Incruse® Ellipta® (umeclidinium bromide) for the treatment of symptoms of COPD

Medicines Evidence Pack to Support Formulary and Guidelines Decision Making

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Incruse Ellipta overview in COPD

<table>
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<th>Brand Name</th>
<th>Incruse Ellipta</th>
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<tr>
<td>Generic Name</td>
<td>Umeclidinium bromide</td>
</tr>
<tr>
<td>Inhaler</td>
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<tr>
<td>Licensed Indication</td>
<td>Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)</td>
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<tr>
<td>BNF (therapeutic) class</td>
<td>Incruse Ellipta is a long acting muscarinic receptor antagonist (LAMA)</td>
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<td>Anticipated Place in Therapy</td>
<td>Where LAMAs are currently positioned within UK guidelines for the treatment of patients with COPD, either as monotherapy or triple therapy with an ICS/LABA</td>
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<td>Dosage</td>
<td>The recommended dose is one inhalation of Incruse Ellipta once daily Each single inhalation provides a delivered dose of 55 mcg umeclidinium which corresponds to a pre-dispensed dose of 62.5 mcg umeclidinium</td>
</tr>
<tr>
<td>Administration</td>
<td>Inhaled via the Ellipta multi-dose dry powder inhaler</td>
</tr>
<tr>
<td>Cost</td>
<td>The 30-day cost of Incruse Ellipta is £27.50</td>
</tr>
</tbody>
</table>

Zinc code: UK/INC/0005/14(12)  
Date of preparation: September 2017
Background to COPD

Epidemiology

COPD is the second most common cause of emergency admission to hospital.²,³

Around a third of those admitted to hospital as a result of their COPD are readmitted within a month of discharge.³

The total annual cost of COPD to the NHS is estimated to be over £800 million.²

NICE recommendations

In the UK, COPD treatment is managed in line with the NICE guideline (‘Management of chronic obstructive pulmonary disease in primary and secondary care (CG101)’) which can be found at www.nice.org.uk⁴

NICE recommend once-daily long-acting muscarinic antagonist (LAMA) in preference to four-times-daily short-acting muscarinic antagonist (SAMa) to people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, and in whom a decision has been made to commence regular maintenance bronchodilator therapy with a muscarinic antagonist⁵.

In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy:

- if FEV₁ ≥ 50% predicted: either long-acting beta₂ agonist (LABA) or LAMA
- if FEV₁ < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or LAMA.

In people with stable COPD and an FEV₁ ≥ 50% who remain breathless or have exacerbations despite maintenance therapy with a LABA:

- consider LABA+ICS in a combination inhaler
- consider LAMA in addition to LABA where ICS is declined or not tolerated.

Offer LAMA in addition to LABA+ICS to people with COPD who remain breathless or have exacerbations despite taking LABA+ICS, irrespective of their FEV₁.

Consider LABA+ICS in a combination inhaler in addition to LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with LAMA irrespective of their FEV₁.

Current Management

In the UK, 65% of LAMA use is alongside an ICS/LABA inhaler as part of triple therapy.⁶

Incruse plus Relvar are both delivered by the Ellipta inhaler, and this is the only triple therapy (LAMA plus ICS/LABA) option in the UK where all of the medicines are delivered in the same type of inhaler.

There is also a globally recognised strategy for the diagnosis, management and prevention of COPD, published by the Global initiative for Chronic Obstructive Lung Disease (GOLD), which can be found at www.goldcopd.org⁷

*Prescribing statistics may vary in different health economies. Your GSK account manager can provide this type of information for your local health economy if required.

**Incruse**<br>**Ellipta**

umeclidinium
Efficacy Studies

The airflow classification and GOLD groups in the efficacy studies in this document are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 Strategy.

Study Design

This was a randomised, double-blind, placebo-controlled, parallel-group efficacy study comparing once daily Incruse Ellipta 55 mcg (umeclidinium) versus placebo over 12 weeks in patients with moderate to very severe COPD.

Patients were randomised in a 1:1:1 ratio to receive Incruse Ellipta 55 mcg, umeclidinium 113 mcg* or placebo. Randomisation was preceded by a 5-9 day run-in period. Patients were instructed to take one dose of the study medication as a single inhalation each morning delivered via the Ellipta DPI.

* Umeclidinium 113 mcg is an unlicensed investigational medicinal product

Patient population:

• Clinical history of COPD in line with the ATS/ERS Task Force definition
• ≥10 pack year smoking history
• Post salbutamol FEV1/FVC ratio of <0.7 and FEV1 <70% predicted normal
• Dyspnoea score of ≥3 on the MRC Dyspnoea Scale

Key exclusion criteria included current diagnosis of asthma or other clinically significant respiratory disorders other than COPD, any unstable, clinically significant disease, or hospitalisation for COPD or pneumonia within 12 weeks of screening.

Inhaled corticosteroids (ICS) were allowed at a stable dose of up to 1000 mcg/day of fluticasone propionate or equivalent, within 30 days of screening.

Primary efficacy endpoint assessment

• Trough FEV1 on day 85 (defined as the mean of FEV1 values obtained 23 and 24 hours post-dose on day 84 visit).

Secondary efficacy endpoint assessment

• Weighted mean FEV1 over 0-6 h post-dose on days 1, 28 and 84
• Serial FEV1 at 1, 3, 6, 23, and 24 h post-dose days 1 and 84

Other notable endpoints include

• Breathlessness measured by transition dyspnoea index (TDI) focal score
• Rescue medication use
• Health-related Quality of Life measured using the St George’s Respiratory Questionnaire (SGRQ)
Results

Demographics and Baseline Characteristics

246 patients were enrolled, 206 were randomised (ITT population) and 168 completed the study. The baseline and demographic characteristics in the ITT population were similar between the Incruse Ellipta treatment group and placebo (Table 2).

Table 2: Patient demographics and baseline characteristics (n=206)

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Placebo N=68</th>
<th>Incruse Ellipta N=69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years ± SD)</td>
<td>62.5 ± 8.72</td>
<td>62.3 ± 9.5</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>42 (62)</td>
<td>44 (64)</td>
</tr>
<tr>
<td>Smoking pack years (mean ± SD)</td>
<td>52.3 ± 30.2</td>
<td>45.2 ± 21.2</td>
</tr>
<tr>
<td>Post-bronchodilator FEV₁ (% predicted; mean ± SD)</td>
<td>47 ± 13.05</td>
<td>44.5 ± 13.99</td>
</tr>
</tbody>
</table>

NB: only the results from the licensed dose of umeclidinium (55 mcg) are shown. Data from the unlicensed dose of umeclidinium (113 mcg) treatment group are not shown.

