New Medicine Assessment

Atectura Breezhaler (indacaterol (as acetate) and mometasone furoate) 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.

Recommendation: GREEN

Atectura Breezhaler offers a once daily, fixed dose regimen which fits within the LSCMMG 'Asthma Treatment Guideline for Adults (aged 17 and over)'.

Atectura Breezhaler is available in three different ICS doses providing the flexibility to adjust the dose to the individual patients needs**.**

Summary of supporting evidence:

QUARTZ Study Details[1]

- A 12-week treatment, randomised, double-blind, double-dummy, parallel-group study in 802 asthma patients aged ≥12 and ≤75 years with a documented diagnosis of asthma for a period of ≥3 months prior to screening, who were taking low-dose ICS (with or without controller, e.g. LABA) for at least 1 month prior to screening visit.
- Primary endpoint was met: Atectura Breezhaler low-dose significantly improved trough FEV1 compared to MF low-dose after 12 weeks of treatment – mean difference 182mL (95% CI: 148, 217; p<0.001).
- Key secondary endpoint, superiority in ACQ-7 score (low-dose Atectura Breezhaler vs low-dose MF) after 12 weeks, was met with Atectura Breezhaler low-dose demonstrating statistically significant improvements in asthma control compared with MF low-dose, as measured by ACQ-7 after 12 weeks of treatment – mean treatment difference: -0.218 (95% CI: -0.293, -0.143; p<0.001)

PALLADIUM Study Details[2]

- A 52-week randomised study in 2,216 asthma patients ≥12 years and ≤75 years, inadequately controlled on medium- or high-dose ICS and/or low-dose LABA/ICS.
- Primary endpoint was met: Atectura Breezhaler significantly improved trough FEV1 by +211 mL (95% CI: 167, 255) and +132 mL (95% CI: 88, 176) for medium- and high-doses respectively at Week 26 vs MF, p<0.001.
- Key secondary endpoint, superiority in ACQ-7 score (combined doses of Atectura Breezhaler vs MF) at Week 26, was met with Atectura Breezhaler combined doses significantly improving ACQ-7 vs MF combined doses (treatment difference was -0.209 [95% CI: -0.270, -0.149]; p<0.001).

Details of Review

Name of medicine (generic & brand name)**:**

Atectura Breezhaler (indacaterol (as acetate) and mometasone furoate)

Strength(s) and form(s):

125 micrograms/62.5 micrograms inhalation powder, hard capsules (low dose steroid)

125 micrograms/127.5 micrograms inhalation powder, hard capsules (medium dose steroid)

125 micrograms/260 micrograms inhalation powder, hard capsules (high dose steroid)

Dose and administration:[3]

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 dosage 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.

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

The capsules must be administered only using the inhaler provided with each new prescription.

BNF therapeutic class / mode of action

Indacaterol is a long acting $beta_2$ - agonist (LABA) and mometasone is an inhaled corticosteroid (ICS)

Licensed indication(s):

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.

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication

Course and cost:

Ongoing maintenance therapy.

125 micrograms/62.5 micrograms inhalation powder, hard capsules (low dose steroid)

NHS list price 30 capsules = £17.49

125 micrograms/127.5 micrograms inhalation powder, hard capsules (medium dose steroid)

NHS list price 30 capsules = £21.50

125 micrograms/260 micrograms inhalation powder, hard capsules (high dose steroid)

NHS list price 30 capsules = £27.97

Current standard of care/comparator therapies: (NHS list price Feb 2021 DT)[4]

Symbicort 100/6, 200/6, 400/12 used twice daily

NHS list price 100/6, 200/6 and 400/12 =£28.00

Fostair Nexthaler 100/6, 200/6 used twice daily

NHS list price 100/6 and 200/6 = £29.32

Fostair 100/6, 200/6 used twice daily

NHS list price 100/6 and 200/6 = £29.32

Flutiform 50, 125, 250 used twice daily

NHS list price 50 =£14.40, 125 = £28.00 and 250 = £45.56

Relvar Ellipta 92/22, 184/22 used once daily

NHS list price 92/22 = £22.00 and 184/22 = £29.50

Relevant NICE guidance:

Asthma: diagnosis, monitoring and chronic asthma management. NICE guideline [NG80] Published date: 29 November 2017 Last updated: 12 February 2020.[5]

NICE have indicated that they will not undertake a technology appraisal of Atectura.

In Scotland, a submission will be made as part of an abbreviated process in February 2021.

