University Hospitals of North Midlands NHS Trust | North Staffordshire Combined Healthcare NHS Trust | Staffordshire and Stoke on Trent Partnership NHS Trust | NHS North Staffordshire Clinical Commissioning Group | NHS Stoke-on-Trent Clinical Commissioning Group

New Medicines Committee Briefing

January 2018

Trimbow® 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution

Trimbow® is to be reviewed for use within:

Primary Care	√
Secondary Care	√

- Trimbow® is a fixed-dose combination of inhaled corticosteroid (ICS), long-acting beta-2 agonist (LABA) and long-acting muscarinic antagonist (LAMA). It is licenced for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of ICS and LABA.[1]

- Trimbow® was launched in UK in August 2017 as a triple inhaler with each metered dose (the dose leaving the valve) containing 100 micrograms of beclometasone dipropionate, 6 micrograms of formoterol fumarate and 10 micrograms of glycopyrronium (as 12.5 micrograms glycopyrronium bromide).

- Trimbow® is more cost effective compared to use of the 2 component inhalers Fostair® and Seebri® administered separately hence improve complaince.

- The Global Initiative for Obstructive Lung Disease (GOLD) management strategy for COPD recommends stepping up to triple therapy (ICS+LABA+LAMA) in patients who despite currently on combination of LABA and LAMA are having further exacerbation.[2]

- Scottish Medicines Consortium accepted the use of Trimbow® for restricted use within NHS Scotland in severe COPD (forced expiratory volume in one second less than 50% predicted normal).[3]

Formulary application

Dr Imran Hussain requested the inclusion of Trimbow® to the Joint Formulary stating that the individual inhalers are already in routine clinical practice with no issues. He also noted that the use of Trimbow® will be a CIP for the local health economy.

Currently on our formulary are the individual inhalers Fostair® (beclomethasone & formoterol) and Seebri® (glycopyrronium bromide).

3.1.2 Antimuscarinic bronchodilators			
Incruse Ellipta® (Umeclidinium)		**For use in COPD only**	At a glance guide: Stable COPD
Eklira Genuair® (Aclidinium)		**For use in COPD with end of day deterioration**	At a glance guide: Stable COPD ☑ MTRAC
Ipratropium			At a glance guide: Stable COPD
Braltus Zonda® (Tiotropium)		**For use in COPD only** **10 microgram per delivered dose**	
Seebri® Breezhaler (Glycopyrronium bromide)		**For use in COPD only**	
Spiriva Respimat® (Tiotropium)	**2**	**For use in Asthma only**	☑ MTRAC

Beclometasone		**For use in Asthma only** **Restriction: See APC Advice**	☑ APC FF Article
Budesonide		**Restriction: Nebuliser use only**	
Alvesco® (Ciclesonide)		**Not approved for inclusion in the North Staffordshire Joint Formulary**	Medicines Review Verdict Sheet
Combination inhalers			
Flutiform® (Fluticasone & formoterol)		**For use in Asthma only**	☑ MTRAC
Fostair® (Beclometasone & formoterol)		**For use in both Asthma and COPD** **Please note that high strength is for Asthma only**	At a glance guide: Stable COPD
Relvar Ellipta® (Fluticasone & vilanterol)		**For use in both Asthma and COPD**	At a glance guide: Stable COPD
DuoResp Spiromax® (Budesonide & formoterol)		**For use in both Asthma and COPD**	At a glance guide: Stable COPD
For paediatric use only			
Seretide® (Fluticasone & salmeterol)		**Restriction: For use in Asthma only**	
Symbicort® (Budesonide & formoterol)		**Restriction: For use in Asthma only**	

Summary of Evidence:

TRILOGY[4] was a 52 week, double-blind, randomised, multicentre, two-arm, active-controlled clinical trial to test the superiority of Trimbow® over a fixed combination of beclometasone dipropionate and formoterol 100/6 micrograms (Fostair®) two puffs twice daily administered via pMDI (1,368 randomised patients). The three co-primary end points were pre-dose FEV1, 2 hour post-dose FEV1 and transition dyspnea index (TDI) focal score, all measured at week 26. The secondary endpoints included moderate-to-severe COPD exacerbation rate over 52 weeks.

