



All Wales Therapeutics  
and Toxicology Centre

Canolfan Therapiwteg a  
Thocsicoleg Cymru Gyfan

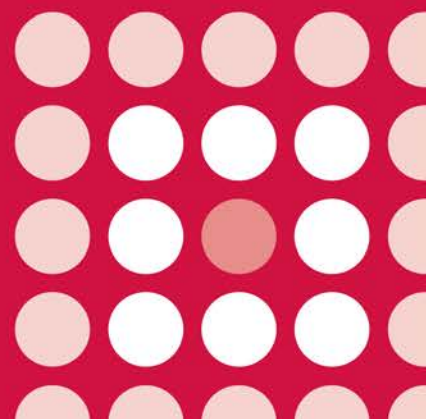
## AWMSG SECRETARIAT ASSESSMENT REPORT

**Umeclidinium (Incruse<sup>®</sup>▼)**

55 micrograms inhalation powder

Reference number: 1352

**FULL SUBMISSION**



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)  
University Hospital Llandough  
Penlan Road  
Llandough  
Vale of Glamorgan  
CF64 2XX

[awttc@wales.nhs.uk](mailto:awttc@wales.nhs.uk)  
029 2071 6900

This report should be cited as:  
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Umeclidinium (Incruse<sup>®</sup>) 55 micrograms inhalation powder.  
Reference number:1352. October 2014.

**AWMSG Secretariat Assessment Report**  
**Umeclidinium (Incruse<sup>®</sup>▼) 55 micrograms inhalation powder**

This assessment report is based on evidence submitted by GlaxoSmithKline on 24 July 2014<sup>1</sup>.

## 1.0 PRODUCT DETAILS

<b>Licensed indication under consideration</b>	Umeclidinium (Incruse <sup>®</sup> ▼) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) <sup>2</sup> .
<b>Dosing</b>	Each single inhalation provides a delivered dose (the dose leaving the mouthpiece of the inhaler) of 55 micrograms umeclidinium (equivalent to 62.5 micrograms of umeclidinium bromide). The recommended dose is one inhalation of umeclidinium once daily <sup>2</sup> .
<b>Marketing authorisation date</b>	28 April 2014 <sup>3</sup> .
<b>UK launch date</b>	September 2014 <sup>1</sup> .

## 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<sup>4</sup>. 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<sup>4</sup>. Smoking is the main cause of COPD, but other factors include exposure to dusts, fumes and certain chemicals<sup>5</sup>. It is estimated that three million people have COPD in the UK, of which approximately 900,000 have been diagnosed<sup>6</sup>. The number of patients diagnosed with COPD in Wales in 2012–2013 was 67,773<sup>7</sup>. COPD prevalence increases with age and is rarely seen in people under the age of 35 years<sup>4</sup>.

COPD treatment aims to reduce symptoms, lower the frequency and severity of exacerbations, improve health status and increase exercise tolerance<sup>8</sup>. Bronchodilators, including beta<sub>2</sub>-agonist and muscarinic antagonist (anticholinergic) inhalation therapies, are central to the management of COPD symptoms<sup>8</sup>. For patients with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, a once-daily long-acting muscarinic antagonist (LAMA) is recommended to reduce the number of exacerbations and hospitalisations<sup>6,8</sup>. Umeclidinium is a new LAMA licensed to treat the symptoms of COPD in adults<sup>1,2</sup>.

### 2.2 Comparators

The comparators included in the company submission were:

- Tiotropium (Spiriva<sup>®</sup> HandiHaler<sup>®</sup>) 18 micrograms inhalation powder
- Tiotropium (Spiriva<sup>®</sup> Respimat<sup>®</sup>) 2.5 micrograms inhalation powder
- Acclidinium (Eklira<sup>®</sup> Genuair<sup>®</sup>) 322 micrograms inhalation powder

- Glycopyrronium (Seebri<sup>®</sup> Breezhaler<sup>®</sup>▼) 44 micrograms inhalation powder

The applicant company consider tiotropium to be the most relevant comparator to umeclidinium<sup>1</sup>.