Background and context

Atectura Breezhaler has now been licensed for the maintenance treatment of asthma in adults and adolescents 12 years of age and older, not adequately controlled with inhaled corticosteroids and inhaled short acting beta2 - agonists. Atectura offers a once daily dosing with three different ICS doses providing the flexibility to adjust treatment to the patients needs, whilst using the same inhalation device. This fits with the recommendations contained within the LSCMMG 'Asthma Treatment Guideline for Adults (aged 17 and over)'.

Summary of evidence

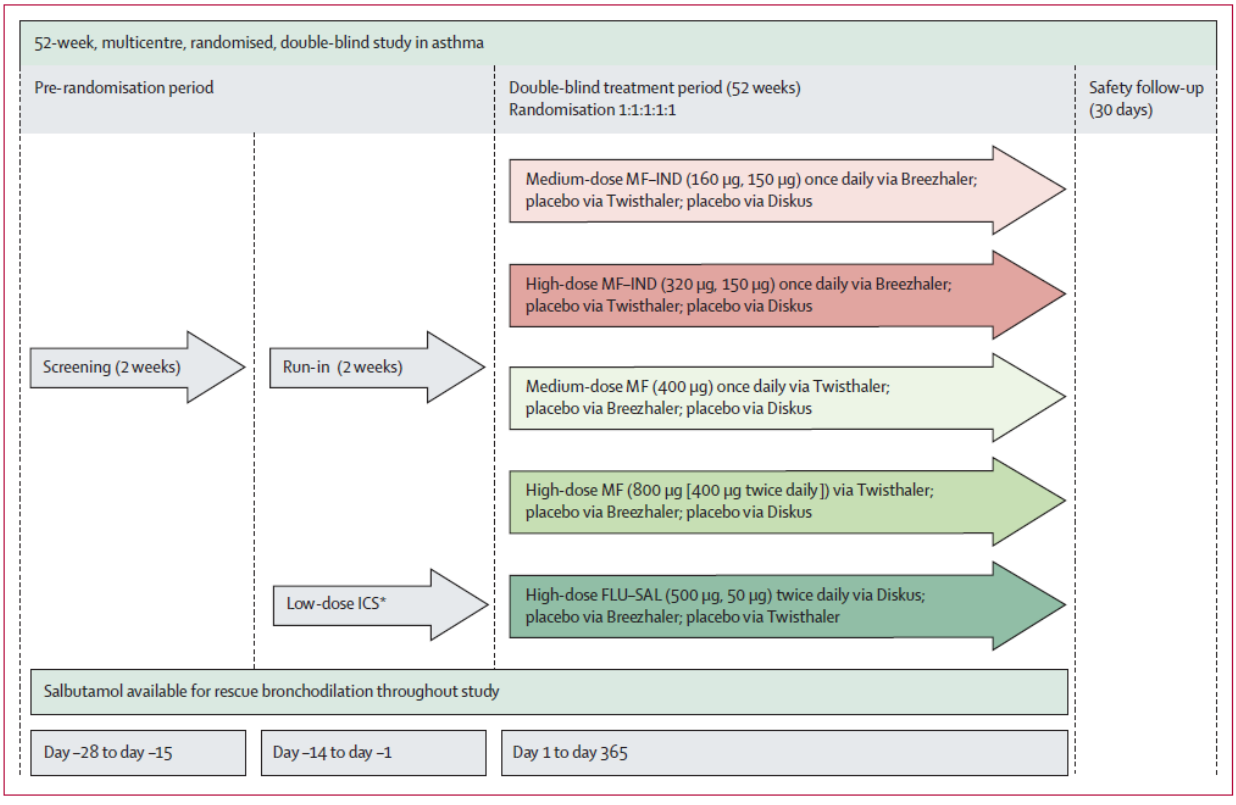
Summary of efficacy data in proposed use:

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

PALLADIUM study

The PALLADIUM study was a 52-week pivotal study evaluating indacaterol/mometasone 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.[2,6] 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 ≥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%).

Figure 1: PALLADIUM study design



Overall, participants had a mean (SD) age of 48 (14·78) years with 107 (5%) of 2216 being adolescent (aged 12–17 years) patients.

The primary objective of the study was to demonstrate superiority of either indacaterol/mometasone 125 mcg/127.5 mcg once daily over mometasone furoate 400 mcg once daily or indacaterol/mometasone 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, indacaterol/mometasone 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 1). High-dose indacaterol/mometasone was non-inferior to high-dose FLU–SAL in improving trough FEV_1 from baseline at week 26. Findings at week 52 were consistent with week 26.

