SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each capsule contains 150 mcg indacaterol (as acetate) and 80 mcg mometasone furoate.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 125 mcg indacaterol (as acetate) and 62.5 mcg mometasone furoate.

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

Each capsule contains 150 mcg indacaterol (as acetate) and 160 mcg mometasone furoate.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 125 mcg indacaterol (as acetate) and 127.5 mcg mometasone furoate.

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

Each capsule contains 150 mcg of indacaterol (as acetate) and 320 mcg mometasone furoate.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 125 mcg indacaterol (as acetate) and 260 mcg mometasone furoate.

Excipient with known effect

Each capsule contains approximately 24 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation powder, hard capsule (inhalation powder).

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

Transparent capsules containing a white powder, with the product code “IM150 80” printed in blue above one blue bar on the body and with the product logo printed in blue and surrounded by two blue bars on the cap.

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

Transparent capsules containing a white powder, with the product code “IM150 160” printed in grey on the body and with the product logo printed in grey on the cap.

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

Transparent capsules containing a white powder, with the product code “IM150 320” printed in black above two black bars on the body and with the product 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 maintenance treatment of asthma in adults and adolescents 12 years of age and older not adequately controlled with inhaled corticosteroids and inhaled short-acting beta$_2$-agonists.

4.2 Posology and method of administration

Posology

Adults and adolescents aged 12 years and over
The recommended dose is one capsule to be inhaled once daily.

Patients should be given the strength containing the appropriate mometasone furoate dose for the severity of their disease and should be regularly reassessed by a healthcare professional.

The maximum recommended dose is 125 mcg/260 mcg once daily.

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

Special populations
Elderly population
No dose adjustment is required in elderly patients (65 years of age or older) (see section 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of the medicinal product in patients with severe hepatic impairment, therefore it should be used in these patients only if the expected benefit outweighs the potential risk (see section 5.2).

Paediatric population
The posology in patients 12 years of age and older is the same posology as in adults.

The safety and efficacy in paediatric patients below 12 years of age have not been established. No data are available.

Method of administration

For inhalation use only. The capsules must not be swallowed.

The capsules must be administered only using the inhaler provided (see section 6.6) with each new prescription.

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 medicinal product rather than inhaling it.

The capsules must only be removed from the blister immediately before use.

After inhalation, patients should rinse their mouth with water without swallowing (see sections 4.4 and 6.6).

For instructions on use of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

This medicinal product 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 treatment without physician supervision since symptoms may recur after discontinuation.

It is recommended that treatment with this medicinal product should not be stopped abruptly. If patients find the treatment ineffective, they should continue treatment but must seek medical attention. Increasing use of reliever bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the therapy. Sudden and progressive deterioration in the symptoms of asthma is potentially life-threatening and the patient should undergo urgent medical assessment.

Hypersensitivity

Immediate hypersensitivity reactions have been observed after administration of this medicinal product. 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, treatment should be discontinued immediately and alternative therapy instituted.

Paradoxical bronchospasm

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

Cardiovascular effects of beta agonists

Like other medicinal products containing beta$_2$-adrenergic agonists, this medicinal product 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.

This medicinal product 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.

Patients with unstable ischaemic heart disease, a history of myocardial infarction in last 12 months, New York Heart Association (NYHA) class III/IV left ventricular failure, arrhythmia, uncontrolled hypertension, cerebrovascular disease or history of long QT syndrome and patients being

treated with medicinal products known to prolong QTc were excluded from studies in the indacaterol/mometasone furoate clinical development programme. Thus safety outcomes in these populations are considered unknown.

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 observations is unknown.

Long-acting beta$_2$-adrenergic agonists (LABA) or LABA-containing combination products such as Atectura Breezhaler should therefore 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 asthma hypokalaemia may be potentiated by hypoxia and concomitant treatment, which may increase the susceptibility to cardiac arrhythmias (see section 4.5).

