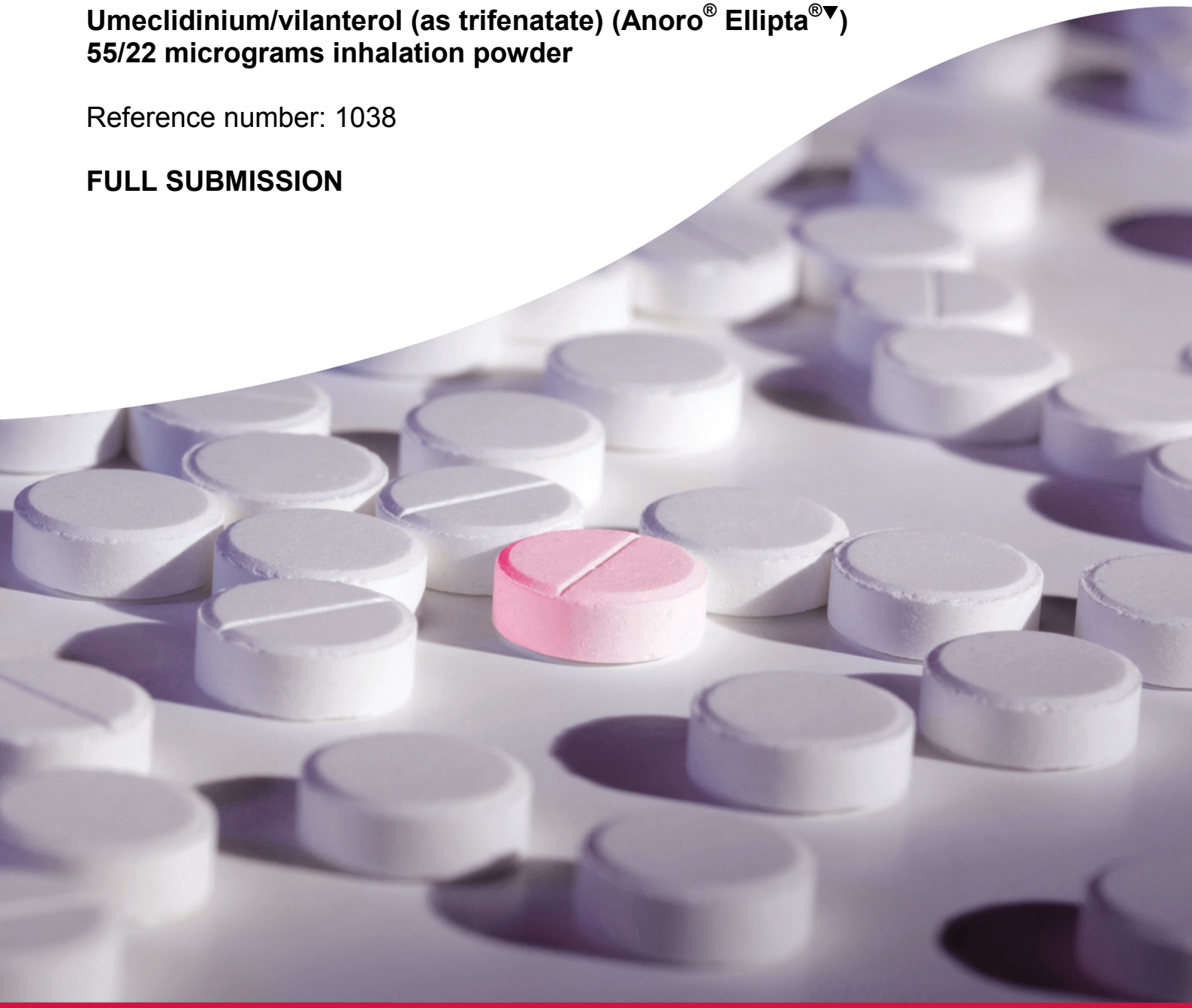
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼) 55/22 micrograms inhalation powder

Reference number: 1038

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼) 55/22 micrograms inhalation powder. Reference number: 1038. January 2015.

AWMSG Secretariat Assessment Report
Umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼) 55/22 micrograms inhalation powder

This assessment report is based on evidence submitted by GlaxoSmithKline on 29 September 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)[2].
Dosing	The recommended dose is one inhalation of umeclidinium/vilanterol (as trifenatate) 55/22 micrograms once daily using the Ellipta® inhaler[2].
Marketing authorisation date	8 May 2014[2]

2.0 DECISION CONTEXT

2.1 Background

Chronic obstructive pulmonary disease (COPD) is characterised by consistent airflow obstruction, which is usually progressive and not fully reversible[3]. This is associated with persistent and progressive breathlessness, a chronic productive cough and limited exercise capacity. COPD can be used to describe a number of conditions, such as chronic bronchitis, emphysema, chronic obstructive airways disease and chronic airflow limitation[3]. Smoking is the main cause of COPD, but other factors include exposure to dusts, fumes and certain chemicals[4]. It is estimated that three million people have COPD in the UK, of which approximately 900,000 have been diagnosed[5]. The number of patients with COPD in Wales in 2013–2014 was 68,419[6]. COPD prevalence increases with age and is rarely seen in people under the age of 35 years[3].