### 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)<sup>8</sup>.
- National Institute for Health and Care Excellence (NICE) Pathways. Inhaled therapy in COPD (2013)<sup>9</sup>.
- NICE. Chronic obstructive pulmonary disease. Clinical Guideline 101 (2010)<sup>6</sup>.

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of the LAMAs acclidinium bromide (Eklira<sup>®</sup> Genuair<sup>®</sup>), and glycopyrronium bromide (Seebri<sup>®</sup> Breezhaler<sup>®</sup>▼), the long-acting beta2-agonist (LABA)/LAMA fixed dose combination (FDC) indacaterol/glycopyrronium (Ultibro<sup>®</sup> Breezhaler<sup>®</sup>▼) and the inhaled corticosteroid (ICS)/LABA fluticasone/vilanterol (Revlar Ellipta<sup>®</sup>▼)<sup>10–13</sup>.

### 3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

There are a number of studies included in the company submission which evaluate the efficacy and safety of umeclidinium for the treatment of COPD, although not all of the studies provide evidence for the licensed indication under consideration<sup>1</sup>. Four placebo studies in particular have been highlighted by the applicant company (see Section 3.1).

In order to address the lack of direct comparative data, the company performed a systematic review. Results of the systematic review were used to conduct three indirect treatment comparisons (ITCs) to assess the relative efficacy of umeclidinium versus tiotropium, acclidinium and glycopyrronium<sup>1</sup>.

#### 3.1 Placebo studies

Studies AC4115408 and DB2113373 demonstrated statistically significant and clinically meaningful improvements in lung function through FEV<sub>1</sub> (i.e. forced expiratory volume in one second; see Glossary) and 0-6h weighted mean FEV<sub>1</sub> for umeclidinium compared to placebo over 12 and 24 weeks, respectively<sup>2</sup>. Quality of life was recorded for both of these studies using the St George's Respiratory Questionnaire (SGRQ, see glossary). In study AC4115408, a statistically significant improvement in SGRQ was demonstrated for umeclidinium over placebo whereas, in study DB2113373, scores were numerically greater but a statistically significant improvement could not be demonstrated<sup>1,14</sup>.

Two exercise studies measured exercise endurance time (EET) as the primary outcome: in the first study (DB2114417), umeclidinium (55 micrograms) did not demonstrate statistically significant improvement in EET at week 12 and was considered a failed study by the Committee for Medicinal Products for Human Use (CHMP)<sup>14</sup>. The second exercise study (DB2114418) demonstrated a relevant increase in EET with umeclidinium (113 micrograms) but not with umeclidinium (55 micrograms) compared to placebo. It was noted that a higher than anticipated response in the placebo group in this study may have resulted in the lower treatment difference between placebo and umeclidinium<sup>14</sup>.

As none of these studies compared umeclidinium with an active comparator, these trials will not be discussed further in detail<sup>1</sup>.

### 3.2 Systematic review and ITCs

The company conducted a systematic review of the literature to identify randomised control trials (RCTs) with outcomes of interest evaluated at 12 and 24 weeks in adult patients with COPD<sup>1</sup>. The selection process identified 24 RCTs including four clinical study reports plus an integrated summary of efficiency from GlaxoSmithKline which synthesised data from four clinical studies (AC4115408, DB2113361, DB2113373 and DB2113374). Using placebo as a common comparator, base case ITCs comparing umeclidinium 55 micrograms versus tiotropium 18 micrograms, aclidinium 322 micrograms and glycopyrronium 44 micrograms were performed. The primary endpoint assessed was the difference in change from baseline (CFB) for trough FEV<sub>1</sub> at 12 weeks. Secondary endpoints were: CFB for trough FEV<sub>1</sub> at 24 weeks; health-related quality-of-life as the difference in CFB in SGRQ total score; difference in transitional dyspnoea index (TDI) focal score at 12 and 24 weeks, and rescue medication use as decrease in mean daily number of puffs<sup>1</sup>.

For umeclidinium versus all three comparators, the base case ITCs showed no significant difference in the primary endpoint. All values were smaller than the minimal clinically important difference (MCID) of 100 ml. Likewise, for all of the secondary endpoints, no significant difference was demonstrated, and all values for differences in trough FEV<sub>1</sub>, SGRQ total score and TDI focal score were below the MCIDs<sup>1</sup>.