The study showed that triple therapy with Trimbow® had a greater effect on pre-dose and 2-h post-dose FEV1 than Fostair® in patients with COPD who have severe or very severe airflow limitation, symptoms, and an exacerbation history. Trimbow was superior to Fostair® for both pre-dose FEV_1 (adjusted mean difference 81mL) [95% CI 0.052; 0.109]; p<0.001) and 2-h post-dose FEV_1 (adjusted mean difference 117mL) [95% CI 0.086; 0.147]; p<0.001 at week 26).

The rate of moderate-to-severe COPD exacerbations was 23% lower with Trimbow® compared with Fostair® (rate: 0.41 versus 0.53 events per patient/year; p = 0.005). The time to first exacerbation

significantly longer with triple therapy (hazard ratio 0.80 and 0.84 respectively; p = 0.020 and 0.015 respectively).

For SGRQ total score, clinically relevant improvements from baseline (decrease ≥4 units) occurred for the Trimbow® group at all visits from week 12 onwards, with statistically significant differences between the two groups at weeks 4, 12, and 52 (mean treatment difference at week 52 of –1·69 [95% CI –3·20 to –0·17]; p=0·029. The use of rescue medication in puffs per day was significantly lower with Trimbow® than with Fostair® up to week 26; patients in the Trimbow® group had a significantly greater percentage of days with no rescue use than those in the Fostair® group up to week 12.

There was no evidence of superiority of Trimbow® over Fostair® for measuring breathlessness (TDI). There was an increase TDI focal score in both groups at all visits, with a statistically significant difference between treatments favouring Trimbow® at the two earliest visits (weeks 4 and 12). More than 50% of patients in each group reported clinically relevant improvements (≥1 unit) in TDI focal score at weeks 26 and 52. TDI focal score improved at week 26 in both groups; the mean difference between treatments (0·21 units [95% CI –0·08 to 0·51]) was not statistically significant.

Adverse events were reported by 368 (54%) patients with Trimbow® and 379 (56%) with FOSTAIR®. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the Trimbow® group, but this event resolved in 15 days, and did not cause study drug discontinuation.

Conclusion: Trimbow® had a greater effect on pre-dose and 2 hr post-dose FEV1 than Fostair in patients with COPD who have severe or very severe airflow limitation, symptoms and exacerbation history. There was no superiority shown in relation to TDI and there was a significant prolonged time to first exacerbation with Trimbow®. Thus, the greater improvement in lung function with Trimbow® compared with Fostair® was more clearly accompanied by a reduction in exacerbations than an improvement in breathlessness in this group of patients. Furthermore, Trimbow® had a greater effect on health related quality of life than Fostair®.

Limitation: Most patients will progress from LABA +LAMA to triple therapy hence the comparator arm bears little relevance to this recommendation by GOLD. The authors did recognise this as they stated that their study did not address the benefit of escalation to triple therapy from LABA+LAMA. Patients already on triple therapy as two separate inhalers were excluded from the study hence there was no direct comparison made.

TRINITY[5] was a double-blind, parallel-group, randomised, controlled trial across 15 countries in 224 sites. The study compared Trimbow® with tiotropium 18 micrograms inhalation powder, hard capsule, one inhalation once daily; in addition, effects were compared with an extemporary triple combination made of a fixed combination of Fostair® 100/6 micrograms two inhalations twice daily plus tiotropium 18 micrograms inhalation powder, hard capsule, one inhalation once daily. The aim of the study was to evaluate the use of extrafine fixed triple inhaler Trimbow® over a monotherapy triotropium, with a free combination of Fostair® in one inhaler and tiotropium in a second inhaler (open triple) as a control.

Eligible patients were those with a clinical diagnosis of COPD with severe to very severe airflow limitation (FEV_1 less than 50% predicted), with symptoms assessed as a COPD Assessment Test (CAT) score of 10 or above, and with at least one COPD exacerbation in the previous year. 2,691 patients

were randomised (2:2:1) to 52 weeks treatment with triotropium (n=1075), Trimbow® (n=1078) or open triple (n=538). The primary endpoint was moderate-to-severe COPD exacerbation rate while the secondary endpoint was change from baseline in pre-dose FEV_1 at week 52.