Clinically relevant hypokalaemia has not been observed in clinical studies of indacaterol/mometasone furoate 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, plasma glucose should be monitored more closely in diabetic patients.

This medicinal product has not been investigated in patients with Type I diabetes mellitus or uncontrolled Type II diabetes mellitus.

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 of inhaled corticosteroids may occur, 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.

This medicinal product should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies were conducted with indacaterol/mometasone furoate. Information on the potential for interactions is based on the potential for each of the monotherapy components.

Medicinal products known to prolong the QTc interval

Like other medicinal products containing a $beta_2$-adrenergic agonist, this medicinal product 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 sections 4.4 and 5.1).

Hypokalaemic treatment

Concomitant hypokalaemic 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).

Beta-adrenergic blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Therefore, this medicinal product 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.

Due to the very low plasma concentration achieved after inhaled dosing, clinically significant 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 this medicinal product 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 4.8 and 4.9).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data from the use of Atectura Breezhaler or its individual components (indacaterol and mometasone furoate) in pregnant women to determine whether there is a risk.

Indacaterol was not teratogenic in rats and rabbits following subcutaneous administration (see section 5.3). In animal reproduction studies with pregnant mice, rats and rabbits, mometasone furoate caused increased foetal malformations and decreased foetal survival and growth.

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

muscle.

This medicinal product should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the foetus.

Breast-feeding

There is no information available on the presence of indacaterol or mometasone furoate in human milk, on the effects on a breast-fed infant, 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.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions over 52 weeks were asthma (exacerbation) (26.9%), nasopharyngitis (12.9%), upper respiratory tract infection (5.9%) and headache (5.8%).

Tabulated list of adverse reactions

Adverse reactions are listed by MedDRA system organ class (Table 1). The frequency of the adverse reactions is based on the PALLADIUM study. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse 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 Adverse reactions

System organ class	**Adverse reactions**	**Frequency category**
Infections and infestations	Nasopharyngitis	Very common
	Upper respiratory tract infection	Common
	Candidiasis*[1]	Uncommon
Immune system disorders	Hypersensitivity*[2]	Common
	Angioedema*[3]	Uncommon
Metabolism and nutrition disorders	Hyperglycaemia*[4]	Uncommon
Nervous system disorders	Headache*[5]	Common
Eye disorders	Vision blurred	Uncommon
	Cataract*[6]	Uncommon
Cardiac disorders	Tachycardia*[7]	Uncommon
Respiratory, thoracic and mediastinal disorders	Asthma (exacerbation)	Very common
	Oropharyngeal pain*[8]	Common
	Dysphonia	Common
Skin and subcutaneous tissue disorders	Rash*[9]	Uncommon
	Pruritus*[10]	Uncommon
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*[11]	Common
	Muscle spasms	Uncommon

* Indicates grouping of preferred terms (PTs):
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 Cataract, cataract cortical.
7 Heart rate increased, tachycardia, sinus tachycardia, supraventricular tachycardia.
8 Oral pain, oropharyngeal discomfort, oropharyngeal pain, throat irritation, odynophagia.
9 Drug eruption, rash, rash erythematous, rash pruritic.
10 Anal pruritus, eye pruritus, nasal pruritus, pruritus, pruritus genital.
11 Back pain, musculoskeletal pain, myalgia, neck pain, musculoskeletal chest pain.

Paediatric population

The safety profile of the medicinal product was assessed in the phase III study in adolescents (12 years and older) and adults. Frequency, type and severity of adverse reactions in adolescents are similar to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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$_2$-adrenergic blockers may provoke bronchospasm. In serious cases, patients should be hospitalised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, ATC code: R03AK14

Mechanism of action

This medicinal product is a combination of indacaterol, a long-acting beta$_2$-adrenergic agonist (LABA), and mometasone furoate, an inhaled synthetic corticosteroid (ICS).