In addition to the base case ITC analyses, two further scenarios were analysed for umeclidinium versus tiotropium:

- Scenario one where the integrated summary of efficiency results and placebo were used as common comparators.
- Scenario two in which placebo, umeclidinium 113 micrograms, umeclidinium/vilanterol 55/22 micrograms and vilanterol 22 micrograms were common comparators and then a random effects meta-analysis performed to synthesise the results of the separate ITCs<sup>1</sup>.

Scenario one results were found to be consistent with the base case analyses results. The results of the scenario two meta-analysis showed umeclidinium resulted in a significant increase in trough FEV<sub>1</sub> at 12 weeks when compared to tiotropium with a mean difference of 27.94 ml (95% confidence interval [CI]: 3.40–52.47,  $p = 0.026$ ). The difference was below the MCID for trough FEV<sub>1</sub>. Other secondary outcomes were consistent with scenario one and base case analyses results<sup>1</sup>.

### 3.3 Comparative safety

The company submission did not include any studies to provide direct comparative evidence of safety of umeclidinium versus other LAMA medicines; no safety outcomes were included in the ITCs. The longest term safety data available using umeclidinium 55 micrograms was a 24-week, placebo-controlled study, DB2113373<sup>15</sup>. A 52-week safety study (DB2113359) which used the higher strength 113 microgram dose of umeclidinium was also considered relevant as the dose is 2-fold higher than umeclidinium 55 micrograms and provided a relevant safety margin<sup>1,16</sup>. Both studies concluded that umeclidinium was well tolerated over the treatment periods with no clinically meaningful treatment-related changes in vital signs or laboratory parameters<sup>15,16</sup>. In addition, the applicant company provided pooled safety data from eight studies (four efficacy studies: AC4115408, DB2113361, DB2113373, DB2113374; one long-term safety study: DB2113359; two exercise studies: DB2114417, DB2114418; and one additional study: AC4113589)<sup>1,14</sup>. CHMP concluded that the overall safety profile of umeclidinium was consistent with that of other LAMAs and the comorbidities commonly present in patients with COPD. However, they also stated that, although umeclidinium belongs to a well-established and known class of molecules, it is a new active substance and safety data from this class may not be necessarily applicable. CHMP recommended a further investigation of the potential risk

of cardiovascular and cerebrovascular events with umeclidinium compared to tiotropium to address issues related to safety<sup>14</sup>.

### 3.4 AW TTC critique

- CHMP concluded that the efficacy of umeclidinium versus placebo was demonstrated; however, it was noted that outcome measures (e.g. TDI score, SGRQ score) did not always reach clinically relevant difference versus placebo. This was considered to be in line with other medicines in the LAMA class<sup>14</sup>.
- In the absence of any head-to-head comparative data, the applicant company conducted three ITCs<sup>1</sup>. Although the ITCs appear to be methodologically sound, results should be interpreted with caution due to the heterogeneity of trials, inherent limitations in the methodology and differences in study patient populations.
- No long term data were provided by the applicant company to support the efficacy of umeclidinium 55 micrograms beyond 24 weeks, which may not be long enough to investigate certain clinical endpoints such as exacerbations<sup>1</sup>. CHMP consider the minimum duration of study to investigate the frequency of exacerbations to be one year to capture seasonal variation in rates<sup>17</sup>.
- CHMP stated that the available safety data are limited for patients over 75 years old. Therefore, they have advised the applicant company to ensure that sufficient representation of patients over 75 years old are included in the post-authorisation safety study in order for relevant adverse events (particularly cardiovascular and cerebrovascular) to be appropriately assessed<sup>14</sup>.
- Umeclidinium (55 micrograms) is provided in a new dry powder device (Ellipta<sup>®</sup> inhaler), which is pre-loaded with 30 doses. The applicant company considers this to be an advantage over some other devices used to deliver medicines of this class which require loading of individual doses prior to each use. In the two exercise studies (DB2114417 and DB2114418), ease of use was collected via a patient questionnaire where 99% of users rated it as easy or very easy to use after six weeks of treatment<sup>1,18</sup>.
- The primary and secondary endpoint results of the two exercise studies (DB2114417 and DB2114418) differ both in terms of significance and the size of the treatment differences. CHMP consider these studies as supportive only; there are no claims on exercise intolerance in the Summary of Product Characteristics (SPC)<sup>14</sup>.