COPD treatment aims to reduce symptoms, lower the frequency and severity of exacerbations, improve health status and increase exercise tolerance[7]. Bronchodilators, including beta$_2$-agonist and muscarinic antagonist (anticholinergic) inhalation therapies, are central to the management of COPD symptoms[7]. For patients with stable COPD, who remain breathless or have exacerbations despite maintenance therapy with either a long-acting beta$_2$-agonist (LABA) alone or a long-acting muscarinic receptor antagonist (LAMA) alone, treatment with a LAMA/LABA combination may be considered[5,7,8]. Umeclidinium/vilanterol is a LAMA/LABA fixed dose combination (FDC), licensed to treat symptoms of COPD in adults[1,2].

2.2 Comparators

The comparators included in the company submission were:

- Tiotropium (Spiriva® Handihaler®) 18 micrograms inhalation powder.
- Tiotropium (Spiriva® Handihaler®) 18 micrograms inhalation powder and indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder.
- Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) 85/43 micrograms FDC inhalation powder.

- Tiotropium (Spiriva® Handihaler®) 18 micrograms inhalation powder and salmeterol (Serevent®) 50 micrograms inhalation powder.
- Tiotropium (Spiriva® Handihaler®) 18 micrograms inhalation powder and formoterol (Foradil®, Oxis®, Atimos-Modulite®, Formoterol Easyhaler®) 12 micrograms inhalation powder

2.3 Guidance and related advice

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of COPD (updated 2014)[7].
- National Institute for Health and Care Excellence (NICE) Pathways. Inhaled therapy in COPD (2013)[8].
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline 101 (2010)[5].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of the LAMAs aclidinium bromide (Eklira® Genuair®▼), and glycopyrronium bromide (Seebri® Breezhaler®▼) and the LABA/LAMA FDC indacaterol/glycopyrronium (Ultibro® Breezhaler®▼)[9–11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included nine phase III trials in which the efficacy of umeclidinium/vilanterol as a treatment for patients with COPD was investigated. Since none of these studies compared umeclidinium/vilanterol with both a LAMA and a LABA, these trials will not be discussed further. The studies comparing umeclidinium/vilanterol with tiotropium monotherapy were not included as NICE guidelines suggest that the principal place in therapy of a LABA/LAMA combination would be after LABA or LAMA monotherapy and therefore tiotropium monotherapy would not be displaced by umeclidinium/vilanterol[5,7,8]. The company have provided indirect treatment comparisons (ITCs) and network meta analyses (NMAs) evaluating umeclidinium/vilanterol 55/22 micrograms FDC versus indacaterol/glycopyrronium 85/43 micrograms FDC, and the combinations: tiotropium 18 micrograms and indacaterol 150 micrograms, tiotropium 18 micrograms and salmeterol 50 micrograms, tiotropium 18 micrograms and formoterol 12 micrograms[1].

3.1 Indirect treatment comparisons (ITCs)

In the absence of trials directly comparing umeclidinium/vilanterol and the combination of a LAMA and a LABA, the company conducted two systematic reviews to identify evidence which would enable an ITC between umeclidinium/vilanterol 55/22 micrograms and the comparators.

The first review was carried out to identify evidence which would enable ITC between umeclidinium/vilanterol 55/22 micrograms, indacaterol/glycopyrronium 85/43 micrograms and the combination of tiotropium 18 micrograms and indacaterol 150 micrograms. This included randomised controlled trials (RCTs) with a minimum duration of 12 weeks in patients with COPD and with forced expiratory volume (FEV_1) ≤ 80% FEV_1 predicted (see Glossary). Outcomes included in the review were: COPD exacerbations, change from baseline in FEV_1, exercise capacity, inspiratory capacity, patient-reported outcomes and safety/tolerability endpoints.

A second review was carried out to identify evidence which would enable ITC between umeclidinium/vilanterol 55/22 micrograms and the combinations: tiotropium 18 micrograms and salmeterol 50 micrograms, tiotropium 18 micrograms and formoterol 12 micrograms. Outcomes included in the second review were change from baseline in FEV_1, patient-reported outcomes, transition dyspnoea index (TDI) and rescue medication. RCTs of patients with COPD and with a minimum duration of 10 weeks were included.

Twelve studies which included results for either umeclidinium/vilanterol 55/22 micrograms, indacaterol/glycopyrronium 85/43 micrograms or tiotropium 18 micrograms and salmeterol 50 micrograms; and tiotropium 18 micrograms and formoterol 12 micrograms were used to perform ITCs. Analyses reported no statistical difference between LAMA/LABA treatments for any of the endpoints for which data was available (see Table 1). The differences between least square mean changes from baseline for the treatments for trough FEV_1 (i.e. FEV_1 24 hours post-dose) were less than the minimally clinically important difference of 100 ml[1,12].

Table 1. Results of ITC

Treatment	Comparator	Difference between treatments¶	95% confidence interval	p value
Trough FEV_1 at 12 weeks				
Umeclidinium/vilanterol	Tiotropium and indacaterol	25.10 ml*	−2.11 to 52.30	0.071
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	10.45 ml†	−22.51 to 43.41	0.535
Umeclidinium/vilanterol	Tiotropium and formoterol	9.00 ml*	−50.34 to 68.34	0.766
Trough FEV_1 at 24 weeks				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	6.99 ml†	−24.05 to 38.02	0.659
Umeclidinium/vilanterol	Tiotropium and salmeterol	73.68 ml*	−20.56 to 167.91	0.125
Rescue medication use§ (puffs/day) at 12 weeks				
Umeclidinium/vilanterol	Tiotropium and indacaterol	0.24*	−0.34 to 0.82	0.426
Rescue medication use§ (puffs/day) at 24 weeks				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	0.16**	−0.45 to 0.77	–
SGRQ total score at 12 weeks (estimate)				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	−0.73**	−3.57 to 2.12	–
SGRQ total score at 24 weeks (estimate)				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	0.18**	−1.28 to 1.63	–
Umeclidinium/vilanterol	Tiotropium and formoterol	−0.68**	−1.77 to 0.39	–
Umeclidinium/vilanterol	Tiotropium and salmeterol	−0.11**	−1.84 to 1.61	–
TDI focal score at 12 weeks (estimate)				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	−0. 10**	−0.59 to 0.38	–
Umeclidinium/vilanterol	Tiotropium and formoterol	0.39**	−0.43 to 1.22	–
TDI focal score at 24 weeks (estimate)				
Umeclidinium/vilanterol	Indacaterol/glycopyrronium	−0.30**	−0.73 to 0.13	–
Umeclidinium/vilanterol	Tiotropium and salmeterol	0.58**	−0.33 to 1.50	–

