New Medicine Assessment

Trimbow NEXThaler (DPI) 88 micrograms/5 micrograms/9 micrograms per actuation inhalation powder for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist

Recommendation: GREEN (Restricted)

Restriction: Triple therapy should be reserved for patients who have failed to achieve or maintain an adequate response to an appropriate course of dual therapy.

This is in agreement with the LSCMMG RAG recommendations for the other inhaled triple therapies licensed for COPD.

Trimbow NEXThaler is licensed for the maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist. This is also in line with the GOLD 2019 guidelines[1] and the LSCMMG COPD desktop guideline.[2]

Trimbow NEXThaler provides a beclomethasone/ formoterol/ glycopyrronium DPI device option for patients with COPD with equivalent efficacy to the Trimbow pMDI.

Summary of supporting evidence:

The key regulatory trial (phase II) for Trimbow NEXThaler 88/5/9 is the TRI-D study.[3,8]

The non-inferiority of Trimbow NEXThaler 88/5/9 vs. Trimbow pMDI 87/5/9 in terms of lung function was demonstrated in the TRI-D study which was a randomised, double-blind, active-controlled three-way cross-over study (n=366).

Co-primary endpoints:

- Changes from baseline in FEV1 AUC0–12h (Trimbow NEXThaler, N=351; Trimbow pMDI, N=351; Fostair pMDI 100/6, N=353) and trough FEV1 (Trimbow NEXThaler, N=351; Trimbow pMDI, N=350; Fostair pMDI 100/6, N=351) on day 28 were similar for Trimbow pMDI and Trimbow NEXThaler with the CIs for the difference lying entirely within the pre-specified non-inferiority criterion (-50 mL)
- Adjusted mean differences (95% CI) between Trimbow MDI and Trimbow NEXThaler were -20 mL (-35; -6) for FEV1 AUC0–12h, and 3 mL (-15; 20) for trough FEV1 at 24 hours on day 28
- Assay sensitivity demonstrated by statistical superiority of Trimbow NEXThaler and Trimbow pMDI vs. Fostair pMDI 100/6 (n=353) for change from baseline in both FEV1 AUC0–12h and trough FEV1 on day 28 ($p<0.001$)

Key secondary endpoints:

There was no relevant difference between Trimbow NEXThaler 88/5/9 and Trimbow pMDI 87/5/9 for pre-dose morning FEV1 or FEV1 AUC0–4h on day 28, and peak FEV1 on days 1 and 28

Date: April 2022

Details of Review

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

Trimbow 88 micrograms/5 micrograms/9 micrograms inhalation powder.[4]

Each delivered dose (the dose leaving the mouthpiece) contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide).

Strength(s) and form(s):

Inhalation powder (DPI)

Each delivered dose (the dose leaving the mouthpiece) contains 88 micrograms of beclometasone dipropionate, 5 micrograms of formoterol fumarate dihydrate and 9 micrograms of glycopyrronium (as 11 micrograms glycopyrronium bromide).

Each metered dose contains 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate dihydrate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide).

Dose and administration:4

The recommended dose is two inhalations twice daily.

The maximum dose is two inhalations twice daily.

BNF therapeutic class / mode of action

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids.

Beclometasone dipropionate given by inhalation at recommended doses has a glucocorticoid anti-inflammatory action within the lungs. Glucocorticoids are widely used for the suppression of inflammation in chronic inflammatory diseases of the airways. Their action is mediated by the binding to glucocorticoid receptors in the cytoplasm resulting in the increased transcription of genes coding for anti-inflammatory proteins.

Formoterol is a selective beta2-adrenergic agonist that produces relaxation of bronchial smooth muscle in patients with reversible airways obstruction. The bronchodilating effect sets in rapidly, within 1-3 minutes after inhalation, and has a duration of 12 hours after a single dose.

Glycopyrronium is a high-affinity, long-acting muscarinic receptor antagonist (anticholinergic) used for inhalation as bronchodilator treatment. Glycopyrronium works by blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, thereby dilating the airways. Glycopyrronium bromide is a high affinity muscarinic receptor antagonist with a greater than 4-fold selectivity for the human M3 receptors over the human M2 receptor as it has been demonstrated.

Licensed indication(s):

Maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting beta2-agonist or a combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist.