The moderate to severe exacerbation rates were 0.57 for monotherapy tiotropium, 0.46 for Trimbow® and 0.45 for open triple therapy. Compared with monotherapy tiotropium, Trimbow® reduced the rate of moderate/severe exacerbations over 52 weeks by 20% (rate: 0.46 versus 0.57 events per patient/year; p = 0.003). Compared with tiotropium, Trimbow also reduced the rate of severe exacerbations (i.e. excluding moderate exacerbations) by 32% (rate: 0.067 versus 0.098 events per patient/year; p = 0.017). Pre-dose FEV1 at week 52 was also significantly superior in Trimbow® compared to monotherapy tiotropium (mean difference 61mL [0.037 to 0.086]; p<0.0001) but was non-inferior to open triple (-3mL [0.033 to 0.027]; p=0.85). No differences were also observed when comparing Trimbow and the open triple combination (moderate/severe exacerbation rate: 0.46 versus 0.45 events per patient/year).

The time to first severe exacerbation was prolonged with Trimbow® compared to monotherapy tiotropium (hazard ratio 0.70 [95% CI 0.52-0.95]; p=0.02) but was similar between Trimbow® and triple open therapy (1.05 [0.70-1.56]; p=0.82).

The adjusted mean changes from baseline in pre-dose FEV_1 at week 52 were 82mL for Trimbow®, 21mL for monotherapy tiotropium and 85mL for open triple therapy. Trimbow® was superior to tiotropium (61mL; p<0.0001) and non-inferior to open triple (3mL; p=0.85) in pre-dose FEV_1 at week 52.

Conclusion: both the primary and secondary endpoints were met. Trimbow® reduced the rate of moderate to severe COPD exacerbations by 20% compared to tiotropium with 61mL mean improvement in pre-dose FEV_1. There was non-inferiority in pre-dose FEV_1 between Trimbow® and open triple therapy. There was general similarity between Trimbow® and open triple therapy in moderate and severe exacerbation rates, use of rescue medication, SGRQ responders but superior to tiotropium monotherapy.

Limitation: The trial does not reflect current clinical practice. As per GOLD 2017 guideline, patients will not progress from tiotropium to triple therapy but will progress to LABA+LAMA combination. Majority of the patients in the study were on ICS+LABA at study entry which is not representative of current clinical treatment pathway.

There will be issue with prescribing Trimbow outside its licencing as it is recommended to be prescribed when patients are not adequately managed by combination of ICS+LABA. This is not the recommendation by GOLD guideline where triple therapy is recommended following LABA+LAMA. GOLD also makes it clear that LAMA+LABA is superior to ICS+LABA in preventing exacerbation.

Cost

Trimbrow® represents a cost saving when compared to the two separate inhalers

LabelDescription	Tradename	Pack size (doses)	Price exc VAT	UHNM Price inc VAT	Price comparison incl VAT	**Price difference incl VAT**
TRIMBOW 87microgram/ 5microgram/9microgram INHALER (120)	**TRIMBOW**	**120**				**£9.13**
FOSTAIR 200/6 INHALER (120-dose)	FOSTAIR	120				
FOSTAIR 100/6 INHALER (120-dose)	FOSTAIR	120				
GLYCOPYRRONIUM 44microgram BREEZHALER & 30 CAPSULES	SEEBRI BREEZHALER	30				
TRELEGY 92/55/22 INHALER	**TRELEGY ELLIPTA**	**30**				**£6.00**
RELVAR ELLIPTA 92/22 INHALER (30-dose)	RELVAR ELLIPTA	30				
RELVAR ELLIPTA 184/22 INHALER (30-dose)	RELVAR ELLIPTA	30				
UMECLIDINIUM 55microgram INHALER (30 dose)	INCRUSE ELLIPTA	30				

Trelegy® ▼ Ellipta (fluticasone furaote/umeclidinium/vilanterol)

Trelegy® Ellipta is to be reviewed for use within:

Primary Care	√
Secondary Care	√

- Trelegy® Ellipta contains in each single inhalation 100 microgram of fluticasone, 62.5 microgram of umeclidinium and 25 microgram of vilanterol which delivers dose of 921 mcg fluticasone, 55mcg of umeclidinium and 22 mcg of vilanterol.
- Trelegy® Ellipta is licensed for maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled ICS and LABA.
- Trelegy® Ellipta is the only COPD triple therapy delivered in a single daily inhalation and has comparable safety profile to that of its components.
- All Wales Medicines Strategy Group noted that Trelegy® has been granted an exclusion from undergoing a technology appraisal since the combination of established Incruse® Ellipta and Relvar® Ellipta have been previously assessed and approved.
- Trelegy® Ellipta a black triangle drug (▼) and is monitored intensively by the CHM and MHRA.