## 4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

### 4.1 Cost-effectiveness evidence

#### 4.1.1 Context

The company submission included a cost minimisation analysis (CMA) of the LAMA umeclidinium 55 micrograms used once daily through the Ellipta<sup>®</sup> inhaler compared against tiotropium bromide (Spiriva<sup>®</sup> Handihaler<sup>®</sup>) 18 micrograms once daily, tiotropium bromide (Spiriva<sup>®</sup> Respimat<sup>®</sup>) 5 micrograms once daily, aclidinium (Eklira<sup>®</sup> Genuair<sup>®</sup>) 322 micrograms twice daily and glycopyrronium bromide (Seebri<sup>®</sup> Breezhaler<sup>®</sup>) 44 micrograms once daily as a monotherapy for patients with COPD<sup>1</sup>.

There are no direct comparative trial data for umeclidinium and these comparators. The company has described the key trials of umeclidinium and all comparators as part of their evidence synthesis for an ITC. Broadly equivalent efficacy is assumed between umeclidinium and the comparator treatments of the same class regarding change in baseline FEV<sub>1</sub>, SGRQ total score, TDI focal score and rescue medication use. No ITC was provided for umeclidinium and tiotropium (Spiriva<sup>®</sup> Respimat<sup>®</sup>) 5 micrograms as the efficacy of the latter was assumed to be similar to tiotropium (Spiriva<sup>®</sup> Handihaler<sup>®</sup>) 18 micrograms based on a trial suggesting noninferiority<sup>19</sup>.

The analysis is limited to only consider medicine acquisition costs over five years with a discount of 3.5% applied to costs in each year after the first. Unit costs were taken from MIMS<sup>20</sup> and exclude VAT. The assumption is made that relative costs and effects are constant over time and that no other health or social care costs will arise from the introduction of umeclidinium 55 micrograms. The company justifies their approach with the fact that all medicines are of the same pharmacological class and on the grounds of unreferenced clinical consensus which purports to indicate broadly comparable efficacy. The cost of managing adverse events was not considered in the analysis.

#### 4.1.2 Results

The results of the base case analysis are presented in Table 1. Umeclidinium is reported to produce cost savings compared to tiotropium and aclidinium and to be cost-neutral compared to glycopyrronium.

**Table 1. Cost and cost difference of umeclidinium compared to other licensed LAMA treatments over 1 and 5 years**

	Total costs in year 1	Total, discounted costs over 5 years	Difference in year 1	Difference over 5 years
<b>Umeclidinium 55 micrograms</b>	£334.58	£1,563.53	–	–
<b>Tiotropium 18 micrograms</b>	£407.58	£1,904.67	-£73.00	-£341.13
<b>Tiotropium 2.5 micrograms</b>	£407.58	£1,904.67	-£73.00	-£341.13
<b>Aclidinium 322 micrograms</b>	£347.97	£1,626.08	-£13.38	-£62.54
<b>Glycopyrronium 44 micrograms</b>	£334.58	£1,563.53	£0.00	£0.00

Sensitivity analysis investigated the effect of changes in the discount rate between 0% and 6% on results. Cost savings only changed marginally in these calculations and umeclidinium remained cost-saving compared to tiotropium and aclidinium and cost-neutral compared to glycopyrronium in all analyses.

An additional analysis, in which costs are weighted according to usage, estimates a saving of £69 in year one and £337 over five years, based on 85.63% of patients currently receiving tiotropium, 3.67% use aclidinium and 2.18% glycopyrronium.