Indacaterol
The pharmacological effects of beta$_2$-adrenoceptor agonists, including indacaterol, are at least in part attributable to increased cyclic-3', 5'-adenosine monophosphate (cyclic AMP) levels, which cause relaxation of bronchial smooth muscle.

When inhaled, indacaterol acts locally in the lung as a bronchodilator. Indacaterol is a partial 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.

Mometasone furoate
Mometasone furoate is a synthetic corticosteroid with high affinity for glucocorticoid receptors and local anti-inflammatory properties. *In vitro*, mometasone furoate inhibits the release of leukotrienes 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 leukotriene production and of the production of the Th2 cytokines IL-4 and IL-5 from human CD4+ T-cells.

Pharmacodynamic effects

The pharmacodynamic response profile of this medicinal product is characterised by rapid onset of action within 5 minutes after dosing and sustained effect over the 24-hour dosing interval, as evidenced by improvements in trough forced expiratory volume in the first second (FEV_1) improvements versus comparators 24 hours after dosing.

No tachyphylaxis to the lung function benefits of this medicinal product was observed over time.

QTc interval
The effect of this medicinal product on the QTc interval has not been evaluated in a thorough QT (TQT) study. For mometasone furoate, no QTc-prolonging properties are known.

Clinical efficacy and safety

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

The PALLADIUM study was a 52-week pivotal study evaluating Atectura Breezhaler 125 mcg/127.5 mcg once daily (N=439) and 125 mcg/260 mcg once daily (N=445) compared to mometasone furoate 400 mcg once daily (N=444) and 800 mcg per day (given as 400 mcg twice daily) (N=442), respectively. A third active control arm included subjects treated with salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily (N=446). All subjects were required to have symptomatic asthma (ACQ-7 score $\geq$1.5) and were on asthma maintenance therapy using an inhaled synthetic corticosteroid (ICS) with or without LABA for at least 3 months prior to study entry. At screening, 31% of patients had history of exacerbation in the previous year. At study entry, the most common asthma medications reported were medium dose of ICS (20%), high dose of ICS (7%) or low dose of ICS in combination with a LABA (69%).

The primary objective of the study was to demonstrate superiority of either

Atectura Breezhaler 125 mcg/127.5 mcg once daily over mometasone furoate 400 mcg once daily or Atectura Breezhaler 125 mcg/260 mcg once daily over mometasone furoate 400 mcg twice daily in terms of trough FEV_1 at week 26.

At week 26, Atectura Breezhaler 125 mcg/127.5 mcg and 125 mcg/260 mcg once daily both demonstrated statistically significant improvements in trough FEV_1 and Asthma Control Questionnaire (ACQ-7) score compared to mometasone furoate 400 mcg once or twice daily, respectively (see Table 2). Findings at week 52 were consistent with week 26.

Atectura Breezhaler 125 mcg/127.5 mcg and 125 mcg/260 mcg once daily both demonstrated a clinically meaningful reduction in the annual rate of moderate or severe exacerbations (secondary endpoint), compared to mometasone furoate 400 mcg 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 in PALLADIUM study at weeks 26 and 52