¶difference between least square mean changes from baseline; *mixed difference from ITC; †pooled effect size from ITC; §mean daily number of puffs of albuterol/salbutamol; **mean differences obtained from network meta analysis; SGRQ: St George's respiratory questionnaire; TDI: transition dyspnoea index (see glossary).

3.2 Comparative safety

The company submission did not include any studies which provided evidence of comparative safety for the use of umeclidinium/vilanterol versus other LAMA/LABA treatments. The longest term safety data available using umeclidinium/vilanterol 55/22 micrograms was 24 weeks[12]. However, safety data from a 52 week study, DB2113359, which used a higher unlicensed strength FDC of umeclidinium/vilanterol 113/22 micrograms, was found to be supportive of the long term safety of the lower dose umeclidinium/vilanterol 55/22 micrograms[12]. Based on safety data from studies of umeclidinium/vilanterol versus placebo and the single treatments of tiotropium, vilanterol and umeclidinium, the Committee for Medicinal products for Human Use (CHMP) concluded that the overall safety profile of umeclidinium/vilanterol was in line with that of other LAMAs and LABAs and that there were no significant safety concerns with the combination versus the two individual components[12]. There is a lack of long term safety data for the use of umeclidinium/vilanterol 55/22 micrograms and an

observational follow up study over 24 months is planned to quantify the incidence of cardiovascular and cerebrovascular events post-marketing.

3.3 AWTTC critique

- The company were unable to provide direct clinical evidence comparing the efficacy of umeclidinium/vilanterol versus other comparator LAMA/LABA combinations[1].
- Indirect comparisons showed no significant differences in clinical efficacy between umeclidinium/vilanterol FDC versus indacaterol/glycopyrronium FDC or the combinations: tiotropium and salmeterol, tiotropium and formoterol, or tiotropium and indacaterol. However, due to a lack of appropriate clinical study data, indirect comparisons were only available for limited endpoints, in particular comparisons versus tiotropium and indacaterol and versus tiotropium and formoterol were limited to 12 week periods. Results of the ITCs should be interpreted with caution due to the inherent limitations in the methodology and differences in the severity of COPD in the study patient populations. No comparative safety data was presented as part of the ITC.
- CHMP noted a lack of data for the impact of the umeclidinium/vilanterol FDC on the rate of exacerbations[12].
- The availability of umeclidinium/vilanterol 55/22 micrograms as a combination inhaler as opposed to two separate inhalers may be more convenient for patients.
- Umeclidinium/vilanterol (as trifenatate) is provided in a dry powder device (Ellipta® inhaler), which is pre-loaded with 30 doses. The Ellipta® inhaler therefore does not require loading of individual doses prior to each use, which is a requirement of some other dry powder inhalers. The company state that during the development of the product, 98-99% of patients rated the product as either very easy or easy to use after six weeks of treatment[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost-utility analysis (CUA) of umeclidinium/vilanterol 55/22 micrograms once daily delivered via a single inhaler device compared to tiotropium 18 micrograms LAMA monotherapy and the LAMA/LABA combination of tiotropium 18 micrograms and indacaterol 150 micrograms once daily delivered in separate inhaler devices. In addition, the company has submitted a cost-minimisation analysis (CMA) comparing umeclidinium/vilanterol 55/22 micrograms with the following LAMA/LABA combinations: tiotropium and salmeterol (the most prescribed combination), tiotropium and formoterol, and tiotropium and indacaterol. A comparison versus indacaterol/glycopyrronium 85/43 micrograms FDC was subsequently provided by the company when the price became available in the public domain (1 December 2014)[13]. The economic model for the CUA consisted of a simulation model with a 20-year time horizon in which risk equations link the baseline characteristics for a cohort of hypothetical COPD patients with intermediate outcomes of FEV_1, dyspnoea, exacerbation, six minute walk test (6MWT) and final outcomes of mortality, health-related quality of life (St Georges Respiratory Questionnaire [SGRQ]), and health service costs.

Clinical data used in the model for the calculation of FEV_1 were based on a meta-analysis of three 24 week phase III RCTs of umeclidinium/vilanterol 55/22 micrograms versus tiotropium 18 micrograms; and a frequentist-adjusted indirect comparison with the combination of tiotropium 18 micrograms and indacaterol 150 micrograms using two 12 week studies (INTRUST1 and 2)[14]. All other outcomes in the model were estimated using risk equations which were derived from correlation among outcomes

from two other studies: ECLIPSE for clinical outcomes, and TORCH for resource use outcomes[15,16]. An assumption was made in the base case that the duration of FEV_1 treatment effect would be 52 weeks, supported by a 52-week safety study using umeclidinium/vilanterol at the higher dose of 113/22 micrograms[12] . Adverse events and discontinuations were assumed to be the same for each treatment considered and were not included in the model. A premise for a CMA is that equivalent outcomes are demonstrated; for this the company has used the results of both the frequentist indirect comparison and a Bayesian network meta-analysis to support the conclusion of comparable trough FEV_1, SGRQ score, total TDI and rescue medication use outcomes. The CMA included only medicine acquisition costs analysed over a one–five year period, with costs discounted at 3.5% after year one.

