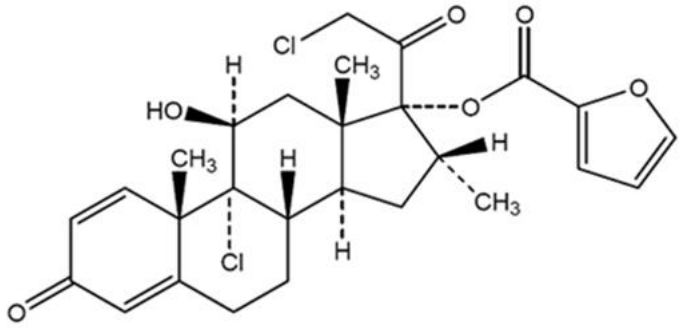
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Indacaterol acetate



Mometasone furoate



CAS number

Indacaterol acetate: 1000160-96-2

Mometasone furoate: 83919-23-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription medicine

8 SPONSOR

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Section Changed	Summary of new information
N/A	N/A

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