Endpoint	**Time point/ Duration**	**Atectura Breezhaler[1] vs MF[2]**		**Atectura Breezhaler[1] vs SAL/FP[3]**
		Medium dose vs medium dose	High dose vs high dose	High dose vs high dose
Lung function				
Trough FEV_1[4]				
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 (95% CI)	Week 52	30.2 l/min (24.2, 36.3)	28.7 l/min (22.7, 34.8)	13.8 l/min (7.7, 19.8)
*Mean evening peak expiratory flow (PEF)**				
Treatment difference (95% CI)	Week 52	29.1 l/min (23.3, 34.8)	23.7 l/min (18.0, 29.5)	9.1 l/min (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 (-0.354, -0.177)	-0.141 (-0.229, -0.053)	0.010 (-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 (95% CI)	Week 26	1.73 (1.26, 2.37)	1.31 (0.95, 1.81)	1.06 (0.76, 1.46)
Percentage	Week 52	82% vs 69%	78% vs 74%	78% vs 77%
Odds ratio (95% CI)	Week 52	2.24 (1.58, 3.17)	1.34 (0.96, 1.87)	1.05 (0.75, 1.49)
*Percentage of rescue medication free days**				
Treatment difference (95% CI)	Week 52	8.6 (4.7, 12.6)	9.6 (5.7, 13.6)	4.3 (0.3, 8.3)
*Percentage of days with no symptoms**				
Treatment difference (95% CI)	Week 52	9.1 (4.6, 13.6)	5.8 (1.3, 10.2)	3.4 (-1.1, 7.9)
Annualised rate of asthma exacerbations**				
Moderate or severe exacerbations				
AR	Week 52	0.27 vs 0.56	0.25 vs 0.39	0.25 vs 0.27
RR (95% CI)	Week 52	0.47 (0.35, 0.64)	0.65 (0.48, 0.89)	0.93 (0.67, 1.29)
Severe exacerbations				
AR	Week 52	0.13 vs 0.29	0.13 vs 0.18	0.13 vs 0.14
RR (95% CI)	Week 52	0.46 (0.31, 0.67)	0.71 (0.47, 1.08)	0.89 (0.58, 1.37)

* Mean value for the treatment duration

** 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] SAL/FP: salmeterol/fluticasone propionate high dose: 50 mcg/500 mcg bid (content dose).

[4] 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

Pre-specified pooled analysis

Atectura Breezhaler 125 mcg/260 mcg once daily was also studied as an active comparator in another phase III study (IRIDIUM) in which all subjects had a history of asthma exacerbation requiring systemic corticosteroids in the past year. A pre-specified pooled analysis across the IRIDIUM and PALLADIUM studies was conducted to compare Atectura Breezhaler 125 mcg/260 mcg once daily to salmeterol/fluticasone 50 mcg/500 mcg twice daily for the endpoints of trough FEV_1 and ACQ-7 at week 26 and annualised rate of exacerbations. The pooled analysis demonstrated that Atectura Breezhaler improved trough FEV_1 by 43 ml (95% CI: 17, 69) and ACQ-7 score by -0.091 (95% CI: -0.153,

-0.030) at week 26 and reduced the annualised rate of moderate or severe asthma exacerbations by 22% (RR: 0.78; 95% CI: 0.66, 0.93) and of severe exacerbations by 26% (RR: 0.74; 95% CI: 0.61, 0.91) versus salmeterol/fluticasone.

The QUARTZ study was a 12-week study evaluating Atectura Breezhaler 125 mcg/62.5 mcg once daily (N=398) compared to mometasone furoate 200 mcg 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 ICS (43%) and LABA/low-dose ICS (56%). The primary endpoint of the study was to demonstrate superiority of Atectura Breezhaler 125 mcg/62.5 mcg once daily over mometasone furoate 200 mcg once daily in terms of trough FEV_1 at week 12.

Atectura Breezhaler 125 mcg/62.5 mcg once daily demonstrated a statistically significant improvement in baseline trough FEV_1 at week 12 and Asthma Control Questionnaire (ACQ-7) score compared to mometasone furoate 200 mcg once daily.

Results for the most clinically relevant endpoints are described in Table 3.

Table 3 Results of primary and secondary endpoints in QUARTZ study 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)
Mean morning peak expiratory flow (PEF)	
Treatment difference (95% CI)	27.2 l/min (22.1, 32.4)
Evening peak expiratory flow (PEF)	
Treatment difference (95% CI)	26.1 l/min (21.0, 31.2)
Symptoms	
ACQ-7 (key secondary endpoint)	
Treatment difference P value (95% CI)	-0.218 <0.001 (-0.293, -0.143)
Percentage of patients achieving MCID from baseline with ACQ ≥0.5	
Percentage Odds ratio (95% CI)	75% vs 65% 1.69 (1.23, 2.33)
Percentage of rescue medication free days	
Treatment difference (95% CI)	8.1 (4.3, 11.8)
Percentage of days with no symptoms	
Treatment difference (95% CI)	2.7 (-1.0, 6.4)
* 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, bid = twice daily	

