Ultibro Breezhaler® (indacaterol/glycopyrronium) - Maintenance bronchodilator treatment to relieve symptoms in adults with COPD

February 2014

Summary of Ultibro Breezhaler® (indacaterol/glycopyrronium)

Indication
Ultibro Breezhaler® (indacaterol 85mcg/glycopyrronium 43mcg) is a fixed dose combination of a long acting beta agonist (LABA) and a long acting muscarinic antagonist (LAMA). It is the first dual-action long-acting bronchodilator combination inhaler licensed for relieving symptoms in adults with COPD.

Status
UK launch is expected in Spring 2014

Commissioning/ funding pathway
Ultibro will be in tariff and funded by CCGs

Efficacy data – See Section 3
- **SHINE** and **SPARK** – Efficacy data from two large studies, up to 76 weeks duration, showed Ultibro significantly improved bronchodilation and thereby improved lung function compared to its individually licensed components. These outcomes were regardless of disease severity and baseline steroid use. The clinical importance of these improvements in comparison to the active comparator treatments is not known.
- **SPARK** - Statistically significant improvements in moderate-severe exacerbations were achieved with Ultibro in comparison to the glycopyrronium comparator (12% reduction) but did not achieve a 20% reduction deemed to be clinically important. The mean number of moderate or severe exacerbations per patient was 1.11 with Ultibro and 1.22 with both glycopyrronium and tiotropium. See Section 4 Critical Evaluation for comparisons with other inhalers.
- **ILLUMINATE** - Based on one small study (n=523) powered for superiority against a LABA/ICS, Ultibro was also shown to be superior to the salmeterol-fluticasone combination in improving bronchodilation in patients with moderate-severe COPD and no history of exacerbations.
- Ultibro achieved clinically significant improvements in dyspnoea severity and health status (as measured by TDI focal score and SGRQ score respectively). Although no significant difference was seen for Ultibro over its individual components.

National Guidance – See Section 1 and Appendix 1
GOLD recommend a LABA and LAMA combination as an option in those patients who have a low risk of exacerbation but have significant symptoms with single agents, and both NICE and GOLD recommend the combination as an alternative option to fixed dose LABA/ICS. GOLD acknowledge however good clinical evidence for combining long-acting bronchodilators in patients with high risk of exacerbations is lacking but the principle for combining treatment seems sound.

Place in therapy – See Appendix 1, figure 1 and table 1
- Ultibro is viewed by respiratory specialists as an option in mild to moderate COPD patients who have a low risk of exacerbation but have significant symptoms despite single long-acting bronchodilator therapy
- Ultibro could be used as an alternative option when combined corticosteroids inhalers with LABA are declined or not tolerated. Note, comparative data with combined corticosteroids inhalers only exists for those patients with no history of exacerbations
- There may be patients who are over treated (i.e. being treated with LABA/ICS but rarely exacerbating) in primary care who would benefit from Ultibro. These patients will need to be carefully assessed before switching as withdrawal from treatment with inhaled corticosteroids may lead to exacerbations
- Ultibro could also be used as a single inhaler to replace use of LAMA and LABA inhalers prescribed separately
- Patients that are initiated on a combination of long-acting bronchodilators should be carefully monitored and their treatment effect evaluated

Costing – See Section 5.3.2 and Appendix 1, table 1
Costing and Health economic analyses are currently not available for Ultibro. See appendix 1 for cost of other licensed inhalers for COPD.

Point for consideration
- Ultibro is dual bronchodilator therapy, given via one single inhaler and is once daily dosing
- Currently only a handful of inhalers are licensed to be used once daily for COPD; these are monotherapies and include Oxis® Turbohaler, Onbrez Breezhaler®, Seebri Breezhaler®, and Spiriva HandiHaler®. It could be postulated that using Ultibro is advantageous but currently there is no evidence to show that using once daily dosing is better than twice daily dosing or that one combination inhaler is better than using two separate inhalers
1. **Background and introduction**

Chronic obstructive pulmonary disease (COPD) is a long term progressive condition characterised by persistent airflow obstruction that is not fully reversible.\(^1,2\) The estimated prevalence rate is between 2-4% with 3 million people estimated to have COPD in the UK.\(^2\) About 900,000 have diagnosed COPD and an estimated 2 million people have COPD which remains undiagnosed. Most patients are not diagnosed until they are in their late fifties. COPD is predominantly caused by smoking but other factors, particularly occupational exposures, may also contribute to the development of the disease. COPD can lead to severe symptoms, disability and impaired quality of life. Exacerbations often occur, when there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations.\(^2\)