Evidence Summary:

FULFIL Trial[6] is a randomised, double-blind, double-dummy study comparing once daily triple therapy Trelegy® Ellipta with twice daily ICS+LABA therapy (budesonide/formeterol (BUD/FOR) 400microgram/12microgram Turbuhaher) over 52 weeks (1810 patients). The aim of the study was to compare the effects of Trelegy® on lung function and health-related quality of life with twice-daily BUD/FOR therapy in patients with COPD over 24 weeks. A patient subgroup (Extension population = 430 patients) remained on blinded treatment for up to 52 weeks. The co-primary endpoints included changes from baseline in trough FEV1 ($\geq$100ml) and SGRQ total score ($\geq$4 unit) at week 24.

Patients were randomised to either Trelegy® once daily using the Ellipta inhaler device plus twice daily placebo using Turbuhaler or twice-daily BUD/FOR using the Turbuhaler and once daily placebo using the Ellipta inhaler device. There were 1810 patients included in the intent-to-treat (ITT) population (Trelegy® =911; BUD/FOR =899). The extension population comprised of 430 patient (Trelegy® = 210 and BUD/FOR = 220).

Trelegy® demonstrated significant clinical improvement in the ITT population with a mean change from baseline FEV1 at week 24 of 142ml (95% CI, 126 to 158) for Trelegy® and -29 ml (95% CI, -46 to -13) for BUD/FOR ($p<0.001$). The mean changes from baseline in SGRQ scores were -6.6 units (95% CI, -7.4 to -5.7) for Trelegy® and -4.3 units (95% CI, -5.2 to -3.4) for BUD/FOR ($p<0.001$). For both endpoints, the between-group differences were statistically significant ($P < 0.001$).

In the Extension population at week 52, the mean changes from baseline in trough FEV1 were 126ml (95% CI, 92 to 159) for Trelegy® and -53ml (95% CI, -87 to -20) for BUD/FOR. The mean changes from baseline SGRQ total score were -4.6 units (95% CI, -6.5 to -2.6) for Trelegy® and -1.9 units (95% CI, -3.9 to 0.1) in BUD/FOR group. This however did not reach statistical significance despite similar magnitude in the between treatment difference observed in ITT population.

There was a statistically significant reduction in moderate/severe exacerbation rate with triple ICS/LABA/LAMA therapy versus dual ICS/LABA therapy (35% reduction; 95% CI, 14-51; P = 0.002) over the 24 week treatment period in the ITT population. Fewer patients were hospitalised for exacerbations in triple therapy group (n=12) compared to double therapy (n=22).

The safety profile of Trelegy® therapy and BUD/FOR therapy reflected the known profiles of the components. The most common adverse events were nasopharyngitis (7% and 5% for Trelegy® and BUD/FOR respectively) and headache (5% and 6% for Trelegy® and BUD/FOR respectively).

CONCLUSIONS:

Although these results support the benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD it still does not reflect the recommendation by GOLD guideline of stepping up from LABA+LAMA to triple therapy. There is no comparison with LABA+LAMA. The combination therapy is still a better option than the use of two different inhalers in relation to compliance and good inhaler technique.

Cost:

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UMECLIDINIUM 55microgram INHALER (30 dose)	INCRUSE ELLIPTA	30				

References:

[1] Summary of Product Characteristics Trimbow 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution. Last Updated on eMC 26-Jul-2017 https://www.medicines.org.uk/emc/medicine/33828 (Accessed online 27th December 2017)

[2] Global Initiative for Chronic Obstructive Lung Disease global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease 2017 report.

[3] Beclometasone dipropionate / formoterol fumarate dihydrate / glycopyrronium 87 micrograms / 5 micrograms / 9 micrograms metered dose inhaler (Trimbow®) SMC No 1274/1. Published 9th October 2017. https://www.scottishmedicines.org.uk/files/advice/beclometasone_Trimbow_Abbreviated_FINAL_Sept_2107_for_website.pdf. Accessed online 29/12/2017.

[4] Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Singh D et al; The Lancet, Vol 388 September 3, 2016; 963 – 973.

[5] Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Vestbo J et al; www.thelancet.com Published online April 3, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30188-5.

[6] Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. American journal of respiratory and critical care medicine. 2017;196(4):438-446