Paediatric population

In the PALLADIUM study, which included 106 adolescents (12-17 years old), the improvements in trough FEV_1 at week 26 were 0.173 litres (95% CI: -0.021, 0.368) for Atectura Breezhaler 125 mcg/260 mcg once daily vs mometasone furoate 800 mcg (i.e. high doses) and 0.397 litres (95% CI: 0.195, 0.599) for Atectura Breezhaler 125 mcg/127.5 mcg once daily vs mometasone furoate 400 mcg once daily (i.e. medium doses).

In the QUARTZ study, which included 63 adolescents (12-17 years old), the

Least Square means treatment difference for trough FEV_1 at day 85 (week 12) was 0.251 litres (95% CI: 0.130, 0.371).

For the adolescent subgroups, improvements in lung function, symptoms and exacerbation reductions were consistent with the overall population.

The European Medicines Agency has deferred the obligation to submit the results of studies with indacaterol/mometasone furoate in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

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

Following inhalation of the combination, 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-h 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 mcg (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 inhaler. Steady state was achieved after 12 days. The mean accumulation ratio of mometasone furoate, i.e. AUC over the 24-h dosing interval on day 14 compared to day 1, was in the range of 1.61 to 1.71 for once-daily inhaled doses between 62.5 and 260 mcg as part of the indacaterol/mometasone furoate combination.

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 2 557 litres, 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 332 litres. The *in vitro* protein binding for mometasone furoate is high, 98% to 99% in concentration range of 5 to 500 ng/ml.

Biotransformation

Indacaterol
After oral administration of radiolabelled indacaterol in a human ADME (absorption, distribution, metabolism, excretion) 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 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 litres/hour. Compared with the serum clearance of indacaterol of 18.8 to 23.3 litres/hour, 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 in which 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 $T_{½}$ 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%).

Interactions

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

Linearity/non-linearity

Systemic exposure of mometasone furoate increased in a dose proportional manner following single and multiple doses of Atectura Breezhaler 125 mcg/62.5 mcg and 125 mcg/260 mcg 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 mcg/62.5 mcg to 125 mcg/260 mcg. Dose proportionality assessments were not performed for indacaterol as only one dose was used across all dose strengths.

Paediatric population

Atectura Breezhaler may be used in adolescent patients (12 years of age and older) at the same posology as in adults.

Special populations

A population pharmacokinetic analysis in patients with asthma after inhalation of indacaterol/mometasone furoate 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.

Patients with 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 (see section 4.2).

Patients with hepatic impairment
The effect of indacaterol/mometasone furoate has not been evaluated in subjects with hepatic impairment. However, studies have been conducted with the monotherapy components (see section 4.2).

Indacaterol
Patients with mild and 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 mcg 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 50 pcg/ml) were few.

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

5.3 Preclinical safety data

Indacaterol and mometasone furoate combination

The findings during the 13-week inhalation toxicity studies were predominantly attributable to the mometasone furoate component 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 beta2 agonistic properties of indacaterol included tachycardia, arrhythmias and myocardial lesions in dogs. Mild irritation of the nasal cavity and larynx was 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 beta2 adrenergic agonists. No evidence of carcinogenicity was seen in mice.

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

Following subcutaneous administration in a rabbit study, adverse effects of indacaterol with respect to pregnancy and embryonal/foetal development could only be demonstrated at doses more than 500-fold those achieved following daily inhalation of 150 mcg in humans (based on AUC0 24 h).

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 at an exposure 14-fold higher than in humans treated with indacaterol. Indacaterol was not embryotoxic or teratogenic in rats or rabbits.

Mometasone furoate

All observed effects are typical of the glucocorticoid class of compounds and are related to exaggerated pharmacological 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.