#### 4.1.3 AWTTTC critique

The reliability of the CMA presented in the company submission is dependent on the extent to which umeclidinium 55 micrograms is considered to be therapeutically equivalent to the comparator therapies. There is a lack of direct comparative data, but the company has provided adjusted ITCs which show non-significant differences in outcomes. However, 95% CIs for the main clinical outcomes are large and in the case of FEV<sub>1</sub> for example, are close to (smallest interval 73.19 ml for comparison with glycopyrronium at 12 weeks) or even span the minimal clinically important difference threshold of 100 ml (116.96 ml compared with aclidinium at 24 weeks). Furthermore, the rate of adverse events has not been included in the analysis as the overall safety profile of umeclidinium 55 micrograms was assumed to be consistent with that of other LAMAs and no noteworthy differences in the incidence of adverse events were reported between the treatment and placebo groups in clinical trials. The assumption of constant costs and effects over five years is based on trials with 12 and 24 weeks follow-up. CMA does not account for uncertainty in outcomes as they are considered equal which substantially limits the validity of the results of the company's analysis considering the high level of uncertainty in the assumptions.

Strengths and limitations with the economic analysis are as follows:

- While the economic evaluation makes no direct assumption of the licensed indication, all relevant comparators licensed as maintenance bronchodilators of the LAMA class have been included in the analysis. Adjusted ITCs were conducted for all comparators except tiotropium (Spiriva® Respimat®) 5 micrograms which is assumed to have similar efficacy as tiotropium (Spiriva® Handihaler®) 18 micrograms based on noninferiority reported in one trial<sup>19</sup>. This might increase uncertainty for the comparison with tiotropium (Spiriva® Respimat®) 5 micrograms in particular.
- Trials used in the ITCs were similar in terms of treatment (dose, dosage regimen), clinical situation (concomitant treatments including interventions other than drugs), disease (definition, diagnostic criteria, criteria of severity and progression of disease) and timing (same treatment period and similar follow-up). However, some inconsistency in treatment effects with regard to a number of treatment pathways was reported. In the ITC, the relative effects of treatment were sensitive to the selection of the common comparator which gave inconsistent results with respect to some pair-wise comparisons<sup>1</sup>. The estimated effect size should consequently be interpreted cautiously. This situation is problematic because the result should be the same irrespective of the path. The estimates should therefore be interpreted very cautiously.
- The analysis assumes that cost and effects remain the same over the chosen time horizon of five years. However, this is not supported by the ITC results which compare outcomes at 12 and 24 weeks and show that umeclidinium had a numerically larger improvement of FEV<sub>1</sub> than all other comparators at 12 weeks (by 18.06 ml to 35.77 ml) but differences had decreased at 24 weeks (to between 3.97 ml and -13.00 ml). If we assume that this decrease in efficacy in 12 weeks would be continued over five years, it may reach clinical significant levels at some point during the time horizon of the CMA. Due to the lack of long-term follow-up data for umeclidinium 55 micrograms the assumption that effects remain equal over five years should be considered cautiously.
- While the ITCs support the observation of absence of difference, no conclusion of equivalence can be made based on the results due to inconsistencies and wide confidence intervals and the lack of direct comparative data which does not allow for a more robust mixed treatment comparison. This will severely limit the applicability of the CMA results as CMA precludes exploration of uncertainty in all outcomes but costs.

#### **4.2 Review of published evidence on cost-effectiveness**

Standard literature searches conducted by AWTTTC have not identified any published evidence on the cost-effectiveness of umeclidinium 55 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<sup>7,21</sup> and mortality derived from statistics available on deaths due to bronchitis, emphysema and other COPD in England and Wales in 2012<sup>22</sup>. It is estimated that the yearly incidence of COPD in Wales is 84 individuals per 100,000 which approximates to 2,589 new patients per year assuming incidence to be constant over the first five years after introduction of umeclidinium 55 micrograms. The company assumes that all diagnosed patients are treated for COPD and that 62.56% of patients receive a LAMA and are therefore eligible for treatment with umeclidinium 55 micrograms. Expected uptake rate is assumed to be 3% in year one rising to 15% in year five which translates

into 1,289 patients receiving umeclidinium 55 micrograms in year one increasing to 6,782 patients in year five.

### 5.1.2 Results

The estimated net budget impact is presented in Table 2. The company assumes that umeclidinium will displace tiotropium (Spiriva<sup>®</sup> Handihaler<sup>®</sup> and Spiriva<sup>®</sup> Respimat<sup>®</sup>), aclidinium and glycopyrronium monotherapies which would result in a net saving of £88,941 in year one increasing to £467,958 in year five.

