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Disease orientated primary and secondary outcomes (lung function)

- In an RCT, compared with beclometasone/formoterol (Fostair® 100/6 micrograms), Trimbow® significantly improved predose FEV1 by 0.081L (95% CI 0.052–0.109, p<0.001) and 2-hour post-dose FEV1 by 0.117L (95% CI 0.086–0.147, p<0.001) at week 26 (primary outcome).
- In an RCT, compared with tiotropium (18 micrograms) in a dry powder inhaler plus a dummy metered dose inhaler and open triple therapy with beclometasone/formoterol (100/6 micrograms) in a metered dose inhaler plus tiotropium (18 micrograms) in a dry powder inhaler, at week 52 pre-dose FEV1 for fixed triple was superior to tiotropium (mean difference 0.061 L [0.037 to 0.086]; p<0.0001) and non-inferior to open triple therapy (–0.003L [–0.033 to 0.027]; p=0.85) (secondary end point).

Safety: The adverse events reported most frequently during the clinical development of beclometasone / formoterol / glycopyrronium were: oral candidiasis (0.5%), which is normally associated with ICS, muscle spasms (0.5%), which can be attributed to the long-acting beta-2agonist, and dry mouth (0.5%), which is a typical anticholinergic effect.

- Study vs beclometasone/formoterol (Fostair® 100/6 micrograms): a similar proportion of participants using beclometasone/formoterol/glycopyrronium and beclometasone/formoterol had treatment-emergent adverse events (54% compared with 56% respectively). Most of these were COPD-related (58% and 63% respectively), and most were mild or moderate in severity. About 3% of participants in each group had pneumonia, and about 2% of participants in each group had major adverse cardiovascular events.
- Study vs tiotropium (18 micrograms) and open triple therapy with beclometasone/formoterol (100/6 micrograms): adverse events were reported by 55% of patients on Trimbow®, 58% with tiotropium and, 58% with Fostair® + Tiotropium. Pneumonia was reported in a small number of patients, with similar incidence in the three treatment groups. Most events were mild or moderate in severity.
- Study vs indacaterol/glycopyrronium bromide (110/63 micrograms): a similar proportion of adverse events were reported in participants using beclometasone/formoterol/glycopyrronium and indacaterol/glycopyrronium (64% vs 67% respectively). In both groups, 56% of these were COPD-related, and most were mild or moderate in severity. Pneumonia was seen in 4% of participants in each group, and adverse cardiovascular events were seen in 6% of participants using beclometasone/formoterol/glycopyrronium & 7% of participants using indacaterol/glycopyrronium.

General Comments and Study limitations

- Limited long term efficacy and safety data.
- The RCTs were funded by Chiesi Farmaceutici SpA (the manufacturer).
- Patients already on triple therapy (as two separate inhalers - LABA/ICS + LAMA) were excluded from the study and so no direct comparison available.
- Some differences seen although statistically significant are of uncertain clinical relevance, especially vs LABA/LAMA combination inhaler.
- No comparison vs alternative fixed dose triple therapy inhaler.
- It is also not known whether the triple-therapy inhaler has any advantages in terms of patient factors such as adherence to treatment and ease of use of the device.
- Some treatment escalations eg LAMA to triple therapy would not be in line with local/GOLD treatment guidelines.
- Studies were in more severe disease and there were many exclusion criteria so outcomes uncertain in the wider population with COPD.
- Some of the primary outcomes were disease-oriented, rather than patient-oriented.

Cost of treatment and Cost Effectiveness

- No cost-effectiveness analysis available.
- Scottish Medicines Consortium (SMC): Trimbow® (beclometasone, formoterol and glycopyrronium) costs less than inhalers containing beclometasone dipropionate / formoterol fumarate 100 micrograms/6 micrograms and glycopyrronium 44 micrograms administered separately.
- The monthly and annual cost of Trimbow® is less than:
  - inhalers containing beclometasone dipropionate / formoterol fumarate 100 micrograms/6 micrograms and glycopyrronium 44 micrograms administered separately.
  - 1st line (licensed) LABA/ICS + LAMA choices administered together as separate inhalers: £541/year vs £548 - £671/year.
- Where triple therapy is indicated and effective there is a potential for reduced costs by using fixed dose triple therapy (ICS, LABA & LAMA) in a single inhaler versus 2 separate inhalers (e.g. ICS/LABA + LAMA).

The needs of the population

- The needs of the population appear to be low as there are a range of single (LAMA, LABA) and dual therapy (LABA/ICS, LAMA/LABA) combination inhalers available to treat COPD.
- Like all LABA/ICS combination inhalers (except Relvar) it is administered twice daily.
- Where triple therapy is indicated, twice daily administration with one inhaler vs two may be an attractive option for...
patient adherence (including difficulty using more than 1 device or who find their medication regimen difficult or confusing) even though the clinical relevance has not been established.

- Fixed triple therapy lacks flexibility and makes it difficult to amend the individual medicines if treatment needs changing for any reason.
- There are concerns that the availability of a fixed dose triple therapy inhaler may lead to rapid escalation to triple therapy with no assessment of the need, efficacy and safety of the separate individual drugs (especially the ICS – given safety concerns).
- Trimbow is a MDI and can be used with a spacer. Alternative fixed dose triple therapy combination (Trelegy) is a DPI
- Trimbow contains a medium strength ICS which is preferred 1st line strength for COPD (supports using the lowest effective ICS dose and hence lowering risk of adverse-effects)

The needs of the community

- The needs of the community may be low as cost of Trimbow® is less than:
  1. Inhalers containing beclometasone dipropionate / formoterol fumarate 100 micrograms/ 6 micrograms (LABA/ICS) and glycopyrronium 44 micrograms (LAMA) administered separately
  2. The most commonly prescribed alternative triple therapy regimes prescribed as 2 separate inhalers (LABA/ICS + LAMA)
- Costs would be increased if there is rapid escalation to triple therapy and subsequent reduced use of lower cost LABA/ICS or LABA/LAMA inhalers

Policy Drivers

- Local COPD Guidelines: triple therapy (currently as separate inhalers) as an option for category D patients if continued frequent exacerbations or persistent breathlessness on LABA/ICS or LAMA/LABA inhalers
- SMC (September 2017) following an abbreviated submission: Trimbow® is accepted for restricted use within NHS Scotland. SMC restriction: severe COPD (forced expiratory volume in one second less than 50% predicted normal).
- MTRAC evidence review for Trimbow advises that in patients who need triple combination of ICS/LABA/LAMA, there may be benefit in terms of increased patient convenience & compliance with the use of a single inhaler instead of 2.
- Local formulary status:
  - Included in Cambridge and Peterborough CCG Adult COPD pathway as a first line treatment option
  - Not recommended for primary care prescribing by West Essex CCG (currently on Red list i.e. hospital only prescribing)
  - Included in Adult COPD guidelines for Bedfordshire CCG
  - North Central London JFC - not listed as formulary for COPD

Equity: No impact anticipated.

Implementability: No issues identified.

References

- NICE Evidence Summary: new medicine (ES17)- Chronic obstructive pulmonary disease: beclometasone, formoterol and glycopyrronium (Trimbow) May 2018— evidence and key issues summary: https://www.nice.org.uk/advice/es17/chapter/Key-points
- Hertfordshire COPD guidelines, updated Sept 2018 https://www.enhertscgg.nhs.uk/respiratory-system

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