Indacaterol/mometasone 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 1).

Table 1 Results of primary and secondary endpoints in PALLADIUM study at weeks 26 and 52

Endpoint	Time point/ Duration	Indacaterol/mometasone [1] vs mometasone[2]		Indacaterol/mometasone[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]	Indacaterol/mometasone 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 indacaterol/mometasone 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

QUARTZ study

The QUARTZ study was a 12-week study evaluating Atectura Breezhaler (indacaterol/mometasone) 125 mcg/62.5 mcg once daily (N=398) compared to mometasone furoate 200 mcg once daily (N=404).[1,6] The mean age was 45.6 years with 13.5% of randomised patients aged ≥65 years. This study also included 64 (8.0%) adolescent patients (aged ≥12 to <18 years). 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 indacaterol/mometasone 125 mcg/62.5 mcg once daily over mometasone furoate 200 mcg once daily in terms of trough FEV_1 at week 12.

Indacaterol/mometasone 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 2.

Table 2 Results of primary and secondary endpoints in QUARTZ study at week 12

Endpoints	**Indacaterol/mometasone low dose* vs mometasone 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)

* Indacaterol/mometasone 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 indacaterol/mometasone 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 indacaterol/mometasone 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.

Other relevant data:

Metered dose inhalers (pMDIs) require two or four doses daily and have estimated carbon footprints of 500g CO_2 eq / dose.[7]

The Atectura Breezhaler once daily device delivers 13g CO_2 eq / dose.[8]

The Breezhaler device is HFA / CFC free.

Summary of safety data:

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%).[3]

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

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).
* 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.

Strengths and limitations of the evidence:

Strengths:

- Both pivotal studies enrolled large number of patients, and were, randomised / double blind
- The PALLADIUM study included one arm of comparator combination product

Limitations:

- The majority of supporting data was derived from combination product versus corticosteroid inhaler.
- The QUARTZ study lasted 12 weeks which did not allow for longer-term safety data to be evaluated. In addition, limited conclusions can be drawn from the exacerbation results due to the short duration of the study
- The combination comparator in PALLADIUM did not use a once daily product (a comparator containing vilanterol e.g. Relvar Ellipta could have provided such a comparator)

Summary of evidence on cost effectiveness:

The NHS list price of Atectura Breezhaler ranges from £17.49 to £27.97 dependent on ICS strength. This is the equivalent to the cost of one months treatment ie 30 capsules, with a dose of one capsule daily.

The other once daily inhaler device Relvar Ellipta, ranges in price from £22.00 to £29.50 dependent on ICS dose, but only offers the option of two ICS strengths whilst Atectura offers three.

Atectura is also slightly less expensive than examples of other twice daily ICS / LABA combination inhalers.

Prescribing and risk management issues:

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

Innovation, need, equity:

Atectura offers a once daily dosing regimen which also provides flexibility in ICS dosing, enabling the patient to stay on the same inhalation device throughout the treatment pathway, with potentially improved compliance.

References

[1] Kornmann O et al, Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: Phase III randomised QUARTZ study findings, Respir Med. 2020 Jan;161:105809. doi: 10.1016/j.rmed.2019.105809 Epub 2019 Nov 14.

[2] van Zyl-Smit RN et al., Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study, Lancet Respir Med. 2020 Oct;8(10):987-999. doi: 10.1016/S2213-2600(20)30178-8. Epub 2020 Jul 9.

[3] SmPC https://www.medicines.org.uk/emc/product/11885

[4] Drug Tariff February 2021 https://www.drugtariff.nhsbsa.nhs.uk/#/00797108-DC/DC00797101/Home

[5] Asthma: diagnosis, monitoring and chronic asthma management NICE guideline [NG80] https://www.nice.org.uk/guidance/ng80

[6] European Medicines Agency, Assessment report: Atectura Breezhaler, EMA/206547/2020, 02 April 2020 https://www.ema.europa.eu/en/documents/assessment-report/atectura-breezhaler-epar-public-assessment-report_en.pdf

[7] NICE news article https://www.nice.org.uk/news/article/nice-encourages-use-of-greener-asthma-inhalers

[8] Novartis case study https://www.novartis.com/our-company/corporate-responsibility/environmental-sustainability/climate/case-study-breezhaler-carbon-footprint