**Table 2. Company-reported costs associated with use of umeclidinium 55 micrograms for the treatment of COPD**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Number of eligible patients currently treated with a LAMA*</b>	42,961	43,524	44,086	44,648	45,211
<b>Uptake estimate (%)</b>	3	6	9	12	15
<b>Treated patients</b>	1,289	2,611	3,968	5,358	6,782
<b>Net costs based on displacement of tiotropium (Spiriva<sup>®</sup> Handihaler<sup>®</sup> and Spiriva<sup>®</sup> Respimat<sup>®</sup>), aclidinium and glycopyrronium</b>					
<b>Yearly cost of umeclidinium 55 micrograms</b>	£335	£335	£335	£335	£335
<b>Yearly cost of displaced LAMAs<sup>†</sup></b>	£404	£404	£404	£404	£404
<b>Net costs (medicine costs only)</b>	-£88,941	-£180,159	-£273,792	-£369,702	-£467,958
*Assumes some growth in prevalence of COPD in line with a growth in population size, but incidence and mortality staying stable over 5 years.					
<sup>†</sup> Weighted annual cost based on 85.63% market share for tiotropium (Spiriva <sup>®</sup> Handihaler <sup>®</sup> ) 18 microgram, 8.52% tiotropium (Spiriva <sup>®</sup> Respimat <sup>®</sup> ) 2.5 micrograms, 3.67% aclidinium 322 microgram and 2.18% glycopyrronium 44 micrograms.					

No sensitivity analyses or other scenarios were presented by the company.

### 5.1.3 AWTTTC critique

Due to the fact that the budget impact analysis as presented by the company is based on medicine acquisition cost only, the uncertainties regarding therapeutic equivalence as noted above for the CMA apply. Other limitations are as follows:

- The company assumes that costs to NHS Wales (defined as service and administration costs) of umeclidinium 55 micrograms will be equal to other LAMAs. However, adverse events have not been considered in the analysis and there is no indication of the budget impact of potential differences in healthcare contacts and hospital admissions. While the overall safety profile of umeclidinium 55 micrograms was assumed to be consistent with that of other LAMAs, and no noteworthy differences in the incidence of adverse events were reported between the treatment and placebo groups in the clinical trials presented by the company, this assumption remains a source of uncertainty.
- The estimates of net costs are dependent on the estimates of patient uptake rates. As the rationale for the uptake rates is based on an assumption, there is uncertainty regarding the budget impact of umeclidinium 55 micrograms.
- No sensitivity analysis has been provided by the company and the robustness of the results to changes in the parameters is unknown. Considering the uncertainty surrounding the assumptions of therapeutic equivalence and constant costs and effects over time, the results of the budget impact calculations should be interpreted with caution.

## 5.2 Comparative unit costs

Acquisition costs for umeclidinium 55 micrograms and alternative bronchodilator monotherapy options for the maintenance treatment of COPD are shown in Table 3.

**Table 3. Examples of medicine acquisition costs for maintenance bronchodilators**

Regimens	Example doses	Approximate annual costs per patient
<b>Long-acting muscarinic antagonists (LAMAs)</b>		
<b>Umeclidinium (Incruse<sup>®</sup>▼)</b> 55 micrograms inhalation powder, blister	One inhalation daily	£335 (including the cost of Ellipta <sup>®</sup> device)*
<b>Tiotropium (Spiriva<sup>®</sup> Handihaler<sup>®</sup>)</b> 18 micrograms inhalation powder, hard capsule	One inhalation daily	£424 (including the cost of Handihaler <sup>®</sup> device)
<b>Tiotropium (Spiriva<sup>®</sup> Respimat<sup>®</sup>)</b> 2.5 micrograms inhalation solution, metered	Two puffs once daily (5 micrograms)	£408 (including the cost of Respimat <sup>®</sup> device)
<b>Aclidinium (Eklira<sup>®</sup> Genuair<sup>®</sup>)</b> 322 micrograms inhalation powder	One inhalation twice daily	£348 (including the cost of Genuair <sup>®</sup> device)
<b>Glycopyrronium (Seebri<sup>®</sup> Breezhaler<sup>®</sup>▼)</b> 44 micrograms inhalation powder, hard capsule	One inhalation daily	£335 (including the cost of Breezhaler <sup>®</sup> device)
<b>Long-acting beta<sub>2</sub>-agonists (LABAs)</b>		
<b>Indacaterol (Onbrez<sup>®</sup> Breezhaler<sup>®</sup>)</b> 150 micrograms inhalation powder, hard capsule	One inhalation daily	£356 (including the cost of Breezhaler <sup>®</sup> device)
<b>Indacaterol (Onbrez<sup>®</sup> Breezhaler<sup>®</sup>)</b> 300 micrograms inhalation powder, hard capsule	One inhalation daily	£356 (including the cost of Breezhaler <sup>®</sup> device)
<b>Olodaterol (Striverdi<sup>®</sup> Respimat<sup>®</sup>▼)</b> 2.5 micrograms inhalation solution, metered	Two puffs once daily (5 micrograms)	£321 (including the cost of Respimat <sup>®</sup> device)
Not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details. Costs are based on drug tariff and British National Formulary (BNF) prices as of August 2014 <sup>23,24</sup> . This table does not imply therapeutic equivalence of drugs or the stated doses. *Cost for umeclidinium 55 micrograms are supplied by company <sup>1</sup> .		