NICE provides recommendations for the use of bronchodilator therapy according to the severity of COPD symptoms (see Figure 1). Either a Long Acting Beta Agonist (LABA) or Long Acting Muscarinic Antagonist (LAMA) are recommended in all patients who remain uncontrolled on short-acting bronchodilators.\(^2\) Combination therapy of LABA and inhaled corticosteroid (ICS) can be used in patients with FEV\(_1\)<50% or those with FEV\(_1\)≥50% plus continued loss of control despite LABA therapy. A LABA and LAMA combination is recommended where inhaled corticosteroids in combination are declined or not tolerated.\(^2\)

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 guidelines classifies patients according to their degree of FEV\(_1\) severity, quality of life and exacerbation history. GOLD recommends the combined use of LAMA and LABA as an option in patients who have a low risk of exacerbation but have significant symptoms with monotherapy. GOLD also recommends a LAMA + LABA combination as an alternative option to combined ICS with LABA or LAMA, which are generally used in patients with few symptoms but a high risk of exacerbations, but acknowledge good clinical evidence for combining long-acting bronchodilators in patients with high risk of exacerbations is lacking. Triple therapy (ICS with LABA and LAMA) is recommended as an option in patients with significant symptoms and high risk of exacerbations.\(^1\)

Ultibro Breezhaler\(^8\) (indacaterol 85mcg/glycopyrronium 43mcg) is a fixed dose combination of a LABA (indacaterol) and a LAMA (glycopyrronium), and is the first licensed dual-action long-acting bronchodilator combination. UK launch is expected in H2 2014. Ultibro is approved as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD. The recommended dosing is inhalation of the content of one capsule once a day using the Breezhaler inhaler.\(^3\) Currently the individual components are licensed in the UK for COPD. Glycopyrronium (Seebri Breezhaler\(^8\)) received marketing authorisation at the end of 2012\(^4\) and was accepted for use in both NHS Scotland and NHS Wales as maintenance bronchodilator treatment to relieve symptoms in adults with COPD.\(^4,6\) Indacaterol (Onbrez Breezhaler\(^8\)) was accepted for use in NHS Scotland in July 2010 as maintenance bronchodilator treatment of airflow obstruction in adults with COPD.\(^7\) See NICE Evidence for a full review on glycopyrronium.

2. **Proposed place in therapy**

Novartis propose Ultibro to be used as a step-up therapy from mono-bronchodilator therapy in COPD patients that remain symptomatic. They also predict Ultibro to be used in COPD patients who are non-exacerbating and have either been prescribed inhaled corticosteroids inappropriately or are intolerant of them.\(^8\)

3. **Evidence selected for inclusion**

A number of phase III randomised-controlled trials were designed to establish the clinical efficacy of Ultibro in COPD. Five of these trials used active comparators and were conducted in multi-centers across the EU.\(^9,11\) The pivotal studies are SHINE (n=2144)\(^11\) and SPARK (n=2224)\(^10\), large studies conducted over 26 weeks and 18 months respectively. BLAZE (n=247) is a smaller study of only 6 weeks duration.\(^11\) ILLUMINATE (n=523) is of 26 week duration and the only study which included a steroid combination inhaler (fluticasone/salmeterol) as a double-blind comparator.\(^11\) BRIGHT is a short 21 day study which assessed exercise endurance time and was not published fully at the time of writing.\(^6\)

In the parallel-group, placebo-controlled SHINE study, patients with moderate-severe stable COPD (GOLD stage II or III) treated with fixed-dose combinations of LABA/ICS were randomised to 26 weeks of double-blind treatment with Ultibro (n=475), indacaterol 150mcg (n=477), glycopyrronium 50mcg (n=475), or placebo (n=234), all administered using the Breezhaler device; in addition there was an open-label tiotropium 18mcg arm (n=483), administered using a different inhaler device. At baseline, all patients had a pre-bronchodilator FEV\(_1\) of 1.3L.