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 studies of reproductive function, subcutaneous mometasone furoate at 15 mcg/kg prolonged gestation and difficult labour occurred, with a reduction in offspring survival and body weight.

Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that mometasone may pose a risk to surface water (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Lactose monohydrate

Capsule shell

Gelatin
Printing ink

Atectura Breezhaler 125 micrograms/62.5 micrograms inhalation powder, hard capsules
Shellac
Brilliant blue FCF (E133)
Propylene glycol (E1520)
Titanium dioxide (E171)
Black iron oxide (E172)

Atectura Breezhaler 125 micrograms/127.5 micrograms inhalation powder, hard capsules
Shellac
Titanium dioxide (E171)
Black iron oxide (E172)
Propylene glycol (E1520)
Yellow iron oxide (E172)
Ammonia hydroxide (E527)

Atectura Breezhaler 125 micrograms/260 micrograms inhalation powder, hard capsules
Shellac
Black iron oxide (E172)
Propylene glycol (E1520)
Ammonia hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package in order to protect from light and moisture.

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.

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

Single pack containing 10 x 1 or 30 x 1 hard capsules, together with 1 inhaler.
Multipacks containing 90 (3 packs of 30 x 1) hard capsules and 3 inhalers.
Multipacks containing 150 (15 packs of 10 x 1) hard capsules and 15 inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The inhaler provided with each new prescription should be used. The inhaler in each pack should be disposed of after all capsules in that pack have been used.

This medicinal product may pose a risk to the environment (see section 5.3).

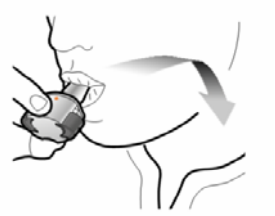
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for handling and use

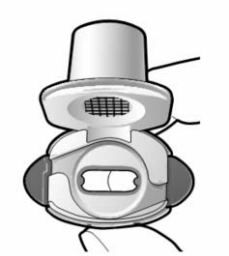
Please read the full **Instructions for Use** before using the Atectura Breezhaler.

Insert

Pierce and release

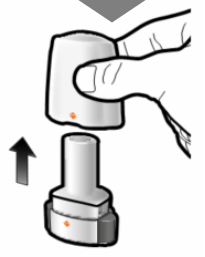


Inhale deeply



Check capsule is empty

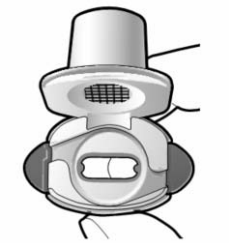
1 **2** **3** **Check**



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.

If there is powder left in the capsule:

- Close the inhaler.
- Repeat steps 3a to 3d.

Step 1b:
Open inhaler

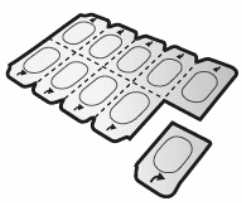
You should hear a noise as the capsule is pierced. Only pierce the capsule once.

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.
Do not press the side buttons.

Step 2b:
Release side buttons

Powder remaining

Empty



Step 1c:
Remove capsule
Separate one of the blisters from the blister card.
Peel open the blister and remove the capsule.
Do not push the capsule through the foil.
Do not swallow the capsule.

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.

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.

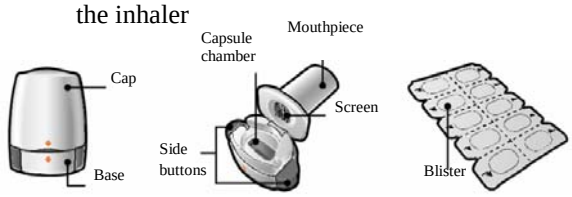
Step 1e:
Close inhaler

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 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?
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.

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.

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.

7 MARKETING AUTHORISATION HOLDER

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W12 7FQ
United Kingdom

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10 DATE OF REVISION OF THE TEXT

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