Lancashire & South Cumbria Medicines Management Group

NHS Midlands and Lancashire Commissioning Support Unit

New Medicine Assessment

Enerzair Breezhaler (indacaterol (as acetate), glycopyrronium bromide and mometasone furoate) as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long acting beta$_2$ agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

Recommendation: Green (restricted)

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Little or no specific monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Brief prescribing document or information sheet may be required.
- Primary care prescribers must be familiar with the drug to take on prescribing responsibility or must get the required information.

Summary of supporting evidence:

The 52 week **IRIDIUM** study assessed the efficacy and safety of a once-daily, single-inhaler combination of mometasone furoate, indacaterol acetate, and glycopyrronium bromide (MF-IND-GLY) versus ICS-LABA in patients with inadequately controlled asthma.
It was found that once-daily, single-inhaler MF-IND-GLY improved lung function (trough FEV_1) versus ICS-LABA combinations (MF-IND and FLU-SAL) in patients with inadequately controlled asthma. The safety profile was similar across treatment groups.

The 24 week **ARGON** study assessed the efficacy and safety of once-daily fixed-dose combination of indacaterol (IND), glycopyrronium (GLY) and mometasone furoate (MF) via Breezhaler versus concurrent administration of salmeterol/fluticasone (SAL/FLU) twice-daily (b.i.d.) via Accuhaler +Tiotropium (TIO) o.d. via Respimat was evaluated in patients with uncontrolled asthma. IND/GLY/MF high- and medium-dose o.d. via a single inhaler were non-inferior to SAL/FLU high-dose b.i.d. + TIO o.d. via two inhalers for Asthma Quality of Life Questionnaire (AQLQ). IND/GLY/MF high-dose o.d. improved lung function, asthma control and health status versus SAL/FLU high dose + TIO, while IND/GLY/MF medium-dose had comparable efficacy but at a corresponding lower steroid dose.

Details of Review

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

Enerzair Breezhaler (indacaterol (as acetate), glycopyrronium bromide and mometasone furoate)

Strength(s) and form(s):

Date: September 2022

Each capsule contains 150 mcg of indacaterol (as acetate), 63 mcg of glycopyrronium bromide equivalent to 50 mcg of glycopyrronium and 160 mcg of mometasone furoate.

Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 114 mcg of indacaterol (as acetate), 58 mcg of glycopyrronium bromide equivalent to 46 mcg of glycopyrronium and 136 mcg of mometasone furoate.

Dose and administration:[1]

Adults (Aged 18 and over):

The recommended dose is one capsule to be inhaled once daily.

The maximum recommended dose is 114 mcg/46 mcg/136 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.

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

BNF therapeutic class / mode of action

Indacaterol is a long acting $beta_2$ - agonist (LABA), mometasone is an inhaled corticosteroid (ICS) and glycopyrronium is a long acting muscarinic receptor antagonist (LAMA)

Licensed indication(s):

Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long acting $beta_2$ agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

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

Licensed indication

Course and cost:

Ongoing maintenance therapy.

Enerzair Breezehaler with / without sensor for 30 capsules = £44.50

Current standard of care/comparator therapies:

The Atectura Breezhaler (indacaterol / mometasone)125 micrograms/127.5 micrograms inhalation powder, hard capsules (medium dose steroid) NHS list price 30 capsules = £21.50

The Seebri Breezhaler (glycopyrronium bromide) 55 micrograms inhalation powder, hard capsules NHS list price 30 capsules = £27.50.

Therefore the cost of these two inhalers together for 1 months treatment would be £49.00

The other triple therapy inhaler, Trimbow (beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium), licensed for maintenance treatment of asthma, in adults not adequately controlled with a maintenance combination of a long-acting $beta_2$-agonist and high dose of inhaled corticosteroid, and who experienced one or more asthma exacerbations in the previous year has an NHS list price of £44.50

Relevant NICE guidance:

Asthma: diagnosis, monitoring and chronic asthma management. NICE guideline [NG80] Published date: 29 November 2017 Last updated: 12 February 2020.[2]

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

In Wales, the AWMSG is currently appraising Enerzair – publication date TBC

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

Background and context

Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long acting $beta_2$ agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year.

Enerzair offers the convenience of one device with a one dose, once daily regimen. This fits with the recommendations contained within the LSCMMG 'Asthma Treatment Guideline for Adults (aged 17 and over)'.

A sensor is available for the Enerzair Breezhaler, this an optional digital component which can be prescribed alongside the medicinal product at no extra cost. The sensor, which tracks every dose taken and if the dose was taken correctly, sends information the Propellor mobile app that records patient compliance. The patient accesses a personalised profile, owns their personal data and can download a report of their last 30 days treatment to share with their doctor.

The sensor also includes a function to set medication reminders.

The Breezhaler inhaler will work equally well with or without the sensor device.