- The **primary endpoint** was superiority in trough FEV\(_1\) at week 26 for Ultibro versus its mono-components. An improvement of
100mL in trough FEV₁ is generally considered as a clinically significant improvement when active components are compared to placebo but unfortunately no standard definition of accepted clinical improvement when comparing active treatments is known; the SHINE investigators defined this as 60mL. With respect to differences in FEV₁, Ultibro achieved statistical superiority to its mono-components, indacaterol and glycopyrronium (differences of +70mL, +90mL, respectively; both p<0.001) and in comparison to placebo (difference of +200mL; p<0.001). Only the difference to placebo was considered clinically significant; the investigators stated that the differences to the mono-components approached clinical significance, despite defining clinical significance as a difference of 60mL. For the open-label tiotropium arm, Ultibro was found to be non-inferior (treatment difference +80mL, p<0.001).

- Sub-group analysis of patients with moderate and those with severe COPD revealed results similar to those for the full cohort: i.e. statistically and clinically significant improvements only for Ultibro vs. placebo (+240mL and +120mL; p<0.001); for active comparators (+60-90mLs and +80mLs; p<0.001).

- Secondary endpoints included the transition dyspnoea index (TDI) focal score at week 26, a clinician rate scale measuring changes in dyspnoea, in which a reduction by ≥1 unit indicates clinically meaningful improvement, and the St George’s Respiratory Questionnaire (SGRQ) score at week 26, a 50-item patient reported questionnaire measuring health status in patients with diseases of airways obstruction, in which a reduction in score by ≥4 units indicates clinically meaningful improvements. TDI focal score and SGRQ score are validated tools widely used in COPD trials. For TDI focal score, clinically significant improvements in dyspnoea were seen with all treatments and these were statistically significant for Ultibro vs. placebo (difference 1.09, p<0.001) and vs. tiotropium (difference 0.51, p=0.007). Clinically important improvements in health status were seen in all treatments groups, with reductions in score ranging from -6.39 with placebo to -10.03 with Ultibro. Differences were statistically significantly with Ultibro vs. placebo (p<0.002) and vs. tiotropium (p=0.009).

- Another secondary objective was to determine if Ultibro was as least as effective as open-label tiotropium in terms of trough FEV₁ at week 26. The difference in trough FEV₁ levels was +80mL in favour of Ultibro (p<0.001).

**SPARK** is another large study and conducted over a longer period of 18 months. Patients with severe (79%) or very severe (21%) airflow limitation (GOLD stage III or IV) and one or more moderate exacerbation in the past year were randomised to double-blind Ultibro (n=741) or glycopyrronium (n=741), or open-label tiotropium (n=742). About 75% of the population had experienced only one exacerbation in the previous year. The primary endpoint was to demonstrate superiority of Ultibro to glycopyrronium for the rate of moderate or severe COPD exacerbations during the treatment period. COPD exacerbations were defined by severity according to the need for additional treatment. Mild exacerbations were defined as those self-managed by patients. Moderate exacerbations were defined as requiring treatment with systemic corticosteroids and/or antibiotics, and severe as those requiring hospitalisation including an emergency visit for longer than 24 hours; these were also reviewed by an independent committee. The study was originally designed to detect a 20% reduction in the rate of COPD exacerbations in the Ultibro group compared with glycopyrronium, with a statistical power of 90% and duration of at least 52 weeks. However re-assessment at 5 months indicated the study was underpowered for the primary endpoint. Subsequently the study duration was increased to 15 months, with an extension period of up to 18 months on a patient voluntary basis, and size increased by 200 patients, to achieve a minimum of 80% power.

**Reduction in moderate to severe COPD exacerbations.** Ultibro significantly reduced moderate or severe COPD exacerbations by 12% (95% CI 0.77-0.99, p=0.038) compared to glycopyrronium (primary endpoint) but only by 10% (95% CI 0.79 – 1.02, p=0.096) when compared to open-label tiotropium (secondary endpoint), which was not statistically significant. The mean number of moderate or severe exacerbations per patient was 1.11 with Ultibro and 1.22 with both glycopyrronium and tiotropium, mean annualised rates of 0.84, 0.95 and 0.93 respectively. The reduction in exacerbation rates was mainly driven by moderate exacerbations as no differences were observed between Ultibro and other comparators in severe exacerbations rates.

**Secondary endpoints.** Differences in trough FEV₁; measurements between Ultibro and both glycopyrronium and tiotropium were significant at each assessment during the treatment period (differences of +70-80mL and +60-80mL, respectively; both p<0.0001). This was statistically significant but as mentioned before no standard definition of accepted clinical improvement when comparing active treatments is known. Improvements in health status, as measured by a SGRQ total score, were clinically significant for all three treatments and the differences were statistically significant with Ultibro when compared to glycopyrronium (-1.9 to -2.8, p<0.01) and tiotropium (-1.7 to -3.1, p<0.05).