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

Licensed Indication

Course and cost:

Ongoing.

Trimbow NEXThaler costs £44.50 for 30 days treatment

Current standard of care/comparator therapies:

The NHS list price of Trimbow NEXThaler is £44.50 per inhaler (120 actuations = 30 days treatment). Other available ICS/LAMA/LABA combination inhalers licensed for COPD are also £44.50 for 30 days treatment. Therefore, there is no cost implication.

The cost of one triple inhaler is less than the cost of a combination of inhalers.

Relevant NICE guidance:

Chronic obstructive pulmonary disease in over 16s: diagnosis and management

NICE guideline [NG115] Published: 05 December 2018 Last updated: 26 July 2019[5]

Trimbow pMDI in COPD was reviewed by SMC via the abbreviated submission route and has accepted Trimbow for restricted use within NHS Scotland.[6] Trimbow NEXThaler was excluded from SMC review under the outwith remit.

Trimbow NEXThaler was excluded from AWMSG review as it met exclusion criteria 6.[7]

Background and context

Trimbow pMDI is an established product and is on the LSCMMG formulary for the treatment of asthma and COPD.

Trimbow NEXThaler offers a DPI alternative for the treatment of COPD – in line with the Green Agenda and allows one inhaler to be used for triple therapy.

Summary of evidence

Summary of efficacy data in proposed use:

Regulatory study

The TRI-D study was a randomised, double-blind, double-dummy, active-controlled, multi-centre, three-way cross-over study that aimed to demonstrate the non-inferiority of Trimbow NEXThaler 88/5/9 (n=351) vs. Trimbow pMDI 87/5/9 (n=351) in terms of lung function in patients with COPD, FEV1 30–80% predicted. [8]

Co-primary endpoints:

- Changes from baseline in FEV1 AUC0–12h (Trimbow NEXThaler, N=351; Trimbow pMDI, N=351; Fostair pMDI 100/6, N=353) and trough FEV1 (Trimbow NEXThaler, N=351; Trimbow pMDI, N=350; Fostair pMDI 100/6, N=351) on day 28 were similar for Trimbow pMDI and Trimbow NEXThaler with the CIs for the difference lying entirely within the pre-specified non-inferiority criterion (-50 mL)
- Adjusted mean differences (95% CI) between Trimbow MDI and Trimbow NEXThaler were -20 mL (-35; -6) for FEV1 AUC0–12h, and 3 mL (-15; 20) for trough FEV1 at 24 hours on day 28
- Assay sensitivity demonstrated by statistical superiority of Trimbow NEXThaler and Trimbow pMDI vs. Fostair pMDI 100/6 (n=353) for change from baseline in both FEV1 AUC0–12h and trough FEV1 on day 28 ($p<0.001$)

Change from baseline in FEV1 AUC0-12h (L) on Day 28, ITT population

			BDP/FF/GB DPI N=354	BDP/FF/GB pMDI N=357	BDP/FF pMDI N=357
Baseline[a]		n	354	357	357
		Mean (SD)	1.315 (0.501)	1.312 (0.480)	1.310 (0.500)
Day 28	**Actual values**	n	351	351	353
		Mean (SD)	1.462 (0.506)	1.480 (0.517)	1.376 (0.515)
	Change from Baseline	n	351	351	353
		Adj. mean (95% CI)	0.146 (0.136; 0.157)	0.167 (0.156; 0.177)	0.062 (0.051; 0.072)
	BDP/FF/GB DPI vs. BDP/FF/GB pMDI	Adj. mean diff. (95% CI)	-0.020 (**-0.035**; -0.006)		
		p-value	0.007		
	BDP/FF/GB pMDI vs. BDP/FF pMDI	Adj. mean diff. (95% CI)	**0.105** (0.090; 0.120)		
		p-value	< 0.001		
	BDP/FF/GB DPI vs. BDP/FF pMDI	Adj. mean diff. (95% CI)	**0.085** (0.070; 0.099)		
		p-value	< 0.001		