Primary Endpoint

A statistically significant improvement from baseline trough FEV₁ was demonstrated for Incruse Ellipta compared with placebo (127 mL, p<0.001) at week 12 (Figure 1). An improvement ≥100 mL in trough FEV₁ is considered clinically meaningful.⁹

The bronchodilatory effect with Incruse Ellipta compared with placebo was evident after the first day of treatment and was maintained over the 12-week treatment period.

Figure 1: Mean change from baseline in trough FEV₁ at week 12 (n=206)
Secondary Endpoints

Incruse Ellipta demonstrated a statistically significant greater improvement from baseline in weighted mean FEV₁ over 0-6 hours post-dose at week 12, compared with placebo (166 mL, p<0.001).

Statistically significant improvements in serial FEV₁ were also demonstrated for Incruse Ellipta compared with placebo at each time point over 24 hours on day 1 and day 84 (p≤0.003).

Other Endpoints

Breathlessness measured by TDI focal score

- On day 84, Incruse Ellipta demonstrated clinically meaningful¹⁰ improvements in TDI focal score compared with placebo (1 unit; p=ns); however, this difference was not statistically significant

Rescue Medication Use

- Incruse Ellipta demonstrated a statistically significant reduction in the use of rescue medication with salbutamol compared with placebo (on average a reduction of 0.7 puffs per day over Weeks 1-12, p=0.025)
- Incruse Ellipta also demonstrated a higher percentage of days when no rescue medication was needed (on average 46.3%) compared with placebo (on average 35.2%; no formal statistical analysis was performed on this endpoint)

Health-related Quality of Life measured by SGRQ

- Incruse Ellipta demonstrated a statistically significant and clinically meaningful improvement in health-related quality of life as indicated by a reduction in SGRQ total score at Week 12 compared with placebo (-7.90 units, p<0.001)
- The proportion of patients who responded with at least the MCID in SGRQ score (defined as a decrease of 4 units from baseline)¹¹ at Week 12 was greater for Incruse Ellipta (44%) compared with placebo (26%)

Safety

An aggregated safety summary for the Incruse Ellipta clinical development programme can be found in the safety section.
Efficacy: 24-week study of Incruse Ellipta versus placebo\textsuperscript{1,12}

Study Design

This was a randomised, double-blind, placebo-controlled, parallel-group efficacy study which included a comparison between once daily Incruse Ellipta 55 mcg (umeclidinium) versus placebo over 24 weeks in patients with moderate-to-severe COPD.

Patients were randomised in a 3:3:3:2 ratio to receive one of three different active treatments or placebo. Randomisation was preceded by a 7-14 day run-in period. Patients were instructed to take one dose of the study medication as a single inhalation each morning delivered via the Ellipta DPI.

Patient population:

- Clinical history of COPD in line with the ATS/ERS Task Force definition
- ≥10 pack year smoking history
- Post salbutamol FEV\textsubscript{1}/FVC ratio of <0.7 and FEV\textsubscript{1} ≤70\% predicted normal
- Dyspnoea score of ≥3 on the MRC Dyspnoea Scale

Key exclusion criteria included current diagnosis of asthma or hospitalisation for COPD or pneumonia within 12 weeks of screening.

Inhaled corticosteroids (ICS) were allowed at a stable dose of up to 1000 mcg/day of fluticasone propionate or equivalent from 30 days prior to screening onward.

Primary efficacy endpoint assessment

- Trough FEV\textsubscript{1} on day 169 (defined as the mean of FEV\textsubscript{1} values obtained 23 and 24 hours post-dose on day 168 visit)

Secondary efficacy endpoint assessment

- Breathlessness measured by transition dyspnoea index (TDI) Score at day 168
- Weighted mean FEV\textsubscript{1} over 0-6 h post-dose on day 168

Other notable endpoints include

- Rescue medication use
- Health-related Quality of Life measured using the St George’s Respiratory Questionnaire (SGRQ)
- Time to first on treatment COPD exacerbation

In this study, in order to account for multiplicity across treatment comparisons for the primary and secondary endpoints, a step-down closed testing procedure was applied, whereby inference for a test in the predefined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy.
Results

Only results from the umeclidinium 55 mcg and placebo arms are shown here.

Demographics and Baseline Characteristics

Of 2210 patients screened, 1532 patients were included in the Intent to Treat (ITT) population. In total, 1178 patients completed the study. The baseline and demographic characteristics in the ITT population were similar between the Incruse Ellipta treatment group and placebo (Table 1).

Table 1: Patient demographics and baseline characteristics (n=1532)

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Placebo N=280</th>
<th>Incruse Ellipta N=418</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean in years ± SD)</td>
<td>62.2 ± 9.04</td>
<td>64 ± 9.16</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>195 (70)</td>
<td>298 (71)</td>
</tr>
<tr>
<td>Smoking pack years (mean ± SD)</td>
<td>47.2 ± 27.21</td>
<td>46.8 ± 27.03</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (% predicted; mean ± SD)</td>
<td>46.7 ± 12.71</td>
<td>46.8 ± 13.39</td>
</tr>
</tbody>
</table>

Primary Endpoint

Incruse Ellipta treatment group demonstrated a clinically meaningful (≥100 mL) and statistically significant greater change from baseline in trough FEV₁ at day 169 compared with placebo (Figure 2).

The bronchodilatory effect with Incruse Ellipta compared with placebo was evident after the first day of treatment and was maintained over the 24-week treatment period.

Figure 2: Mean change from baseline in trough FEV₁ at Day 169
Secondary Endpoints

Breathlessness measured by TDI focal score

- A statistically significant and clinically meaningful improvement in the TDI focal score compared with placebo at Week 24 was demonstrated for Incruse Ellipta (1.0 units, p<0.001)

Weighted mean FEV$_1$ over 0-6 h post-dose

- Incruse Ellipta demonstrated a numerically greater improvement from baseline at Week 24 compared with placebo (150 ml*)
  *statistical significance cannot be inferred due to hierarchical statistical testing.

Other Endpoints

Rescue Medication Use

- The mean (SD) change from baseline in the number of puffs of rescue salbutamol use over the 24-week treatment period was -1.4 (0.20) for placebo and -1.7 (0.16) for Incruse Ellipta (Difference=-0.3; p=0.276);
- Patients receiving Incruse Ellipta had a higher percentage of days when no rescue medication was needed (on average 31.1%) compared with placebo (on average 21.7%). No formal statistical testing was performed on this endpoint

Health-related Quality of Life measured by SGRQ

- A numerically greater improvement compared with placebo in the change from baseline in SGRQ total score at Week 24 was demonstrated for Incruse Ellipta (-4.69 units)* which met the threshold for the minimal clinically important difference (MCID) of 4 units *statistical significance cannot be inferred due to hierarchical statistical testing.
- A greater proportion of patients achieved at least the MCID for SGRQ with Incruse Ellipta at Week 24 (44%) compared with placebo (34%)

Time to first on treatment COPD exacerbation

- Treatment with Incruse Ellipta resulted in a numerically lower risk of COPD exacerbation compared with placebo (analysis of time to first exacerbation 0.6) *statistical significance cannot be inferred due to hierarchical statistical testing. The probability of having an exacerbation in patients receiving Incruse Ellipta at week 24 was 8.9% compared with 13.7% for placebo
- This study was not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the study if an exacerbation occurred
  *A step-down statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred.