## 6.0 ADDITIONAL INFORMATION

### 6.1 Prescribing and supply

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

The company do not anticipate that umeclidinium (Incruse<sup>®</sup>▼) will be supplied by a home healthcare provider.

### 6.2 Ongoing studies

No relevant ongoing studies were highlighted by the company<sup>1</sup>.

### 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:** 6 August 2014.

**Date range of evidence search:** No date limits were applied to database searches.

## GLOSSARY

### **Chronic obstructive pulmonary disease (COPD)**

The National Institute for Health and Care Excellence use the following working definition of COPD:

- Airflow obstruction is defined as a reduced FEV<sub>1</sub>/FVC ratio, such that FEV<sub>1</sub>/FVC is less than 0.7.
- If FEV<sub>1</sub> is  $\geq 80\%$  FEV<sub>1</sub> predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough<sup>6</sup>.

### **Forced Expiratory Volume (FEV<sub>1</sub>) and Trough FEV<sub>1</sub>**

FEV<sub>1</sub> is the volume of air that can be forcefully and rapidly expired in 1 second, from a starting point of maximal inspiration, measured by a spirometer. FEV<sub>1</sub> is reduced in patients with COPD, and is well accepted by the scientific community and regulatory authorities as a marker of COPD severity. Trough FEV<sub>1</sub> is the measure taken in the morning prior to first dosing of any inhaled medications<sup>6,25</sup>.

### **St George's Respiratory Questionnaire**

The SGRQ is a 50-item questionnaire developed to measure health status (i.e. quality of life) in patients with diseases of airway obstruction, such as COPD. The total score is calculated from the scores in the three domains: Symptoms, Activity and Impacts (psycho-social). Psychometric testing has demonstrated its repeatability, reliability and validity; sensitivity has been demonstrated in clinical studies<sup>26</sup>.