Summary of evidence

Summary of efficacy data in proposed use:

IRIDIUM study

The safety and efficacy of Enerzair Breezhaler in adult patients with persistent asthma was evaluated in the phase III randomised, double-blind study (IRIDIUM).[3,4] The IRIDIUM study was a 52-week study evaluating Enerzair Breezhaler 114 mcg/46 mcg/68 mcg once daily (N=620) and 114 mcg/46 mcg/136 mcg once daily (N=619) compared to indacaterol/mometasone furoate 125 mcg/127.5 mcg once daily (N=617) and 125 mcg/260 mcg once daily (N=618), respectively. A third active control arm included subjects treated with salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily (N=618). All subjects were required to have symptomatic asthma (ACQ-7[i] score ≥1.5) and were on asthma maintenance therapy using a medium or high dose inhaled synthetic corticosteroid (ICS) and LABA combination therapy for at least 3 months prior to study entry. The mean age was 52.2 years with 18.4% of patients being 65 years of age or older. At screening, 99.9% of patients reported a history of exacerbation in the past year. At study entry, the most common asthma medications reported were medium dose of ICS in combination with a LABA (62.6%) and high dose of ICS in combination with a LABA (36.7%).

The primary objective of the study was to demonstrate superiority of either Enerzair Breezhaler 114 mcg/46 mcg/68 mcg once daily over indacaterol/mometasone furoate 125 mcg/127.5 mcg once daily or Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily over

[i] Asthma Control Questionnaire

indacaterol/mometasone furoate 125 mcg/260 mcg once daily in terms of trough FEV_1 at week 26.

Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily demonstrated statistically significant improvements in trough FEV_1 at week 26 compared to indacaterol/mometasone furoate at corresponding dose. Clinically meaningful improvements in lung function (change from baseline trough FEV_1 at week 26, morning and evening peak expiratory flow) were also observed compared to salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily. Findings at week 52 were consistent with week 26 (see Table 1).

All treatment groups showed clinically relevant improvements from baseline in ACQ-7 at week 26, however no statistically significant differences between groups were observed. The mean change from baseline in ACQ-7 at week 26 (key secondary endpoint) and week 52 was around -1 for all treatment groups. The ACQ-7 responder rates (defined as a change decrease in score of ≥0.5) at different time points are described in Table 1.

Exacerbations were a secondary endpoint (not part of confirmatory testing strategy). Enerzair Breezhaler 114 mcg/46 mcg/136 mcg once daily demonstrated a reduction in the annual rate of exacerbations compared to salmeterol/fluticasone propionate 50 mcg/500 mcg twice daily and indacaterol/mometasone furoate 125 mcg/260 mcg once daily.

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

Endpoint	**Time point/ Duration**	**Enerzair Breezhaler[1] vs IND/MF[2]**	**Enerzair Breezhaler[1] vs SAL/FP[3]**
Lung function			
Trough FEV_1[4]			
Treatment difference P value (95% CI)	Week 26 (Primary endpoint)	65 ml <0.001 (31, 99)	119 ml <0.001 (85, 154)
	Week 52	86 ml <0.001 (51, 120)	145 ml <0.001 (111, 180)
Mean morning peak expiratory flow (PEF)			
Treatment difference (95% CI)	Week 52*	18.7 l/min (13.4, 24.1)	34.8 l/min (29.5, 40.1)
Mean evening peak expiratory flow (PEF)			
Treatment difference (95% CI)	Week 52*	17.5 l/min (12.3, 22.8)	29.5 l/min (24.2, 34.7)
Symptoms			
ACQ responders (percentage of patients achieving minimal clinical important difference (MCID) from baseline with ACQ ≥0.5)			
Percentage	Week 4	66% vs 63%	66% vs 53%
Odds ratio (95% CI)		1.21 (0.94, 1.54)	1.72 (1.35, 2.20)
Percentage	Week 12	68% vs 67%	68% vs 61%
Odds ratio (95% CI)		1.11 (0.86, 1.42)	1.35 (1.05, 1.73)
Percentage	Week 26	71% vs 74%	71% vs 67%
Odds ratio (95% CI)		0.92 (0.70, 1.20)	1.21 (0.93, 1.57)
Percentage	Week 52	79% vs 78%	79% vs 73%
Odds ratio (95% CI)		1.10 (0.83, 1.47)	1.41 (1.06, 1.86)
Annualised rate of asthma exacerbations			

Moderate or severe exacerbations			
AR	Week 52	0.46 vs 0.54	0.46 vs 0.72
RR** (95% CI)	Week 52	0.85 (0.68, 1.04)	0.64 (0.52, 0.78)
Severe exacerbations			
AR	Week 52	0.26 vs 0.33	0.26 vs 0.45
RR** (95% CI)	Week 52	0.78 (0.61, 1.00)	0.58 (0.45, 0.73)

* Mean value for the treatment duration.
** RR <1.00 favours indacaterol/glycopyrronium/mometasone furoate.
[1] Enerzair Breezhaler 114 mcg/46 mcg/136 mcg od.
[2] IND/MF: indacaterol/mometasone furoate high dose: 125 mcg/260 mcg od. Mometasone furoate 136 mcg in Enerzair Breezhaler is comparable to mometasone furoate 260 mcg in indacaterol/mometasone furoate.
[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

ARGON study

ARGON[5] was a 24 week, multicentre, randomised, parallel group, non- inferiority, open labelled, active controlled Phase IIIb study in 1,426 inadequately controlled asthma patients (18-75 years of age) despite treatment with high dose ICS / LABA. The primary endpoint was to demonstrate non-inferiority in change from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score with IND/GLY/MF high dose compared to SAL/FLU high dose plus tiotropium at week 24. The primary endpoint was met with statistical significance.