Safety

An aggregated safety summary for the Incruse Ellipta clinical development programme can be found in the safety section.
Efficacy: 12-week study of Incruse Ellipta compared with Spiriva® HandiHaler® in patients with moderate-to-severe COPD¹,¹³

Study Design

This was a 12-week, multicentre, randomised, blinded, double-dummy, parallel-group, non-inferiority study in patients with symptomatic, moderate-to-severe COPD. Patients were randomised 1:1 to once-daily Incruse Ellipta 55 mcg (umeclidinium) plus placebo HandiHaler, or once-daily tiotropium 18 mcg HandiHaler plus placebo Ellipta inhaler. All patients were provided salbutamol rescue medication.

Randomisation was preceded by a 7-14 day run-in period. Clinic visits during the 12-week treatment period were on days 2, 28, 56, 84, and 85. Serial spirometry (24-hour) was conducted in a subset of patients at days 1 and 84.

Patient population:

- ≥40 years of age
- Diagnosis of COPD in line with the ATS/ERS Task Force definition
- ≥10 pack year smoking history
- Pre- and post-salbutamol FEV₁/FVC ratio of <0.7, and post-salbutamol FEV₁ of 30%-70% predicted normal
- Dyspnoea score of ≥3 on the MRC Dyspnoea Scale

Key exclusion criteria included pregnancy, current diagnosis of asthma or other clinically significant respiratory disorders other than COPD, any unstable clinically significant disease or hospitalisation for COPD or pneumonia within 12 weeks of screening, long term oxygen therapy, use of non-study COPD maintenance medications with the exception of Inhaled corticosteroids (ICS).

Primary efficacy endpoint assessment

- Trough FEV₁ on day 85 (defined as the mean of FEV₁ values obtained 23 and 24 hours post-dose on day 84 visit) in the per-protocol (PP) population.

Secondary efficacy endpoint assessment

Intent-to-treat (ITT) population:

- Trough FEV₁ on day 85
- Trough FEV₁ on days 2, 28, 56, and 84
- Trough FVC on days 2, 28, 56, 84, and 85

Serial spirometry subset population

- Weighted mean FEV₁ over 0–12, 12–24, 0–24 hours post-dose, each on days 1 and 84
- Serial FEV₁ on days 1 and 84
Other Endpoints

Patient reported outcomes
- Breathlessness measured by transition dyspnoea index (TDI) focal score
- COPD Assessment Test score (CAT)
- Health-related Quality of Life measured using the St George’s Respiratory Questionnaire (SGRQ)
- Rescue medication use

Inhaler assessments: errors, ease of use and preference
- Patient preference was assessed at the end of the treatment phase, and ‘ease of use’ was assessed on days 28 and 84.
- Inhaler errors (IEs) were assessed in a subset of patients on days 1, 28 and 84 using the IE checklists, based on steps in the patient information leaflets for each inhaler. A critical error was predefined as an error that was most likely to result in no or only minimal medication being inhaled. Overall errors encompassed all critical and non critical errors.

Results

Demographics and Baseline Characteristics
The ITT population involved 1,017 patients randomised to treatment, of which 941 patients completed the study (Incruse Ellipta, n=467; tiotropium n=474). The PP population comprised 976 patients (Incruse Ellipta, n=489; tiotropium n=487). Serial spirometry (24-hour) was conducted in a subset of patients (n=250).

Patients had symptomatic moderate-to-severe COPD (GOLD Grade 2–3 and GOLD Groups B and D), and the majority of patients were male. Baseline demographics were similar between the Incruse Ellipta and tiotropium treatment groups (see Table 1).

Table 1: Patient demographics and baseline characteristics (ITT population)

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Incruse Ellipta 55 mcg N=509</th>
<th>Tiotropium Handihaler 18 mcg N=508</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>64.4 (8.1)</td>
<td>64.1 (8.3)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>145 (28)</td>
<td>137 (27)</td>
</tr>
<tr>
<td>Smoking pack years (mean ±SD)</td>
<td>41.2 (21.4)</td>
<td>41.9 (21.9)</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (L; mean ± SD)</td>
<td>1.49 (0.41)</td>
<td>1.51 (0.44)</td>
</tr>
<tr>
<td>GOLD grade 2 (moderate COPD) n (%)</td>
<td>281 (55)</td>
<td>283 (56)</td>
</tr>
<tr>
<td>Group B (low risk, more symptoms) n (%)</td>
<td>244 (48)</td>
<td>229 (45)</td>
</tr>
<tr>
<td>ICS users at screening n (%)</td>
<td>247 (49)</td>
<td>229 (45)</td>
</tr>
</tbody>
</table>

The airflow classification and GOLD groups in the efficacy studies in this document are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 Strategy.

Zinc code: UK/INC/0005/14(12)
Date of preparation: September 2017
Primary Endpoint

Incruse Ellipta was significantly superior to tiotropium at improving lung function measured by trough FEV₁ on Day 85 in the PP population (Figure 1). This met both the non-inferiority and superiority margins (difference: 59 mL; 95% confidence interval [CI]: 29–88; \( p < 0.001 \)).

Figure 1: Least squares mean change from baseline in trough FEV₁ at Day 85 (PP population)

Secondary Endpoints

Incruse Ellipta was significantly superior to tiotropium at improving lung function measured by trough FEV₁ on Day 85 in the ITT population. This met both the non-inferiority and superiority margins (difference: 53 mL, 95% CI: 25–81; \( p < 0.001 \)). Furthermore, Incruse Ellipta demonstrated significant improvements in FEV₁ at each time point over the study period (\( p \leq 0.003 \)), except on Day 2, compared with tiotropium (Figure 2).

Improvements in weighted mean FEV₁ over 0–24 hours post-dose at day 84 were similar with UMEC and TIO but significantly greater with UMEC versus TIO over 12–24 hours post-dose (70 mL; \( p = 0.015 \)).