**ILLUMINATE** was a 26-week study (n=523) and the only phase III trial directly comparing Ultibro to combination LABA and ICS. Patients with moderate-severe COPD (GOLD stage II-III) and with no history of exacerbations requiring treatment in the last year were randomised to double-blind treatment with Ultibro daily (n=259) or salmeterol-fluticasone twice daily (n=264), both plus matching placebo. The primary endpoint was superiority of Ultibro to salmeterol-fluticasone in the area under curve for FEV₁ (FEV₁·AUC₀₋₁₂h) from 0-12 hours post dose after 26 weeks of treatment. According to the European Medicines Agency (EMA) COPD guidelines, trough FEV₁ is generally the preferred measure to assess lung function related to use of COPD inhaled treatments. Nevertheless it was shown that FEV₁·AUC₀₋₁₂h was significantly higher with Ultibro (1.695L) than with salmeterol-fluticasone (1.557L) at week 26, with a treatment difference of 138mL (95% CI 0.1-0.176, p<0.0001). Ultibro was clinically and statistically superior to salmeterol-fluticasone for the secondary endpoint of trough FEV₁ (1.60L vs. 1.49L at week 26, treatment difference +103mL, p<0.0001). However, this difference of 100mL in trough FEV₁ was present at baseline, with values of 1.5L in the Ultibro group and 1.4L in the salmeterol-fluticasone group. At endpoint, a clinically important increase of at least 1 point in the TDI score was achieved by 67.5% in the Ultibro group and 56.8% in the salmeterol-fluticasone group (p=0.046). While significant improvements in the SGRQ were seen in both groups, with reductions of approximately 6, there was no significant difference between the groups.

Data comparing Ultibro to the LAMA, tiotropium, was largely conducted using open-label comparisons (SPARK, SHINE). The smaller
4. Critical evaluation

Efficacy data from the two large studies SHINE and SPARK, which were up to 76 weeks duration, showed Ultibro significantly improved bronchodilation and thereby improved lung function compared to its individually licensed component. These outcomes were regardless of disease severity and baseline steroid use. Statistically significant improvements in moderate-severe exacerbations were also achieved in comparison to the glycopyrronium comparator.

The primary objectives and patient groups of SHINE and SPARK, were different, with SHINE evaluating trough FEV\(_1\) differences in patients with moderate - severe COPD (GOLD stage II to III) and SPARK assessing exacerbation rates in patients with severe - very severe COPD (GOLD stage III and IV). Extrapolation of the results of treatment in one patient group to the other patient group should be done cautiously.

SHINE demonstrated that Ultibro was clinically better than placebo in increasing trough FEV\(_1\), with a difference of ≥100mL which is considered a clinically significant improvement, as would be expected. The trough FEV\(_1\) levels were also greater with Ultibro than the individual components and tiotropium, but there is a lack of definition of what constitutes a clinically significant difference in FEV\(_1\) when comparing two active treatments. However, as the differences approached 100mL, it could be suggested that clinical differences were seen.

Comparisons with other inhalers

SPARK was designed to detect a 20% reduction in exacerbation rate for Ultibro compared to glycopyrronium, but the authors state this was not intended as the minimum clinically meaningful difference. NICE guidance considers a 20% reduction to be clinically important and Ultibro only achieved a 12% reduction in comparison to glycopyrronium, which was statistically significant.\(^{6,10}\)

Comparisons with other inhalers licensed for the treatment of COPD should be done cautiously because of the differences in e.g. disease severity of the patient populations, primary/secondary endpoints and study design/duration. In the 4 year UPLIFT trial in patients with GOLD stage II-IV, (46% had moderate COPD, 44% severe, 8% very severe disease) a 14% reduction in exacerbation rates was seen with tiotropium compared to placebo.\(^{19}\) In the 52 week GLOW-2 study in patients with moderate (64%) or severe (35%) COPD, there was a 34% reduction in moderate-severe exacerbations with glycopyrronium compared to placebo.\(^{20}\) In the 3 year TORCH study in patients with moderate-severe COPD (data not available on % with moderate or severe), a 25% and 15% reduction in moderate or severe exacerbations was seen with Seretide (salmeterol/fluticasone) and salmeterol respectively, versus placebo.\(^{21}\) In these three studies exacerbation rates were assessed as secondary endpoints but in the SPARK study, as the primary endpoint.