Other considerations:

Metered dose inhalers (pMDIs) require two or four doses daily and have estimated carbon footprints of 500g CO_2 eq/dose.[6]

The Enerzair Breezhaler once daily device and Enerzair Breezhaler plus sensor once daily device delivers 12g and 17g CO_2 eq/dose respectively.[7]

The Breezhaler device is HFA / CFC free.

Summary of safety data

The most common adverse reactions over 52 weeks were asthma (exacerbation) (41.8%), nasopharyngitis (10.9%), upper respiratory tract infection (5.6%) and headache (4.2%).[1]

Adverse reactions

System organ class	Adverse reactions	Frequency category
Infections and infestations	Nasopharyngitis	Very common
	Upper respiratory tract infection	Common
	Candidiasis*[1]	Common
	Urinary tract infection*[2]	Common
Immune system disorders	Hypersensitivity*[3]	Common
Metabolism and nutrition disorders	Hyperglycaemia*[4]	Uncommon
Nervous system disorders	Headache*[5]	Common
Eye disorders	Cataract	Uncommon

Cardiac disorders	Tachycardia*[6]	Common
Respiratory, thoracic and mediastinal disorders	Asthma (exacerbation)	Very common
	Oropharyngeal pain*[7]	Common
	Cough	Common
	Dysphonia	Common
Gastrointestinal disorders	Gastroenteritis*[8]	Common
	Dry mouth*[9]	Uncommon
Skin and subcutaneous tissue disorders	Rash*[10]	Uncommon
	Pruritus*[11]	Uncommon
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*[12]	Common
	Muscle spasms	Common
Renal and urinary disorders	Dysuria	Uncommon
General disorders and administration site conditions	Pyrexia	Common

* Indicates grouping of preferred terms (PTs):
1 Oral candidiasis, oropharyngeal candidiasis.
2 Asymptomatic bacteriuria, bacteriuria, cystitis, urethritis, urinary tract infection, urinary tract infection viral.
3 Drug eruption, drug hypersensitivity, hypersensitivity, rash, rash pruritic, urticaria.
4 Blood glucose increased, hyperglycaemia.
5 Headache, tension headache.
6 Sinus tachycardia, supraventricular tachycardia, tachycardia.
7 Odynophagia, oropharyngeal discomfort, oropharyngeal pain, throat irritation.
8 Chronic gastritis, enteritis, gastritis, gastroenteritis, gastrointestinal inflammation.
9 Dry mouth, dry throat.
10 Drug eruption, rash, rash papular, rash pruritic.
11 Eye pruritus, pruritus, pruritus genital.
12 Back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain.

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)

Strengths and limitations of the evidence:

Strengths:

- The large, 52 week IRIDIUM study demonstrated the triple inhaler increased trough FEV_1 when compared to double combination inhalers and this effect continued for the period of the trial
- IRIDIUM showed that comparative symptom control improved, although this was a secondary endpoint
- ARGON study showed noninferiority when Enerzair was compared to a triple component regimen

Limitations:

- IRIDIUM had minimal effect on exacerbations
- The studies did not compare Enerzair with a triple component inhaler device.

Summary of evidence on cost effectiveness:

The NHS list price of the Enerzair Breezhaler with / without sensor = £44.50

Trimbow (beclometasone dipropionate, formoterol fumarate dihydrate and glycopyrronium) is the only other triple therapy inhaler now licensed for asthma and has an NHS list price of £44.50. However, the recommended dose is two inhalations twice daily.

The Atectura Breezhaler (indacaterol / mometasone)125 micrograms/127.5 micrograms inhalation powder, hard capsules (medium dose steroid) NHS list price 30 capsules = £21.50

The Seebri Breezhaler (glycopyrronium bromide) 55 micrograms inhalation powder, hard capsules NHS list price 30 capsules = £27.50.

Therefore the cost of these two inhalers together for 1 months treatment would be £49.00

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:

Enerzair Breezhaler offers a once daily dosing regimen and could enable the patient to stay on the same inhalation device throughout the treatment pathway, with potentially improved compliance

References

[1] SmPC: https://www.medicines.org.uk/emc/product/11886

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

[3] H.A.M Kerstjens et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study Lancet Respir Med. 2020 Oct;8(10):1000-1012. https://pubmed.ncbi.nlm.nih.gov/32653074/

[4] European Medicines Agency, Assessment report: Enerzair, EMA/271332/2020, 30 April 2020 https://www.ema.europa.eu/en/documents/assessment-report/enerzair-breezhaler-epar-public-assessment-report_en.pdf

[5] C.Gessner et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respiratory Medicine, Volume 170, August–September 2020, 106021 https://www.sciencedirect.com/science/article/abs/pii/S095461112030161X

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

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