Utility estimates used in the CUA model were based on the baseline SGRQ scores from the umeclidinium/vilanterol 55/22 micrograms phase III trials with scores over time predicted through a risk equation. The SGRQ scores were mapped to the EuroQol 5 Dimension (EQ-5D) scores to estimate utility values using a published algorithm[17]. Costs included in the economic model covered drug acquisition costs, with resource use associated with GP, home and outpatient visits, accident and emergency (A&E), intensive care unit (ICU) and general ward use estimated for clinical health states through resource risk equations. Unit costs were based on those reported by Personal Social Service Research Unit (PSSRU) 2012 or NHS reference costs for 2011–12. The costs of adverse events were not included, and the model did not include subsequent lines of therapy.

4.1.2 Results

For the comparisons with tiotropium monotherapy and the combination of tiotropium and indacaterol, incremental cost savings and additional quality adjusted life-years (QALYs) have been estimated for umeclidinium/vilanterol 55/22 micrograms. The cost savings are associated with lower estimated medicine costs, especially compared to tiotropium and indacaterol (Table 2). The QALY gains are small but associated with slightly lower cumulative number of exacerbations impacting on patients' health-related quality of life (HRQoL) over the 20 year analysis time horizon. Mean survival was estimated to be 8.97 years (undiscounted), but in the base case no differential impact on survival associated with drug treatment option was estimated.

For the CUA, a range of scenario analyses, one and two way sensitivity analyses, and probabilistic sensitivity analyses was performed relating to cost variables (varied by ±20%) and treatment effect outcomes (FEV_1, varied according to 95% confidence intervals). In most scenario/sensitivity analysis umeclidinium/vilanterol remained a dominant treatment. Assuming a lifetime (20 year) treatment effect for each medicine resulted in increased incremental costs of umeclidinium/vilanterol due to there being a longer estimated survival and resulted in an estimated incremental cost-effectiveness ratio (ICER) of £707 per QALY gained versus tiotropium. The results for the most sensitive scenarios are presented in Table 3. Varying costs and treatment effects in one way sensitivity analysis mostly had insignificant impacts on the cost savings and QALY gains estimated for umeclidinium/vilanterol. In probabilistic sensitivity analysis (PSA), umeclidinium/vilanterol was estimated to have the highest net monetary benefit relative to the comparators at any specified willingness to pay for a QALY.

The results of the CMA are presented in Table 4, which shows the estimated medicine cost savings associated with umeclidinium/vilanterol against each LAMA/LABA comparator. The only sensitivity analysis performed was varying the discount rate for costs, with five year total cost savings of £1,838, £1,404, £1,841 and £266 versus the combinations of tiotropium and salmeterol, tiotropium and formoterol, tiotropium and indacaterol, and indacaterol/glycopyrronium respectively with 0% discount rate, and £1,641, £1,254, £1,644 and £238 respectively at a 6% discount rate.

Table 2. Results of base case CUA (over a 20 year time horizon)

	Umeclidinium/vilanterol 55/22 micrograms	Tiotropium 18 micrograms	Cost difference between umeclidinium/vilanterol 55/22 micrograms and tiotropium 18 micrograms	Tiotropium 18 micrograms and indacaterol 150 micrograms	Difference between umeclidinium/vilanterol 55/22 micrograms and tiotropium 18 micrograms and indacaterol 150 micrograms	Plausibility
Medicine costs	£3,066	£3,159	−£94	£5,920	−£2,856	The base case findings appear plausible against the two comparators considered, although the actual estimates of incremental cost and QALY lack plausibility as discontinuations have not been taken into account. The QALY differences are extremely small, especially versus tiotropium and indacaterol. For this comparison the difference in FEV_1 reduction is derived from a frequentist ITC which shows no statistically significant differences in FEV_1 reduction between umeclidinium/vilanterol and tiotropium and indacaterol.
Other costs*	£4,434	£4,435	−£1	£4,436	−£2	
Total costs	£7,500	£7,594	−£94	£10,356	−£2,856	
QALYs	4.70	4.69	+0.014	4.70	+0.0037	
ICER (Incremental cost per QALY gained)			Umeclidinium/vilanterol 'dominates'		Umeclidinium/vilanterol 'dominates'	
*These include hospital (A & E, general and ICU ward), outpatient and GP visit costs						

Table 3. Results of selected scenario and sensitivity analyses.