Figure 2: Least squares mean change from baseline in trough FEV₁, at all time points (ITT population)
Other Endpoints

Patient reported outcomes

- Whilst clinically meaningful improvements in Transition Dyspnea Index focal score, St George’s Respiratory Questionnaire total score and CAT score were observed with both treatments at all time points, no differences were observed between treatments in patient-reported outcomes.

Rescue Medication Use

- There were no differences between treatments in rescue salbutamol use.

Inhaler Assessments

- At the end of the study, 95% of patients rated the Ellipta inhaler as “very easy or easy” to use; 78% rated the same criteria for the HandiHaler. No formal statistical testing was performed on this endpoint.

- More patients preferred using the Ellipta inhaler than the HandiHaler (57% vs 19%, respectively) however, no formal statistical testing was performed on this endpoint.

- The proportion of patients with at least one overall error ranged between 8% and 13% and was similar between both treatment groups. The proportion of patients with critical errors was very low for both inhalers and ranged between 1% and 4%. Patients were expected to have minimal critical errors in device handling as this was a short-term, supervised study.

Post hoc analysis

Outcomes according to COPD severity and inhaled steroid [ICS] use

- Post hoc analyses in the ITT population indicated that improvement in lung function was greater for patients with GOLD Grade 2 airflow limitation than those with GOLD Grade 3 airflow limitation with both treatments. Lung function improvement was greater with Incruse Ellipta than with tiotropium in moderate COPD patients (GOLD grade 2; 63 mL, 95% CI: 25–100; p=0.001) but did not reach statistical significance in the more severe patients (GOLD Grade 3 patients; 39 mL, 95% CI: -4 to 82; p=0.074).

- Lung function improvements were greater for GOLD Group B and Group D patients, receiving Incruse Ellipta than in those receiving tiotropium (57 mL, 95% CI: 16–98; p=0.006, and 46 mL, 95% CI: 7–85; p=0.020, respectively).

- The reported lung function improvements were greater with Incruse Ellipta than with tiotropium independent of ICS use.

Safety

Safety assessments included the incidence of adverse events and vital sign measurements. The incidence of any adverse events [AEs] was similar between both treatment groups; the most common AEs were headache and nasopharyngitis.

While the incidence of on-treatment COPD exacerbations was also assessed, the comparative efficacy of either treatment on exacerbation rate was not within the scope of the study, based on the study duration.

An aggregated safety summary for the Incruse Ellipta clinical development programme can be found in the safety section.

The airflow classification and GOLD groups in the efficacy studies in this document are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 Strategy.

Zinc code: UK/INC/0005/14(12)
Date of preparation: September 2017
Efficacy: 12-week study of Incruse Ellipta compared with Seebri® Breezhaler® in patients with moderate-to-severe COPD\textsuperscript{1,14}

Study Design

This was a 12-week, multicentre, randomised, open-label, parallel-group non-inferiority study in patients with moderate-to-severe COPD.

Patients were randomised 1:1 to once-daily Incruse Ellipta 55 mcg (umeclidinium) or once-daily glycopyrronium 50 mcg Breezhaler. All patients were provided with salbutamol rescue medication.

Randomisation was preceded by a 7-14 day run-in period. Clinic visits during the 12-week treatment period were on days 2, 28, 56, 84, and 85. Serial spirometry (24-hour) was conducted in a subset of patients at days 1 and 84.

Patient population:

- \( \geq 40 \) years of age
- Diagnosis of COPD in line with the ATS/ERS Task Force definition
- \( \geq 10 \) pack year smoking history
- Pre- and post-salbutamol FEV\(_1\)/FVC ratio of \(<0.7\), and post-salbutamol FEV\(_1\) of 30\% -70\% predicted normal
- Dyspnoea score of \( \geq 3 \) on the MRC Dyspnoea Scale

Key exclusion criteria included current diagnosis of asthma or other clinically significant respiratory disorders other than COPD, hospitalisation for COPD or pneumonia within 12 weeks of screening, long volume reduction surgery within 12 months of this study or long term oxygen therapy.

Use of other COPD maintenance medications, antibiotics or systemic corticosteroids was not permitted before enrolment within designated time intervals. Inhaled corticosteroids (ICS) were allowed, according to specific criteria. Additional criteria for randomisation were that patients must not have experienced a COPD exacerbation during the run-in period or have used any of the prohibited medications in that time.

Primary efficacy endpoint assessment

Trough FEV\(_1\) on day 85 (defined as the mean of FEV\(_1\) values obtained 23 and 24 hours post-dose on day 84 visit) in the per-protocol (PP) population

Secondary efficacy endpoint assessment

Intent-to-treat (ITT) population:

- Trough FEV\(_1\) on day 85
- Trough FEV\(_1\) on days 2, 28, 56, and 84
- Trough FVC on days 2, 28, 56, 84, and 85

Spirometry subset population:

- Weighted mean FEV\(_1\) over 0–24 hours post-dose, each on days 1 and 84
- Serial FEV\(_1\) on days 1 and 84
- Time to onset on day 1
  - The first time to reach an increase in FEV\(_1\) of \( \geq 100 \) mL above baseline in the first 6 hours of spirometry
Other Endpoints

Patient-reported outcomes

- Breathlessness measured by transition dyspnoea index (TDI) focal score
- COPD Assessment Test score (CAT)
- Health-related Quality of Life measured using the St George's Respiratory Questionnaire (SGRQ)
- Rescue medication use

Inhaler assessments: errors, ease of use and preference

- Patient preference and ease of use for the inhalers was assessed at the end of the treatment phase, and ‘ease of use’ was assessed on days 28 and 84.
- Inhaler errors (IEs) were assessed in a subset of patients on days 1, 28, and 84 using the IE checklists, based on steps in the patient information leaflets for each inhaler. A critical error was predefined as an error that was most likely to result in no or only minimal medication being inhaled. Overall errors encompassed all critical and non-critical errors.

Results

Demographics and Baseline Characteristics

The ITT population involved 1,034 patients randomised to treatment, of which 974 patients completed the study (Incruse Ellipta, n=490; glycopyrronium n=484). The PP population comprised 986 patients (Incruse Ellipta, n=494; glycopyrronium n=492). Spirometry was conducted in a subset of patients (n=334) and the inhaler error population comprised 117 patients.

Patients had moderate-to-severe COPD (GOLD Grade 2–3 and GOLD Groups B and D), and the majority of patients were male. Baseline demographics were similar between the Incruse Ellipta and glycopyrronium treatment groups (see Table 1).