Change from baseline in trough FEV1 (L) at 24 hours on Day 28, ITT population

			BDP/FF/GB DPI N=354	BDP/FF/GB pMDI N=357	BDP/FF pMDI N=357
Baseline[a]		n	354	357	357
		Mean (SD)	1.315 (0.501)	1.312 (0.480)	1.312 (0.500)
Day 28	**Actual values**	n	351	350	351
		Mean (SD)	1.310 (0.480)	1.304 (0.496)	1.251 (0.495)
	Change from Baseline	n	351	350	351
		Adj. mean (95% CI)	-0.006 (-0.019; 0.006)	-0.009 (-0.021; 0.003)	-0.063 (-0.076; -0.051)
	BDP/FF/GB DPI vs. BDP/FF/GB pMDI	Adj. mean diff. (95% CI)	0.003 (**-0.015**; 0.020)		
		p-value	0.749		
	BDP/FF/GB pMDI vs. BDP/FF pMDI	Adj. mean diff. (95% CI)	**0.054** (0.037; 0.072)		
		p-value	< 0.001		
	BDP/FF/GB DPI vs. BDP/FF pMDI	Adj. mean diff. (95% CI)	**0.057** (0.040; 0.074)		
		p-value	< 0.001		

Key secondary endpoints:

There was no relevant difference between Trimbow NEXThaler and Trimbow pMDI for pre-dose morning FEV1 or FEV1 AUC0–4h on day 28, and peak FEV1 on days 1 and 28

Summary of safety data

Trimbow is generally well tolerated, with adverse reactions consistent with those of the individual components. (Trimbow SPCs)

A total of 3,346 patients were treated with Trimbow at the target dose regimen (two inhalations twice daily) in multiple dose studies. (Trimbow SPCs)

The most frequently reported adverse reactions with Trimbow pMDI 87/5/9 were consistent with those of the individual components: dysphonia and oral candidiasis (0.3% and 0.8%, respectively, related to beclometasone), muscle spasms (0.4%, related to formoterol), and dry mouth (0.4%, related to glycopyrronium).(Trimbow SPCs) Similarly, dry mouth was reported in 2 patients (0.6%) with Trimbow NEXThaler 88/5/9.(Trimbow NEXThaler SPC)4

In a 4-week study, the safety profile of Trimbow NEXThaler 88/5/9 was similar to that of Trimbow pMDI 87/5/9.(Trimbow NEXThaler SPC).4

Adverse reactions, associated to beclometasone dipropionate/formoterol/glycopyrronium, occurred during clinical trials and post-marketing experience as well as adverse reactions listed for the marketed individual components are provided below, listed by system organ class and frequency.

MedDRA system organ class	Adverse reaction	Frequency
Infections and infestations	Pneumonia (in COPD patients), pharyngitis, oral candidiasis, urinary tract infection[1], nasopharyngitis[1]	Common
	Influenza[1], oral fungal infection, oropharyngeal candidiasis, oesophageal candidiasis, fungal (oro)pharyngitis, sinusitis[1], rhinitis[1], gastroenteritis[1], vulvovaginal candidiasis[1]	Uncommon
	Lower respiratory tract infection (fungal)	Rare
Blood and lymphatic system disorders	Granulocytopenia[1]	Uncommon
	Thrombocytopenia[1]	Very rare
Immune system disorders	Dermatitis allergic[1]	Uncommon
	Hypersensitivity reactions, including erythema, lips, face, eye and pharyngeal oedema	Rare
Endocrine disorders	Adrenal suppression[1]	Very rare
Metabolism and nutrition disorders	Hypokalaemia, hyperglycaemia	Uncommon
	Decreased appetite	Rare
Psychiatric disorders	Restlessness[1]	Uncommon
	Psychomotor hyperactivity[1], sleep disorders[1], anxiety, depression[1], aggression[1], behavioural changes (predominantly in children) [1]	Frequency not known
	Insomnia	Rare
Nervous system disorders	Headache	Common
	Tremor, dizziness, dysgeusia[1], hypoaesthesia[1]	Uncommon
	Hypersomnia	Rare
Eye disorders	Vision, blurred[1] (see also section 4.4)	Frequency not known
	Glaucoma[1], cataract[1]	Very rare
Ear and labyrinth disorders	Otosalpingitis[1]	Uncommon
Cardiac disorders	Atrial fibrillation, electrocardiogram QT prolonged, tachycardia, tachyarrhythmia[1], palpitations	Uncommon
	Angina pectoris (stable[1] and unstable), extrasystoles (ventricular[1] and supraventricular), nodal rhythm, sinus bradycardia	Rare
Vascular disorders	Hyperaemia[1], flushing[1], hypertension	Uncommon
	Extravasation blood	Rare