Scenario and sensitivity analyses	Umeclidinium/vilanterol 55/22 micrograms versus tiotropium 18 micrograms			Umeclidinium/vilanterol 55/22 micrograms versus tiotropium 18 micrograms and indacaterol 150 micrograms			Plausibility
	Incremental costs	Incremental QALYs	Cost/QALY	Incremental costs	Incremental QALYs	Cost/QALY	
Duration of FEV_1 treatment effect to end of clinical trial (24 weeks for comparison with tiotropium and 12 weeks versus tiotropium and indacaterol)	−£95	+0.0106	Dominates	−£2,857	+0.003	Dominates	Evidence for efficacy is limited to 24 weeks. Although a longer treatment effect reduces cost-effectiveness, this does not have a large impact on the results. Given the model does not take account of discontinuations and assumes a continuous duration of effect, the scenario analysis with a five-year time horizon is more plausible
Duration of FEV_1 treatment effect (lifetime maximum of 20 years)	+£126	+0.178	£707	−£2,775	+0.049	Dominates	
Time horizon of five years	-£52	+0.0148	Dominates	-£1,569	+0.004	Dominates	
0% discount rates for costs and QALYs	−£112	+0.014	Dominates	−£3,396	+0.004	Dominates	
6% discount rates for costs and QALYs	−£85	+0.014	Dominates	−£2,561	+0.004	Dominates	
Varying marginal FEV_1 treatment effect of comparator vs umeclidinium/vilanterol by lower bounds 95% CIs: -122.82 (versus. tiotropium) -52.30 (versus tiotropium and indacaterol)	NA	NA	Dominates	NA	NA	Dominates	For the comparison with tiotropium monotherapy the sensitivity analysis demonstrates a statistically significant increase in FEV_1 for umeclidinium/vilanterol, so the finding that umeclidinium/vilanterol dominates tiotropium is plausible. For the comparison with tiotropium and indacaterol, the difference in FEV_1 from a frequentist ITC is not statistically significant, hence estimates of any QALY differences are uncertain, although lower umeclidinium/vilanterol costs would still be expected.
Varying marginal FEV_1 treatment effect of comparator vs umeclidinium/vilanterol by upper bounds 95% CIs: - 61.52 (versus tiotropium +2.11 (versus tiotropium and indacaterol)	NA	NA	Dominates	NA	NA	£9,174*	
NA: not available; CI: confidence interval; *As the comparator is more effective with the upper 95% CI for marginal FEV_1 treatment effect, this ratio represents the incremental cost per QALY gained for the comparator vs umeclidinium/vilanterol.							

Table 4: Results of the CMA

	Umeclidinium/ vilanterol 55/22 micrograms	Tiotropium 18 micrograms and salmeterol 100 micrograms	Cost difference between umeclidinium/ vilanterol 55/22 micrograms and tiotropium 18 micrograms and salmeterol 100 micrograms	Tiotropium 18 micrograms and formoterol 24 micrograms	Cost difference between umeclidinium/ Vilanterol 55/22 micrograms and tiotropium 18 micrograms and formoterol 24 micrograms	Tiotropium 18 micrograms and indacaterol 150 micrograms	Cost difference between umeclidinium/ vilanterol 55/22 micrograms and tiotropium 18 micrograms and indacaterol 150 micrograms	indacaterol/ glycopyrronium 85/43 micrograms	Cost difference between umeclidinium/ vilanterol 55/22 micrograms and indacaterol/ glycopyrronium 85/43 micrograms	Plausibility
Annual medicine costs in year one	£395	£763	−£368	£676	−£281	£764	−£368	£449	−£53	The cost savings estimated are plausible, but dependent on the assumed comparable efficacy and safety from the indirect comparison, which showed no statistically significant differences in FEV_1 reduction or other outcomes for each comparison.
Medicine costs for five years*	£1,848	£3,565	−£1,720	£3,160	−£1,312	£3,568	−£1,720	£2,097	−£249	
Costs are a weighted average of bronchodilators used for tiotropium and salmeterol (based on proportionate use of Spiriva® + Serevent® Evohaler®, and Spiriva® + Vertine®), and for tiotropium and formoterol (based on proportionate use of Spiriva® + Oxis® Turbohaler®, Spiriva® + Foradil®, Spiriva® + Atimos® Modulite®, Spiriva® + Easyhaler® Formoterol). *Costs discounted at 3.5% after year 1										

4.1.3 AWTTC critique

The economic evaluation of umeclidinium/vilanterol utilised a complex economic model in order to take into account broader aspects of disease progression in COPD such as exercise capacity and symptoms which may be related to prognosis and survival outcomes[18]. However, the differences in QALY outcomes in the base case are extremely small and not related to any differences in survival outcomes between umeclidinium/vilanterol and the comparators. The key cost driver is the difference in medicine acquisition costs, with costs for umeclidinium/vilanterol being significantly lower than tiotropium and indacaterol. Head-to-head trial evidence versus tiotropium monotherapy was available; however, this does not provide comparison against the LAMA/LABA combination. In addition, the CMA has been used to provide a comparison with other LAMA/LABA comparators, including (according to prescription data presented by the company) the most prescribed combination of tiotropium and salmeterol.

Limitations with the economic analysis are as follows:

- The validity of the ITCs is dependent on the degree of homogeneity in trial study designs and patient populations and the robustness of the systematic reviews. Differences in the duration of the studies meant that the ITCs had to be based on relatively short 12 week follow-up times for comparisons versus tiotropium and indacaterol and versus tiotropium and formoterol for the key outcome of FEV_1 change from baseline which could introduce bias as the umeclidinium/vilanterol studies were designed for 24 weeks. The Bayesian NMA was useful, in particular for the comparison of FEV_1 change outcomes for umeclidinium/vilanterol versus tiotropium and salmeterol, although the duration of treatment was different for the study data compared (24 weeks versus 20 weeks). The NMA was hampered by the limited data available for the comparisons with LAMA/LABA combinations for the other outcomes considered.
- In the CUA model the duration of treatment with each therapy is assumed to be lifetime (i.e. until death up to a maximum of 20 years) as discontinuation from treatment is not taken into account. This lacks plausibility. The company have argued that discontinuations are assumed to be the same for all treatments, but this is based on limited evidence comparing only umeclidinium/vilanterol and tiotropium.
- The assumption regarding duration of treatment effect of 52 weeks is uncertain and is based on short term clinical trial data of 12 to 24 weeks. The 52-week effect assumption is argued to be supported by a safety trial of this duration, although this study uses an unlicensed higher dose of umeclidinium/vilanterol 113/22 micrograms and was not comparative, and so it is unclear how this supports the sustained treatment effect case for the 55/22 micrograms dose. Scenario analysis indicated the duration of treatment effect did not have a large impact on the cost-effectiveness results. Given the model does not take account of discontinuations and uncertainty regarding duration of effect, the scenario analysis with a five year time horizon appears more plausible than with the 20 year time horizon in the base case. However, using a five year time horizon does not have a significant impact on the results.
- The CMA presented for the LAMA/LABA combinations has the advantage of simplicity and demonstrates the cost savings associated with umeclidinium/vilanterol. However, this approach is based on an indirect comparison and does not take uncertainty in the outcomes considered into account. The Bayesian NMA and CUA model have not been used to provide estimates of the probability of QALY differences for the comparison with tiotropium and salmeterol, or tiotropium and formoterol.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of umeclidinium/vilanterol 55/22 micrograms within its current licensed indication for adult patients with COPD.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Prevalence and incidence data for COPD in Wales were obtained from published sources[6] and mortality derived from statistics available on deaths due to bronchitis, emphysema and other COPD in England and Wales[19]. It was assumed that all diagnosed COPD patients are treated, representing a prevalence of treated COPD patients in Wales of 2.2%. The company described patients expected to be eligible to be treated with umeclidinium/vilanterol 55/22 micrograms as those who continue to experience persistent breathlessness/symptoms (Medical Research Council dyspnoea score (MRC) ≥ 3)[5] and do not experience persistent exacerbations. This represents 28.8% of patients currently treated with LAMA monotherapy or LAMA/LABA combination therapy[1]. Of these patients an uptake rate of 3% in year one rising to 15% in year five was assumed, meaning an expected 594 patients in Wales will be treated with umeclidinium/vilanterol in year one rising to 3,117 in year five. In an alternative scenario in which only LAMA/LABA combinations were assumed to be displaced, the number of patients expected to be treated was estimated at 86 in year one rising to 452 in year five.

5.1.2 Results

The estimated net budget impact is presented in Table 5. In the base case the company has assumed umeclidinium/vilanterol will displace tiotropium monotherapy and tiotropium and indacaterol combination therapy resulting in a net saving of £38,000 in year one rising to £199,500 in year five.

The company provided a scenario based on a weighted use of various LAMA monotherapies and LAMA/LABA combinations available. This resulted in an estimated net medicines budget impact consisting of savings of £34,000 in year one and £181,000 in year five (Table 5). In the alternative scenario in which only LAMA/LABA combinations are displaced, the net medicines budget impact was estimated at savings of £30,000 in year one, and £155,000 in year five.

Table 5. Company-reported comparative costs of umeclidinium/vilanterol.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients currently treated with either a LAMA or LAMA/LABA*	19,792	20,038	20.290	20,531	20,777
Uptake estimates	3%	6%	9%	12%	15%
Estimated number of patients treated with umeclidinium/vilanterol	594	1,202	1,826	2,464	3,117
Net costs based on displacement of tiotropium, and tiotropium and indacaterol (base case)[†]					
Net costs (Medicine costs)	−£38,106	−£76,928	−£116,864	−£157,696	−£199,488
First scenario analysis – weighted average for alternative LAMA monotherapies and LAMA/LABA combinations[§]					
Overall net cost	−£34,452	−£69,716	−£105,908	−£142,912	−£180,786
Second scenario analysis – displacement of LAMA/LABA combinations only[¶]					
Estimated number of patients treated with umeclidinium/vilanterol	86	174	265	357	452
Overall net cost	−£29,530	−£59,794	−£90,818	−£122,530	−£154,997

*Assumes some growth in prevalence of COPD in line with a growth in population size, but incidence and mortality staying stable over five years.
[†]Assumes that uptake of umeclidinium/vilanterol displaces 85.5% of tiotropium and 14.5% of tiotropium and indacaterol.
[§]Assumes that uptake of umeclidinium/vilanterol displaces 85.5% of LAMA monotherapy and 14.5% of LAMA/LABAs.
[¶]Weighted average annual cost of £738.41 for LAMA/LABA combinations based on 75.5%, 15% and 9.5% prescriptions market share of tiotropium + salmeterol, tiotropium + formoterol and tiotropium + indacaterol preparations respectively (UK prescribing data from the Cegedim Longitudinal Patient Database[1]).

5.1.3 AWTTC critique

- The estimates the company have provided, assuming only displacement of LAMA/LABA combinations (second scenario in Table 5), represent the most useful estimates of treated patient numbers and net medicines budget impact.
- The eligible patients and overall net savings based on displacement of tiotropium, and the combination of tiotropium and indacaterol (base case in Table 5) may be overestimated as a large part of this is associated with displacement of tiotropium monotherapy, whereas it is the LAMA/LABA combination therapy that would primarily be expected to be displaced. The scenario analysis based on a weighted average of LAMA/LABA combinations may be more realistic as the basis of the net cost estimates. However, the net cost estimates also include LAMA monotherapy which may not be as relevant.
- The estimates of net costs are dependent on the estimates of patient uptake rates. The uptake rates are the same as were estimated in the recent indacaterol/glycopyrronium AWMSG Secretariat Assessment Report[20]. As the rationale for the uptake rates estimated has not been explained, there is uncertainty with the umeclidinium/vilanterol budget impact estimates.