Table 1: Patient demographics and baseline characteristics (ITT population)

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Incruse Ellipta 55 mcg N=516</th>
<th>Glycopyrronium 50 mcg N=518</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± SD)</td>
<td>64.1 (8.4)</td>
<td>64.0 (8.3)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>355 (69)</td>
<td>350 (68)</td>
</tr>
<tr>
<td>Smoking pack years (mean ±SD)</td>
<td>41.5 (24.1)</td>
<td>42.0 (23.4)</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (L; mean ± SD)</td>
<td>1.49 (0.46)</td>
<td>1.49 (0.45)</td>
</tr>
<tr>
<td>GOLD grade 2 (moderate COPD) n (%)</td>
<td>282 (55)</td>
<td>276 (53)</td>
</tr>
<tr>
<td>Group B (low risk, more symptoms) n (%)</td>
<td>243 (47)</td>
<td>238 (46)</td>
</tr>
<tr>
<td>ICS users at screening n (%)</td>
<td>239 (46)</td>
<td>255 (49)</td>
</tr>
</tbody>
</table>

Primary Endpoint

Incruse Ellipta was non-inferior to glycopyrronium at improving lung function measured by trough FEV1 on Day 85 in the PP population (Figure 1; difference: 24 mL; 95% confidence interval [CI]: -5-54). The superiority criterion at Day 85 was not met.

Over the duration of the study, Incruse Ellipta and glycopyrronium provided similar improvements in trough FEV1; change from baseline was $123±10.5$ mL and $99±10.5$ mL, respectively, at Day 85.

The airflow classification and GOLD groups in the efficacy studies in this document are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 Strategy.

Zinc code: UK/INC/0005/14(12)
Date of preparation: September 2017
Secondary Endpoints

As non-inferiority of the primary endpoint was demonstrated, but not superiority, then the statistical significance of the other lung function endpoints could not be inferred. Similar results in the improvement in lung function [trough FEV₁ and trough FVC] were noted for both treatments [Table 2]. Both treatments produced similar positive outcomes in lung function [weighted mean FEV₁ over 0-12, 12–24 hours post-dose, each on days 1 and 84] and the serial FEV₁ profiles of both treatments on Day 1 and 84 were also similar.

There was a difference in time to reach ≥ 100 mL FEV₁ above baseline on Day 1, favouring glycopyrronium, compared with Incruse Ellipta (15 mins vs 30 mins, respectively). However, the magnitude of the difference is small and the study was not designed to show statistical differences between treatments in time to onset.

Table 2: Changes in lung function: ITT population and spirometry subgroup.

<table>
<thead>
<tr>
<th>Population</th>
<th>Incruse Ellipta</th>
<th>glycopyrronium</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>N=516</td>
<td>N=518</td>
<td></td>
</tr>
<tr>
<td><strong>Trough FEV₁ Day 85</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with analysable data</td>
<td>N=486</td>
<td>N=481</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (mL)</td>
<td>126±10</td>
<td>93±10</td>
<td>33 (5-61)</td>
</tr>
<tr>
<td><strong>Trough FVC Day 85</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with analysable data</td>
<td>N=486</td>
<td>N=481</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (mL)</td>
<td>157±16</td>
<td>143±16</td>
<td>14 (-31-59)</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEV₁ 0-24h Day 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with analysable data</td>
<td>N=166</td>
<td>N=168</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (mL)</td>
<td>61±12</td>
<td>84±12</td>
<td>-23 (-57-10)</td>
</tr>
<tr>
<td><strong>FEV₁ 0-24h Day 84</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with analysable data</td>
<td>N=155</td>
<td>N=159</td>
<td></td>
</tr>
<tr>
<td>Change from baseline (mL)</td>
<td>62±18</td>
<td>67±17</td>
<td>-5 (-54-44)</td>
</tr>
</tbody>
</table>
Other Endpoints

The improvements in lung function achieved with both treatments were accompanied by clinically important improvements in other endpoints. Non-lung function endpoints were assessed in the ITT population, with responders defined according to minimal clinically important difference (MCID)\(^9\).

Patient reported outcomes

- Similar clinically meaningful improvements in Transition Dyspnoea Index focal score and St George’s Respiratory Questionnaire total score were observed at Day 84 for both treatments. While both treatments resulted in an improved CAT score, neither treatment improved it above the MCID. The proportion of responders with both treatments was similar at Day 28 and Day 84 for all three patient-reported outcomes.

Rescue Medication Use

- There were no differences between treatments in rescue medication use over the 12 weeks of the study for both the number of puffs/day salbutamol use (Least squares mean change from baseline -0.8±0.06 vs 0.8±0.07 for Incruse Ellipta and glycopyrronium, respectively) or for the percentage of rescue-free days.

Inhaler Assessments

- The majority of patients found their inhaler ‘easy’ or ‘very easy’ to use. Over 60% of patients found the Ellipta ‘very easy to use’ at Day 28 and Day 84 (61% and 68% of patients, respectively), compared with 50% (at both time points) with Breezhaler.
- The number of overall and critical errors was low for both inhalers and decreased over the course of the study. Patients were expected to have minimal critical errors in device use as this was a short-term, supervised study - where all patients were trained on their assigned device.

Post hoc analysis

Post hoc analyses in the ITT population were made for those achieving a ≥100 mL increase in trough FEV\(_1\) on each day of the study. Also, analyses were performed on lung function according to subgroups of GOLD grade, GOLD category and ICS use [FEV\(_1\) at Day 85]. No inferences from the data can be made because the superiority criterion was not reached for the primary lung function endpoint.

Safety

Safety assessments included adverse events and COPD exacerbations in the ITT population. The incidence of any adverse events [AEs] was similar between both treatment groups; the most common AEs were headache and nasopharyngitis. An aggregated safety summary for the Incruse Ellipta clinical development programme can be found in the safety section.
Efficacy: Incruse Ellipta plus Relvar Ellipta 92/22 versus placebo plus Relvar Ellipta 92/22\textsuperscript{1,15}

**Study Design**

Two 12-week similar add on studies are described together. Each study was a Phase III, multicentre, randomised, double-blind, parallel-group study comparing Incruse Ellipta plus Relvar Ellipta versus Placebo plus Relvar Ellipta.

Patients were randomised in a 1:1:1 ratio to receive Incruse Ellipta 55 mcg + Relvar Ellipta 92/22 mcg, Umeclidinium 113 mcg* + Relvar Ellipta 92/22 mcg or Placebo + Relvar Ellipta 92/22 mcg. Randomisation was preceded by a 4 weeks run-in period with Relvar Ellipta 92/22 mcg once daily. Relvar Ellipta was administered open-label.