Study limitations

Limitations of SHINE are lack of data on exacerbation and hospitalisation rates and the short study duration. There was also a discrepancy in discontinuation rates, with 19.2% discontinuing placebo therapy compared with 8% in the Ultibro group and 11.7%, 11.2% and 8.7% in the indacaterol, glycopyrronium and tiotropium groups respectively.\(^{11}\) There are also limitations to SPARK. The wide geographical area covered by the study and variations such as restricted health-care provision could have influenced results. Around a quarter of patients discontinued therapy; 23%, 27% and 25% in the Ultibro, glycopyrronium and tiotropium groups respectively, with most discontinuations due to adverse events. The primary endpoint was measured at the end of the patient’s treatment period 64, 70 or 76 weeks (15-18months). The authors discuss that the possibility of bias by allowing patients to enter the extension period and it is possible that the primary outcome would not have resulted in a significant reduction if all patients had continued treatment to 18 months.\(^{10}\)

A limitation of both SPARK and SHINE is the use of open-label tiotropium, which could have affected subjective (but not objective) outcomes.

While the ILLUMINATE study evaluated the evidence comparing Ultibro with a LABA/ICS combination and showed that Ultibro was superior to salmeterol +fluticasone, it used a different primary endpoint to SHINE and SPARK, i.e. FEV\(_1\) \(\text{AUC}_{0,12}\), which is not the preferred measurement for COPD therapies. The study did not evaluate exacerbation risk, because of the low-risk, non-exacerbating patients recruited.\(^{13}\)
The BLAZE study results have only been published as a conference abstract at the time of writing, limiting detailed critical evaluation. An advantage of BLAZE was the use of blinded tiotropium, but the study is limited by its short duration (6 weeks). Changes in trough FEV₁ or exacerbation rates were not assessed.\textsuperscript{12}

4.1. Clinical application

Ultibro will be the first licensed once daily fixed dose combination of a LABA and LAMA in the UK: indacaterol 85mcg/glycopyrronium 43mcg per delivered dose. The individual components are also available in the UK as glycopyrronium, 44mcg per delivered dose and indacaterol, 150 or 300mcg strength (120mcg and 240mcg per delivered dose). Other products available in the UK for the treatment of patients with COPD remaining uncontrolled on short-acting bronchodilators are listed in table 1. Few products are licensed to be used once daily; these are all monotherapies and include Oxis® Turbohaler (formoterol), Onbrez Breezhaler® (indacaterol), Seebri Breezhaler® (glycopyrronium), and Spiriva Respimat® (tiotropium).\textsuperscript{22}

Ultibro’s efficacy has been evaluated in RCTs in comparison with long acting bronchodilator therapies and combined ICS with LABA. Currently, the best available data support the use of Ultibro as an alternative to long acting bronchodilator monotherapy and GOLD recommend the combination in those patients who have a low risk of exacerbation but have significant symptoms with monotherapy. NICE also recommend a LABA and LAMA combination in COPD patients where combined ICS + LABA inhalers are declined or not tolerated, and GOLD also recommend the combination as a second line option to combined ICS with LABA or LAMA in those patients with few symptoms but high risk of exacerbations. GOLD acknowledge however good clinical evidence for combining long-acting bronchodilators in patients with high risk of exacerbations is lacking but the principle for combining treatment seems sound.\textsuperscript{22}

Novartis propose Ultibro to be used as a step-up therapy from mono-bronchodilator therapy in COPD patients that remain symptomatic. They also predict Ultibro to be used in COPD patients who are non-exacerbating and have either been prescribed inhaled corticosteroids inappropriately or are intolerant of them.\textsuperscript{8} Ultibro provides a fixed dose combination of a LABA and LAMA combination and can potentially be used as recommended by NICE and GOLD. As the product is a fixed dose combination, the ability to dose titrate indacaterol which is available in two strengths is lost. The studies were not designed to compare the effectiveness of Ultibro with the two separate components used together and neither did they assess patient preference of using one inhaler over two. Current data do not show that using one inhaler (Ultibro) is more effective than using two separate inhalers (indacaterol and glycopyrronium) together. Note that Ultibro contains a lower dose of indacaterol than the Onbrez Breezhaler®.