5.2 Comparative unit costs

Acquisition costs for umeclidinium/vilanterol (Anoro® Ellipta®▼) and alternative bronchodilator treatment options for the maintenance treatment of COPD are shown in Table 6.

Table 6. Examples of medicine acquisition costs.

Treatment	Recommended dose	Annual cost
Umeclidinium/vilanterol (Anoro® Ellipta®▼) 55/22 micrograms inhalation powder*	One inhalation daily	£395 (including the cost of Ellipta® device)
Tiotropium (Spiriva® Handihaler®) 18 micrograms inhalation powder, hard capsule†	One capsule daily	£424 (including the cost of Handihaler® device)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder†, hard capsule plus **tiotropium (Spiriva® Handihaler®)** 18 micrograms inhalation powder, hard capsule†	One capsule of each daily	£780 (including the cost of Breezhaler® and Handihaler® devices)
Indacaterol/glycopyrronium (Ultibro Breezhaler®) 85/43 micrograms inhalation powder capsule†	One capsule daily	£448.71 (including the cost of Breezhaler® device)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder, hard capsule† plus **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder, hard capsule*	One capsule of each daily	£691 (including the cost of Breezhaler® devices)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder†, hard capsule† plus **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	One capsule of indacaterol daily and one inhalation of aclidinium twice daily	£704 (including the cost of Breezhaler® device and metered dose inhaler)
Salmeterol (Serevent® Accuhaler®) 50 micrograms inhalation powder, blister† plus **tiotropium (Spiriva® Handihaler®)** 18 micrograms inhalation powder, hard capsule†	One inhalation of salmeterol twice daily and one capsule of tiotropium daily	£780 (including the cost of Accuhaler® and Handihaler® devices)
Salmeterol (Serevent® Accuhaler®) 50 micrograms inhalation powder, blister† **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder, hard capsule*	One inhalation of salmeterol twice daily and one capsule of glycopyrronium daily	£691 (including the cost of Accuhaler® and Breezhaler® devices)
Salmeterol (Serevent® Accuhaler®) 50 micrograms inhalation powder, blister† **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	One inhalation of each twice daily	£704 (including the cost of Accuhaler® device and metered dose inhaler)
Formoterol fumarate dehydrate (Formoterol Easyhaler®) 12 micrograms inhalation powder§ plus **tiotropium (Spiriva® Handihaler®)**18 micrograms inhalation powder ,hard capsule†	One inhalation of formoterol fumarate dehydrate twice daily and one capsule of tiotropium daily	£569 (including the cost of Easyhaler® and Handihaler® devices)
Formoterol fumarate dehydrate (Formoterol Easyhaler®) 12 micrograms inhalation powder§ plus **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder, hard capsule*	One inhalation of formoterol fumarate dehydrate twice daily and one capsule of glycopyrronium daily	£479 (including the cost of Easyhaler® and Breezhaler® devices)
Formoterol fumarate dehydrate (Formoterol Easyhaler®) 12 micrograms inhalation powder§ plus **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	One inhalation of each twice daily	£492 (including the cost of Easyhaler® and metered dose inhaler)
Costs are based on drug tariff, British National Formulary and MIMs prices as of December 2014[13,21,22] *Delivered dose; †capsule or blister dose; §metered dose This table does not imply therapeutic equivalence of the stated treatments and doses. See Summaries of Product Characteristics (SPCs) for full dosing details[2,23–29].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, umeclidinium/vilanterol (Anoro® Ellipta®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that umeclidinium/vilanterol (Anoro® Ellipta®▼) will be supplied by a home healthcare provider[1].

6.2 Ongoing studies

As part of the risk management plan, the company will be conducting a cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in COPD patients using either umeclidinium/vilanterol or umeclidinium versus tiotropium (Study 201038)[12]

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 19 November 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Chronic obstructive pulmonary disease (COPD)
National Institute for Health and Care Excellence use the following working definition of COPD:

- Airflow obstruction is defined as a reduced FEV_1/FVC ratio, such that FEV_1/FVC is less than 0.7.
- If FEV_1 is ≥ 80% FEV_1 predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough[5].

FEV_1
The forced expired volume in one second is the volume of air that can be expelled from maximum inspiration in the first second[30].

FVC
Forced vital capacity is the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration[30].

FEV_1% predicted
The forced expiratory volume in one second (FEV_1) expressed as a percentage of a predicted value, which depends on the individual's age, height and sex, obtained using a reference population[30].

Transition Dyspnoea Index (TDI)
TDI is a validated scoring system based on patient self-assessment for recording dyspnoea (shortness of breath or difficulty in breathing). Experts have proposed that 1.0 is the minimal clinically important difference difference[31].

REFERENCES

1 GlaxoSmithKline Limited. Form B: Detailed appraisal submission. Umeclidinium/vilanterol (as trifenatate) (Anoro® Ellipta®▼). Sep 2014.

2 GlaxoSmithKline. Anoro® Ellipta®▼ 55/22 micrograms inhalation powder, pre-dispensed. Summary of Product Characteristics. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/28949/SPC/Anoro+Ellipta+55+micrograms+22+micrograms+inhalation+powder%2c+pre-dispensed/. Accessed Dec 2014.

3 National Institute for Health and Care Excellence. Quality Standards 10. Chronic obstructive pulmonary disease quality standard. Jul 2011. Available at: http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-quality-standard-qs10. Accessed Dec 2014.