* Umec 113 mcg is an unlicensed investigational medicinal product

**Patient population:**

- Clinical history of COPD in line with the ATS/ERS Task Force definition
- \(\geq 10\) pack year smoking history
- Post salbutamol FEV\(_1\)/FVC ratio of \(<0.7\) and FEV\(_1\) \(\leq 70\%\) predicted normal
- Dyspnoea score of \(\geq 3\) on the MRC Dyspnoea Scale

Key exclusion criteria included current diagnosis of asthma or hospitalisation for COPD or pneumonia within 12 weeks of screening, lung volume reduction surgery within the 12 months of screening, have had a lower respiratory tract infection requiring antibiotic use within 6 weeks of screening or use of long-term oxygen therapy (LTOT; prescribed for greater than 12 h a day).

**Primary efficacy endpoint assessment**

- Trough FEV\(_1\) on day 85 (defined as the mean of FEV\(_1\) values obtained 23 and 24 hours post-dose on day 84 visit)

**Secondary efficacy endpoint assessment**

- Weighted mean FEV\(_1\) over 0-6 h post-dose on days 1, 28 and 84

**Other efficacy endpoints include**

- Rescue medication use
- Quality of Life measured using the St George’s Respiratory Questionnaire (SGRQ)
Results

Demographics and Baseline Characteristics

The baseline and demographic characteristics in the ITT population were similar between the two studies (Table 4).

Table 4: Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Study 1 - MID200109 (ITT=619)</th>
<th>Study 2 - MID200110 (ITT=619)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Relvar Ellipta N=206</td>
<td>Incruse Ellipta + Relvar Ellipta N=206</td>
<td>Placebo + Relvar Ellipta N=206</td>
</tr>
<tr>
<td>Age (mean in years ± SD)</td>
<td>64.7 ± 7.90</td>
<td>64.9 ± 8.72</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>141 (68)</td>
<td>139 (67)</td>
</tr>
<tr>
<td>Smoking Pack Years (mean ± SD)</td>
<td>50.64 ± 24.76</td>
<td>50.11 ± 24.93</td>
</tr>
<tr>
<td>FEV₁ (% predicted; mean ± SD)</td>
<td>45.9 ± 12.95</td>
<td>44.2 ± 13.41</td>
</tr>
</tbody>
</table>

NB: only the results from the licensed dose of umeclidinium (55 mcg) are shown. Data from the unlicensed dose of umeclidinium (113 mcg) treatment group are not shown.

Primary Endpoint

Statistically significant improvements in change from baseline trough FEV₁ were demonstrated for the Incruse Ellipta + Relvar Ellipta treatment group compared with placebo + Relvar Ellipta at day 85 (Figure 3).

Figure 3: Mean change from baseline in trough FEV₁ at Day 85; MID200109 (n=619) and MID200110 (n=619)

Zinc code: UK/NC/0005/14(12)
Date of preparation: September 2017
Secondary Endpoint

Statistically significant improvements in 0 to 6 hour weighted mean FEV₁ were demonstrated for the Incruse Ellipta + Relvar Ellipta treatment group compared to placebo plus Relvar Ellipta at day 84 for both studies. At day 84, the difference in 0 to 6 hour weighted mean FEV₁ between the Incruse Ellipta + Relvar Ellipta treatment group and the Placebo + Relvar Ellipta group was 153 mL (p<0.001) in study MID200109, and 147 mL (p<0.001) in study MID200110.

Other Endpoints

Rescue Medication Use

- Over 12 weeks, a statistically significant difference in reduction from baseline in rescue salbutamol use was demonstrated in the Incruse Ellipta + Relvar Ellipta (-0.4 puffs/day; p<0.001) treatment group compared with the Placebo + Relvar Ellipta treatment group in study MID200109.

- Similarly in study MID200110 a statistically significant difference in reduction from baseline in rescue salbutamol use was demonstrated in the Incruse Ellipta + Relvar Ellipta (-0.3 puffs/day; p=0.003) treatment group compared with the Placebo + Relvar Ellipta treatment group.

Health-related Quality of Life measured by SGRQ

- In study MID200109, the difference between the Incruse Ellipta plus Relvar Ellipta treatment group versus the Placebo plus Relvar Ellipta treatment group was not statistically significant. However in study MID200110 Incruse Ellipta plus Relvar Ellipta demonstrated a statistically significant reduction (-2.16; p=0.011) compared with Placebo plus Relvar Ellipta in total SGRQ score.

- The difference between the two groups in either study did not meet the threshold for MCID in SGRQ.

Safety

An aggregated safety summary for the Incruse Ellipta clinical development programme can be found in the safety section.
Safety

The safety profile of Incruse Ellipta is based on safety experience with umeclidinium from 1663 patients with COPD who received doses of 55 micrograms or greater for up to one year. This includes 576 patients who received the recommended dose of 55 micrograms once daily. Additional patients were studied in the two 12-week add-on studies.

Table 5: Incruse® Ellipta® (umeclidinium) 55 mcg Safety Table

<table>
<thead>
<tr>
<th>Frequency of adverse event</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common adverse reactions (≥1/100 to &lt;1/10)</td>
<td>Nasopharyngitis, Upper respiratory tract infection, Urinary tract infection, Sinusitis, Headache, Tachycardia, Cough</td>
</tr>
<tr>
<td>Other important adverse reactions include: Frequency Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Atrial fibrillation, Rhythm idioventricular, Supraventricular tachycardia, Supraventricular extrasystoles. Hypersensitivity reactions including rash, urticaria, pruritus.</td>
</tr>
<tr>
<td>Frequency Not Known (cannot be estimated from available data):</td>
<td>Glaucoma, Vision blurred.</td>
</tr>
</tbody>
</table>

No dose adjustment for Incruse Ellipta is needed in:

- patients with renal impairment
- patients with mild or moderate hepatic impairment
- patients aged over 65 years
- Cardiovascular effects, such as cardiac arrhythmias, may be seen after the administration of muscarinic receptor antagonists and sympathomimetic agents, including umeclidinium bromide. Therefore, Incruse Ellipta should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.
- Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.

(Please consult the full Summary of Product Characteristics (SmPC) for other adverse reactions)

An integrated analysis of safety data across four Phase III, 24-week, parallel primary efficacy trials showed that Incruse Ellipta was generally well tolerated.

Most frequently reported adverse events were broadly consistent with the patient population under study; the most frequently reported AEs were headache and nasopharyngitis, with incidences across all treatment groups ranging from 8% to 10% respectively (Table 6).
Cardiovascular Effects

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists including umeclidinium bromide.

- In addition, patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies.
- Therefore, umeclidinium bromide should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.

Additional Points to Note

- No dose adjustment is required in patients with renal impairment or mild to moderate hepatic impairment, or elderly patients.
- Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.
- Umeclidinium bromide is intended for the maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm.
- Umeclidinium bromide should not be used in patients with asthma since it has not been studied in this patient population.
- Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.

Please refer to Incruse Summary of Product Characteristics for more information.