4.2. Safety

4.2.1. Key adverse events

The safety of Ultibro was specifically evaluated in the ENLIGHTEN study.\textsuperscript{23} Patients were randomised to treatment with either Ultibro (n=226) or placebo (n=113) for 52 weeks. The primary endpoint was the safety and tolerability of Ultibro vs. placebo in terms of treatment-emergent adverse events (TEAEs). Most AEs were moderate (30-32%) or mild (12-17%) in severity, with severe AEs occurring in 12.4% of the Ultibro and 8.8% of the placebo groups. The overall incidence of AEs was 57.8% in the Ultibro group and 56.6% in the placebo group. Worsening COPD was the most frequently reported AE, occurring in 28% and 25.7% respectively. AEs thought to be related to the study drug as assessed by the investigators occurred in 25.3% and 21.1% respectively. Two cardiovascular events occurred in the Ultibro group.

Adverse events were also reported in the other studies. Side effects may be related to the anticholinergic and beta-adrenergic symptoms caused by the individual components of Ultibro.\textsuperscript{7} Overall, the most frequently reported adverse events were upper respiratory tract infections (incidence ≥1/10 patients), nasopharyngitis, urinary tract infections, sinusitis, rhinitis, dizziness, headache, cough, oropharyngeal pain including throat irritation, dyspepsia, dental caries, gastroenteritis, musculoskeletal pain, pyrexia and chest pain (incidence common, ≥1/100 to <1/10 patients).\textsuperscript{21}

Long-term use of ICS can lead to side effects such as oral thrush and hoarseness; these were not experienced in ILLUMINATE, which may be due to the relatively short treatment duration.\textsuperscript{13}

4.2.2. Risk assessment

Ultibro is a dry capsule inhaler that requires the patient to put a capsule into the inhaler device. The patient should be counselled not to swallow the capsule.

4.3. Potential advantages and disadvantages over existing technologies

4.3.1. Convenience

With Ultibro, dual bronchodilator therapy is given via one single inhaler and is once daily dosing. Currently only a handful of inhalers are licensed to be used once daily for COPD (see section 5.1 and Table 1). This could be postulated as an advantage but currently there is no evidence to show that using once daily dosing is better than twice daily dosing or that one combination inhaler is better than using two separate inhalers together. The Breezhaler® device is known to have a lower inspiratory resistance than the Accuhaler®, Handihaler® and Turbohaler® devices.\textsuperscript{24}

4.3.2. Drug cost

The cost for Ultibro will be available prior to launch. The patent for salmeterol + fluticasone expired in 2010 but currently no generic products are available on the market.\textsuperscript{25} Tiotropium has marketing exclusivity till 2015 and formoterol + budesonide until 2018.\textsuperscript{25,26}
4.3.3. Healthcare resource utilisation
COPD is a major burden on healthcare resources and the extent of these increases as the severity of COPD increases. In 2000-1, the total annual cost of COPD to the NHS was estimated to be around £491 million for direct costs and £982 million for indirect costs. The average cost per patient (at that time), was £820 per year, of which 54.3% was due to hospitalisation, 18.6% for treatment, 16.4% for GP and specialists visits, 5.7% for A&E or unscheduled GP or specialist visits and 5% for laboratory tests. Both LAMAs and LABAs reduce the risk of exacerbations and thus the principle of combining the two seems sound. Ultibro improved lung function and reduced moderate-severe COPD exacerbations compared to single long-acting bronchodilators and clinically significant improvements in dyspnoea severity or health status were also seen in the trials. Data on hospitalisation rates were not collected in the studies. From the current published evidence it is not possible to determine whether the use of Ultibro in COPD patients would reduce the burden on healthcare resources compared to using a single long-acting bronchodilator or ICS with LABA.

4.3.4. Suitability for shared care
None required

4.3.5. Likely budgetary impact
Not available

5. Health Economics
Health economic analyses are not available for Ultibro. Cost per QALY costs for other COPD treatments were estimated (2010-2011): tiotropium (£7000/QALY), LABA (£8000/QALY), and triple therapy (£35,000-187,000). Health economic analyses are not available for Ultibro.