4 Health and Safety Executive. Chronic Obstructive Pulmonary Disease (COPD) in Great Britain (2014). Oct 2014. Available at: http://www.hse.gov.uk/statistics/causdis/copd/copd.pdf. Accessed Dec 2014.

5 National Institute for Health and Care Excellence. Clinical Guideline 101. Chronic obstructive pulmonary disease. Jun 2010. Available at: http://guidance.nice.org.uk/CG101. Accessed Dec 2014.

6 Welsh Government. Quality and Outcomes Framework Disease Registers. 2014. Available at: https://statswales.wales.gov.uk/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/GMS-Contract/PatientsOnQualityAndOutcomesFramework-by-LocalHealthBoard-DiseaseRegister. Accessed Dec 2014.

7 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. Jan 2014. Available at: http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf. Accessed Dec 2014.

8 National Institute for Health and Care Excellence. NICE Pathways. Inhaled therapy in COPD. 2014. Available at: http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease/inhaled-therapy-in-copd. Accessed Dec 2014.

9 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0814. Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) 85/43 micrograms inhalation powder as hard capsules. Feb 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1535. Accessed Dec 2014.

10 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0813. Aclidinium bromide (Eklira® Genuair®▼) 322 micrograms inhalation powder. May 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/938. Accessed Dec 2014.

11 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0713. Glycopyrronium bromide (Seebri® Breezhaler®▼) 44 micrograms inhalation powder as hard capsules. Mar 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1455. Accessed Dec 2014.

12 European Medicines Agency. Assessment Report for Anoro®▼. Procedure No.: EMEA/H/C/002751/0000. Mar 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002751/WC500168425.pdf. Accessed Dec 2014.

13 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2014. Available at: http://www.mims.co.uk/. Accessed Dec 2014.

14 Mahler DA, D'Urzo A, Bateman ED et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. *Thorax* 2012; 67 (9): 781-8.

15 Agusti A, Calverley PM, Celli B et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11 (122): 1-14.
16 Calverley PM, Anderson JA, Celli B et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *NEJM* 2007; 356 (8): 775-89.
17 Starkie HJ, Briggs A, Chambers MG et al. Predicting EQ-5D values using the SGRQ. *Value Health* 2011; 14 (2): 354-60.
18 Briggs A, Spencer M, Wang H et al. Development and validation of a prognostic index for health outcomes in chronic obstructive pulmonary disease. *Arch Intern Med* 2008; 168 (1): 71-9.
19 European respiratory Society. European lung white book. Chapter 13 COPD. 2014. Available at: http://www.erswhitebook.org/chapters/chronic-obstructive-pulmonary-disease/. Accessed Dec 2014.
20 All Wales Medicines Strategy Group. All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) 85 micrograms/43 micrograms inhalation powder as hard capsules. Reference number: 1535. Feb 2014. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1535. Accessed Dec 2014.
21 Prescribing Services Ltd. drugtariff.co.uk. Dec 2014. Available at: http://www.ppa.org.uk/ppa/edt_intro.htm. Accessed Dec 2014.
22 BMJ Group, Royal Pharmaceutical Society of Great Britain. British National Formulary. Dec 2014. Available at: https://www.medicinescomplete.com/mc/. Accessed Dec 2014.
23 GlaxoSmithKline UK. Serevent® Accuhaler®. Summary of Product Characteristics. Mar 2014. Available at: http://www.medicines.org.uk/emc/medicine/91. Accessed Dec 2014.
24 Almirall Limited. Eklira® Genuair®▼ 322 micrograms inhalation powder. Summary of Product Characteristics. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/27001/SPC/Eklira+Genuair+322+micrograms+inhalation+powder/. Accessed Dec 2014.
25 Boehringer Ingelheim Limited. Spiriva® 18 microgram inhalation powder, hard capsule. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/. Accessed Dec 2014.
26 Novartis Pharmaceuticals Limited. Onbrez® Breezhaler® 150 and 300 microgram inhalation powder, hard capsules. Summary of Product Characteristics. Oct 2014. Available at: http://www.medicines.org.uk/emc/medicine/23260/SPC/Onbrez+Breezhaler+150+and+300+microgram+inhalation+powder%2c+hard+capsules/. Accessed Dec 2014.
27 Orion Pharma UK Limited. Formoterol Easyhaler® 12 micrograms per actuation inhalation powder. Summary of Product Characteristics. Mar 2013. Available at: http://www.medicines.org.uk/emc/medicine/19503/SPC/Formoterol+Easyhaler+12+micrograms+per+actuation+inhalation+powder/. Accessed Dec 2014.
28 Novartis Pharmaceuticals UK Ltd. Seebri® Breezhaler®▼ inhalation powder, hard capsules 44 micrograms. Summary of Product Characteristics. Jul 2014. Available at: http://www.medicines.org.uk/emc/medicine/27138/SPC/Seebri+Breezhaler+Inhalation+Powder,+Hard+Capsules+44mcg/. Accessed Dec 2014.
29 Novartis Pharmaceuticals UK Ltd. Ultibro® Breezhaler®▼. Summary of Product Characteristics. Dec 2014. Available at: http://www.medicines.org.uk/emc/medicine/29533. Accessed Dec 2014.
30 Egton Medical Information Systems Limited. Measurements made in spirometry. Jan 2013. Available at: http://www.patient.co.uk/doctor/Spirometry-Calculator.htm . Accessed Dec 2014.

31 Mahler DA, Witek TJ. The MCID of the transition dyspnea index is a total score of one unit. *J COPD* 2005; 2: 99-103.