Table 6: Most Frequent Adverse Events (Reported by 3% or More Subjects in Any Treatment Group)16

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=623)</th>
<th>Umeclidinium 55 mcg (n=487)</th>
<th>Umeclidinium 113 mcg* (n=698)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>288 (46%)</td>
<td>243 (50%)</td>
<td>376 (54%)</td>
</tr>
<tr>
<td>Headache</td>
<td>65 (10%)</td>
<td>37 (8%)</td>
<td>72 (10%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>55 (9%)</td>
<td>37 (8%)</td>
<td>50 (7%)</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (4%)</td>
<td>16 (3%)</td>
<td>34 (5%)</td>
</tr>
<tr>
<td>URTI</td>
<td>21 (3%)</td>
<td>23 (5%)</td>
<td>25 (4%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>24 (4%)</td>
<td>10 (2%)</td>
<td>27 (4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
<td>19 (3%)</td>
</tr>
</tbody>
</table>

*Umeclidinium 113 mcg is an unlicensed investigational medicinal product. It is included for additional safety data only.

In the two 12-week add-on studies, the adverse event profile of Incruse Ellipta plus Relvar Ellipta was broadly comparable to that of placebo plus Relvar Ellipta.15
National Health Technology Assessment

National Institute for Health and Care Excellence (NICE)

NICE are not considering Incruse Ellipta for a full technology appraisal but have developed an evidence summary.

Evidence summaries produced by NICE can be found at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-advice/evidence-summaries-new-medicines

Scottish Medicines Consortium (SMC)

SMC advice (December 2014) for Incruse in COPD is as follows:

- Advice: following a full submission
- Umeclidinium (Incruse®) is accepted for use within NHS Scotland.
- Indication under review: as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
- Two randomised controlled, phase III studies demonstrated that after 12 and 24 weeks of treatment umeclidinium improved lung function compared with placebo in patients with moderate-to-severe COPD. There was also improvement in symptomatic outcomes such as dyspnoea.
- Umeclidinium is an alternative to other long-acting muscarinic antagonists (LAMAs).

SMC advice on medicines use can be found at www.scottishmedicines.org.uk

All Wales Medicines Strategy Group (AWMSG)

AWMSG recommendation (January 2015) for Incruse in COPD is as follows:

- Umeclidium (Incruse®) is recommended as an option for use within NHS Wales as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.

AWMSG guidance on medicines use can be found at www.awmsg.org
Ellipta inhaler

Administration¹

One inhalation of Incruse Ellipta 55 mcg once daily for adults aged 18 years and over.
Incruse Ellipta should be administered at the same time of the day, every day (morning or evening).
If a dose is missed the next dose should be taken at the usual time the next day.
The Ellipta inhaler consists of two aluminium foil laminate strips of regularly distributed blisters, each containing the active drug.
Every time the inhaler cover is opened one dose of medicine in prepared.
The Ellipta inhaler has a dose counter which shows how many doses of medicine are left in the inhaler.
• Before the inhaler has been used, it shows exactly 30 doses.
• It counts down by 1 each time the cover is opened.
• When fewer than 10 doses are left, half of the dose counter shows red.
• After the last dose has been inhaled, the counter shows 0.
Incruse Ellipta has an in-use shelf life of 6 weeks (from the date of opening the tray) and must not be stored above 30°C.

Figure 4 - Incruse Ellipta Inhaler
Patient Experience

Ease of use

Ease of use of the Ellipta inhaler in COPD patients has been tested during the development programme of another licensed medicinal product, Anoro Ellipta (umeclidinium bromide and vilanterol inhalation powder)\(^{17}\)

- Following initial instruction on how to use the inhaler in two such studies, 98% of COPD patients (n=632) used Ellipta correctly at Day 1 following initial demonstration.
- Correct inhaler use was re-assessed after 6 weeks of treatment; 98-99% of subjects (n=587) still used their Ellipta correctly without further demonstration.
- After 6 weeks of treatment, patients were asked to rate the ease of use of the inhaler; 98-99% rated it as either very easy or easy to use.

Inspiratory flow

- Patients with moderate, severe and very severe COPD were able to generate a peak inspiratory flow rate of greater than 43 L/min through the Ellipta inhaler.\(^{18}\)
- The inhalation profiles generated by this range of patients were replicated using the Electronic Lung (GS) breathing simulator.\(^{19}\)
- In vitro drug delivery to the lung was consistent across a wide range of peak inspiratory flow rate values (PIFR of 42-129 L/min tested in vitro).\(^{19}\)
- As a result the Ellipta inhaler is suitable for patients with all severities of COPD and in whom the medication is within licence.

Patient preference

Patient preference is an important factor when choosing an inhaler device for COPD.

- In a retrospective observational study of 2138 patients, 44.7% preferred a once daily schedule.\(^{20}\)
- In two six-month Anoro Ellipta studies (n=1020) 63% patients preferred the Ellipta inhaler to the Handihaler device in terms of ‘ease of use’ on the basis of time to use and the number of steps required.\(^{17}\)

Adherence

Patient adherence to treatment is paramount in the management of COPD. A published review has shown that patient adherence to COPD treatment is generally low and suboptimal.\(^{21}\)

The frequency of dosing is an important factor in improving adherence.

- In a retrospective analysis of 50,076 patients in the US, looking specifically at adherence, COPD patients who were initiated on treatment with once-daily dosing (tiotropium; n=3678) had significantly higher adherence over 12 months than patients initiated on treatments which were dosed twice a day (e.g. Seretide 500/50 and Symbicort 400/12; n=25,011) 43.3% vs 37.0%, p<0.0001.\(^{22}\)
Incruse Ellipta as part of the GSK respiratory portfolio

Incruse Ellipta in combination with Relvar Ellipta

- Combining Incruse Ellipta with Relvar Ellipta as part of triple therapy means that the patient can benefit from receiving their medicines through the same type of inhaler (Ellipta) with the same dosing regimen (one inhalation once a day, for each medicine).\(^1,2,3\)
- All other currently available treatment options for triple therapy involve the patient having to take their medicines either through two different types of inhalers, or with two different dosing regimens, or both.