## REFERENCES

- 1 GlaxoSmithKline. Form B: detailed appraisal submission. Umeclidinium (Incruse<sup>®</sup>▼). 2014.
- 2 GlaxoSmithKline. Incruse<sup>®</sup>▼. Summary of Product Characteristics. Jan 2014. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002809/WC500167430.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002809/WC500167430.pdf). Accessed Aug 2014.
- 3 European Medicines Agency. Incruse<sup>®</sup>. Authorisation Details. 2014. Available at: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicine\\_s/002809/human\\_med\\_001755.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicine_s/002809/human_med_001755.jsp&mid=WC0b01ac058001d124). Accessed Aug 2014.
- 4 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 Aug 2014.
- 5 Health and Safety Executive. Chronic Obstructive Pulmonary Disease (COPD) in Great Britain (2013). Oct 2013. Available at: <http://www.hse.gov.uk/statistics/causdis/copd/copd.pdf>. Accessed Aug 2014.
- 6 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 Jun 2014.
- 7 Welsh Government. Quality and Outcomes Framework Disease Registers. Oct 2013. Available at: <https://statswales.wales.gov.uk/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/GMS-Contract/PatientsOnQualityAndOutcomesFramework-by-LocalHealthBoard-DiseaseRegister>. Accessed Aug 2014.
- 8 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](http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf). Accessed Aug 2014.
- 9 National Institute for Health and Care Excellence. NICE Pathways. Inhaled therapy in COPD. 2013. Available at: <http://pathways.nice.org.uk/pathways/chronic-obstructive-pulmonary-disease/inhaled-therapy-in-copd>. Accessed Aug 2014.
- 10 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0813. Aclidinium bromide (Eklira<sup>®</sup> Genuair<sup>®</sup>▼) 322 micrograms inhalation powder. May 2013. Available at: <http://www.awmsg.org/awmsgonline/app/appraisalinfo/938>. Accessed Aug 2014.
- 11 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0713. Glycopyrronium bromide (Seebri<sup>®</sup> Breezhaler<sup>®</sup>▼) 44 micrograms inhalation powder as hard capsules. Mar 2013. Available at: <http://www.awmsg.org/awmsgonline/app/appraisalinfo/1455>. Accessed Aug 2014.
- 12 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0814. Indacaterol/glycopyrronium (Ultibro<sup>®</sup> Breezhaler<sup>®</sup>▼) 85/43 micrograms inhalation powder as hard capsules. Feb 2014. Available at: <http://www.awmsg.org/awmsgonline/app/appraisalinfo/1535>. Accessed Aug 2014.
- 13 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1014. Fluticasone furoate/vilanterol (as trifenate) (Revlar<sup>®</sup> Ellipta<sup>®</sup>▼) 92/22 micrograms inhalation powder. Feb 2014. Available at: <http://www.awmsg.org/awmsgonline/app/appraisalinfo/1534>. Accessed Aug 2014.

- 14 European Medicines Agency. Assessment Report for umeclidinium bromide (Incruse®). Procedure No.: EMEA/H/C/002809/0000. Jan 2014. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002809/WC500167431.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002809/WC500167431.pdf). Accessed Aug 2014.
- 15 Kalberg CJ, Kilbride S, Chopra B et al. A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease. 2012. Report No.: DB2113373
- 16 O'Dell DM, Brooks JM, Chopra B et al. A 52-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Tolerability of GSK573719 125 mcg once-daily alone and in combination with GW642444 25 mcg once-daily via novel Dry Powder Inhaler (NDPI) in Subjects with Chronic Obstructive Pulmonary Disease (COPD). 2012. Report No.: DB2113359
- 17 European Medicines Agency. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). Jun 2012. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/08/WC500130880.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/08/WC500130880.pdf). Accessed Sep 2014.
- 18 Riley J, Tabberer M, Richard N et al. Use of a new dry powder inhaler to deliver umeclidinium/vilanterol in the treatment of COPD. Presented at Annual Congress of the European respiratory Society (ERS). 7 Sep 2013.
- 19 Wise RA, Anzueto A, Cotton D et al. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; 369 (16): 1491-501.
- 20 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2014. Available at: <http://www.mims.co.uk/>. Accessed Aug 2014.
- 21 European respiratory Society. European lung white book. Chapter 13 COPD. 2014. Available at: <http://www.erswhitebook.org/chapters/chronic-obstructive-pulmonary-disease/>. Accessed Aug 2014.
- 22 Office for National Statistics. Death Registration Summary Tables - England and Wales. 2012. Available at: <http://www.ons.gov.uk/ons/rel/vsob1/death-reg-sum-tables/2012/index.html>. Accessed Aug 2014.
- 23 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: <http://www.bnf.org/bnf/index.htm>. Accessed Jul 2014.
- 24 Prescribing Services Ltd. drugtariff.co.uk. Apr 2014. Available at: [http://www.ppa.org.uk/ppa/edt\\_intro.htm](http://www.ppa.org.uk/ppa/edt_intro.htm). Accessed Jul 2014.
- 25 Egton Medical Information Systems Limited. Measurements made in spirometry. Jan 2013. Available at: <http://www.patient.co.uk/doctor/Spirometry-Calculator.htm>. Accessed Aug 2014.
- 26 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respiratory Medicine* 1991; 85 (Suppl B): 25-31.