Respiratory, thoracic and mediastinal disorders	Dysphonia	Common
	Asthmatic crisis[1], cough, productive cough[1], throat irritation, epistaxis[1], pharyngeal erythema	Uncommon
	Bronchospasm paradoxical[1], exacerbation of asthma, oropharyngeal pain, pharyngeal inflammation, dry throat	Rare
	Dyspnoea[1]	Very rare
Gastrointestinal disorders	Diarrhoea[1], dry mouth, dysphagia[1], nausea, dyspepsia[1], burning sensation of the lips[1], dental caries[1], (aphthous) stomatitis	Uncommon
Skin and subcutaneous tissue disorders	Rash[1], urticaria, pruritus, hyperhidrosis[1]	Uncommon
	Angioedema[1]	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms, myalgia, pain in extremity[1], musculoskeletal chest pain[1]	Uncommon
	Growth retardation[1]	Very rare
Renal and urinary disorders	Dysuria, urinary retention, nephritis[1]	Rare
General disorders and administration site conditions	Fatigue[1]	Uncommon
	Asthenia	Rare
	Oedema peripheral[1]	Very rare
Investigations	C-reactive protein increased[1], platelet count increased[1], free fatty acids increased[1], blood insulin increased[1], blood ketone body increased[1], cortisol decreased[1]	Uncommon
	Blood pressure increased[1], blood pressure decreased[1]	Rare
	Bone density decreased[1]	Very rare

[1] Adverse reactions reported in the SmPC of at least one of the individual components, but not observed as adverse reactions in the clinical development of Trimbow

Frequencies are defined as: 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) and not known (cannot be estimated from available data).

Strengths and limitations of the evidence:

Strengths: Well established product as pMDI with large clinical trials to support use in COPD.

Non inferiority of NEXThaler device demonstrated vs pMDI with comparative safety data.

Summary of evidence on cost effectiveness:

The NHS list price of Trimbow NEXThaler is £44.50 per inhaler (120 actuations = 30 days treatment). Other available ICS/LAMA/LABA combination inhalers licensed for COPD are also £44.50 for 30 days treatment. Therefore, there is no cost implication.

It is less expensive to use a triple inhaler than a combination of inhalers.

Prescribing and risk management issues:

N/A

Innovation, need, equity:

Trimbow NEXThaler provides an alternative DPI triple inhaler for the treatment of COPD. This allows the use of a single device throughout the treatment pathway which contributes to the Green Agenda.

References

[1] Global Initiative For Chronic Obstructive Lung Disease 2019 report https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

[2] LSCMMG COPD Desktop Guideline v1.8 https://www.lancsmmg.nhs.uk/media/1054/copd-guideline-version-18.pdf

[3] European Medicines Agency Assessment Report: Trimbow, Procedure No. EMEA/H/C/004257/X/0012, 28 January 2021 https://www.ema.europa.eu/en/documents/variation-report/trimbow-h-c-4257-x-0012-epar-assessment-report-extension_en.pdf

[4] Trimbow NEXThaler SPC https://www.medicines.org.uk/emc/product/12829

[5] Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE guideline [NG115]Published: 05 December 2018 Last updated: 26 July 2019 https://www.nice.org.uk/guidance/ng115/chapter/Recommendations#inhaled-therapy

[6] SMC 1274/17 beclometasone dipropionate anhydrous/formoterol fumarate dihydrate/glycopyrronium bromide (Trimbow) https://www.scottishmedicines.org.uk/medicines-advice/beclometasone-dipropionate-anhydrousformoterol-fumarate-dihydrateglycopyrronium-bromide-trimbow-abbreviatedsubmission-127417/

[7] AWMSG criteria for appraising a medicine. https://awttc.nhs.wales/files/appraisal-process/awmsg-exclusion-criteria-pdf-430kb/

[8] Beeh, KM. et al. Comparison of Dry-Powder Inhaler and Pressurized Metered-Dose Inhaler Formulations of Extrafine Beclomethasone Dipropionate/Formoterol Fumarate/Glycopyrronium in Patients with COPD The TRI-D Randomized Controlled Trial. International Journal of Chronic Obstructive Pulmonary Disease 2021;16:79–89. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7814657/