6. Likely commissioning and funding pathway
Ultibro will be in tariff and funded by CCGs.

7. Suggested place in therapy
Ultibro is viewed by respiratory specialists as an option in mild to moderate COPD patients who have a low risk of exacerbation but have significant symptoms despite single long-acting bronchodilator therapy. It is also an alternative when combined corticosteroids inhalers with LABA are declined or not tolerated. There may be patients who are over treated (i.e. being treated with LABA/ICS but rarely exacerbating) in primary care who would also benefit from Ultibro. These patients will need to be carefully assessed before switching as withdrawal from treatment with inhaled corticosteroids may lead to exacerbations. Ultibro could also be used as a single inhaler to replace use of LAMA and LABA inhalers prescribed separately. Patients that are initiated on a combination of long-acting bronchodilators should be carefully monitored and their treatment effect evaluated.
Appendix 1.

Figure 1: NICE recommendations on inhaled therapies in COPD

Advice on the use of inhaled therapies in COPD is based on the recommendations of NICE (2020) and reproduced by the British National Formulary. Full guidance available from www.nice.org.uk

Figure 2: Ultibro Breezhaler®
### Table 1: Licensed inhalers for COPD patients remaining uncontrolled on short-acting bronchodilators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand &amp; strength</th>
<th>Device</th>
<th>Maintenance dosing</th>
<th>Cost of inhaler/cost per month</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAMA + LABA</strong></td>
<td>Indacaterol/ Glycopyrronium</td>
<td>Ultibro Breezhaler® (110mcg/44mcg)</td>
<td>Single-dose capsule based inhaler</td>
<td>One capsule inhalation daily</td>
</tr>
<tr>
<td></td>
<td>Formoterol fumarate</td>
<td>Atimos Modulite® (12mcg)</td>
<td>Metered aerosol inhaler</td>
<td>One inhalation twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foradil® (12mcg)</td>
<td>Single-dose capsule based inhaler</td>
<td>One inhalation twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxis® Turbohaler (6 &amp; 12mcg)</td>
<td>Metered dry powder inhaler</td>
<td>One inhalation once or twice daily</td>
</tr>
<tr>
<td><strong>LABA</strong></td>
<td>Indacaterol</td>
<td>Onbrez Breezhaler® (150 &amp; 300mcg, delivers 120mcg, 240mcg respectively)</td>
<td>Single-dose capsule based inhaler</td>
<td>One inhalation (150 or 300mcg) once daily</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td>Non-proprietary (25mcg)</td>
<td>Metered aerosol inhaler</td>
<td>Two inhalations twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serevent® Accuhaler® (50mcg)</td>
<td>Dry powder inhaler</td>
<td>One inhalation twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serevent® Evihaler® (25mcg)</td>
<td>Metered aerosol inhaler</td>
<td>Two inhalations twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serevent® Diskhaler® (50mcg)</td>
<td>Dry powder inhaler</td>
<td>One inhalation twice daily</td>
</tr>
<tr>
<td><strong>LAMA</strong></td>
<td>Acldinium</td>
<td>Eklira Genuair® (400mcg of aclidinium bromide)</td>
<td>Metered dry powder inhaler</td>
<td>One inhalation twice daily</td>
</tr>
<tr>
<td></td>
<td>Glycopyrronium</td>
<td>Seebri Breezhaler® (50mcg, delivers 44mcg glycopyrronium)</td>
<td>Single-dose capsule based inhaler</td>
<td>One capsule inhalation daily</td>
</tr>
<tr>
<td></td>
<td>Tiotropium</td>
<td>Spiriva Handihaler® (18mcg)</td>
<td>Single-dose capsule based inhaler</td>
<td>One capsule inhalation daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spiriva Respimat® (2.5mcg)</td>
<td>Metered solution inhaler</td>
<td>Two inhalations twice daily</td>
</tr>
<tr>
<td><strong>Combination inhaled corticosteroid + LABA</strong></td>
<td>Budesonide / Formoterol fumarate/</td>
<td>Symbicort Turbohaler® (200/6mcg &amp; 400/12mcg)</td>
<td>Metered dry powder inhaler</td>
<td>One inhalation (400/12) twice daily or two inhalations (200/6) twice daily</td>
</tr>
<tr>
<td></td>
<td>Fluticasone / Salmeterol/</td>
<td>Seretide 500 Accuhaler® (500/50mcg)</td>
<td>Dry powder disk inhaler</td>
<td>One inhalation twice daily</td>
</tr>
</tbody>
</table>

### References


Personal Communication; Medicines Information. AstraZeneca UK Ltd. February 2014.