Relvar Ellipta COPD indication

- Relvar Ellipta 92/22 mcg, is indicated for the symptomatic treatment of adults with COPD with a FEV\(_1\) < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.\(^2,3\)

Relvar Ellipta COPD safety profile

- In the COPD clinical development programme a total of 6,237 subjects were included in an integrated assessment of adverse reactions.\(^2,3\)
- The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis.\(^2,3\)
- With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.\(^2,3\)
- The risk of pneumonia in COPD with Relvar 92/22 mcg is similar to that reported for other ICS/LABAs within independent Cochrane meta-analysis.\(^2,3,25,27\)
- Pneumonia occurred in 6% of patients on Relvar Ellipta 92/22 mcg compared with 3% of patients receiving vilanterol 22 mcg alone.\(^27\)
- The number of pneumonia events per 1000 patient years was 85.7 with Relvar Ellipta 92/22 mcg and 42.3 with vilanterol 22 mcg.\(^2,3\)
**Incruse Ellipta in a treatment pathway with AnoroEllipta (umeclidinium/vilanterol)**

- Anoro Ellipta 55/22 mcg is available as a LAMA/LABA option to provide dual bronchodilation to those breathless COPD patients who require it.\(^2^4\)

Whatever the path of treatment which patients follow, use of Incruse Ellipta as the LAMA option, either before or after Anoro Ellipta, means that the patient can benefit from receiving the same LAMA molecule (umeclidinium) through the same type of inhaler (Ellipta) with the same dosing regimen (one inhalation once a day).\(^1,^2^4\)

**Anoro Ellipta COPD indication**

- Anoro Ellipta is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.\(^2^4\)

**Anoro Ellipta safety profile**

- Anoro Ellipta was generally well tolerated in the clinical trials program, with the most common adverse events being urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth.\(^2^4\)
- As with other muscarinic receptor antagonists and sympathomimetic agents, including Anoro Ellipta, cardiovascular effects (such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia) may be seen after administration. Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, Anoro Ellipta should be used with caution in patients with severe cardiovascular disease.\(^2^4\)
Cost

The 30-day cost of Incruse Ellipta 55 mcg is £27.50.

Data to calculate the budget impact of use of Incruse Ellipta, specific to a locality, can be provided by your local GSK account manager and health outcomes specialists if required.

Information sources

Should you require further medical information on Incruse Ellipta please contact the GSK medical information team via our customer contact centre:

- By phone on 0800 221 441; Lines are open from Monday-Friday 8.30am - 5.30pm. Outside these hours and on bank holidays, an answer phone service is available
- By email at customercontactuk@gsk.com

You may also find the information you require at https://hcp.gsk.co.uk/products/incruse.html or from your local GSK account team of therapy, medical and health outcomes specialists who will be able to support you if required.
References

1. Incruse® Ellipta® SmPC.


5. CSD Patient Data, Cegedim Strategic Data Ltd, Patient Therapy Combinations - GSK7229_ADH.DN2, MAT May 2014.


10. Mahler DA, Witek TJ, Jr. The MCID of the transition dyspnea index is a total score of one unit. COPD 2005; 2(1): 99-103


16. GSK Data on file UK/NC/0004/17


Continues on next page
References


23. Relvar® Ellipta® SmPC.

24. Anoro® Ellipta® SmPC.


Incruse® Ellipta® (umeclidinium bromide) Prescribing information

(Please consult the full Summary of Product Characteristics (SmPC) before prescribing)

Incruse® Ellipta® 55 mcg (umeclidinium) inhalation powder. Each single inhalation provides a delivered dose (the dose leaving the mouthpiece of the inhaler) of 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide). 

**Indications:** Incruse is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

**Dosage and administration:** Inhalation only. One inhalation once daily of Incruse Ellipta at the same time of the day each day. Treatment with Incruse Ellipta should be discontinued in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists, therefore Incruse Ellipta should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias. Incruse Ellipta should be used with caution in patients with urinary retention or narrow angle glaucoma. 

**Contraindications:** Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate).

**Precautions:** Incruse Ellipta should not be used in patients with asthma. Treatment with Incruse Ellipta should be discontinued in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists, therefore Incruse Ellipta should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias. Incruse Ellipta should be used with caution in patients with urinary retention or narrow angle glaucoma. 

**Acute symptoms:** Incruse Ellipta is not indicated for acute episodes of bronchospasm. Warn patients to seek medical advice if short-acting inhaled bronchodilator use increases, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken.

**Interactions with other medicinal products:** Co-administration with other long-acting muscarinic antagonists or medicinal products containing this active substance has not been studied and therefore, is not recommended.

**Fertility, pregnancy, and breast-feeding:** No available human in vivo data. Balance risks against benefits.

**Side effects:** Common (≥1/100 to <1/10): Nasopharyngitis, upper respiratory tract infection, urinary tract infection, sinusitis, headache, tachycardia, cough. 

Other important side effects include: Uncommon (≥1/1,000 to <1/100): Atrial fibrillation, rhythm idioventricular, supraventricular tachycardia, supraventricular extrasystoles. Hypersensitivity reactions including rash, urticaria, pruritus. 

**Legal category:** POM. 

**Presentation and Basic NHS cost:** Incruse® Ellipta® 1 inhaler x 30 doses. Incruse Ellipta 55 mcg - £27.50.

**Marketing authorisation (MA) nos.** 55 mcg 1x30 doses [EU/1/14/922/002]; MA holder: Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK. 

**Last date of revision:** April 2017. UKINC/0001/17(1). Incruse® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. All rights reserved.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.
Anoro® Ellipta® (umeclidinium bromide/vilanterol [as trifenatate]) Prescribing information

(Please consult the full Summary of Product Characteristics (SmPC) before prescribing)

Anoro® 55/22 mcg (umeclidinium bromide/vilanterol [as trifenatate]) inhalation powder. Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms of vilanterol (as trifenatate). Indications: Anoro is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). Dosage and administration: Inhalation only. One inhalation once daily of Anoro. Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and magnesium stearate). Precautions: Anoro should not be used in patients with asthma. Treatment with Anoro should be discontinued in the event of paradoxical bronchospasm and alternative therapy initiated if necessary. Cardiovascular effects may be seen after the administration of muscarinic receptor antagonists and sympathomimetics therefore Anoro should be used with caution in patients with severe cardiovascular disease. Anoro should be used with caution in patients with urinary retention, narrow angle glaucoma, convulsive disorders, thyrotoxicosis, hypokalaemia, hyperglycaemia and severe hepatic impairment. No dosage adjustment is required in renal or mild to moderate hepatic impairment. Acute symptoms: Anoro is not indicated for acute episodes of bronchospasm. Warn patients to seek medical advice if short-acting inhaled bronchodilator use increases, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken. Interactions with other medicinal products: Avoid β-blockers. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin). Anoro should not be used in conjunction with other long-acting β2-adrenergic agonists or medicinal products containing long-acting muscarinic antagonists. Caution is advised with concomitant use with methylxanthine derivatives, steroids or non-potassium-sparing diuretics as it may potentiate possible hypokalaemic effect of β2-adrenergic agonists. Fertility, pregnancy, and breast-feeding: No available data. Side effects: Common (≥1/100 to <1/10): urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth. Other important side effects include: Uncommon (≥1/1,000 to <1/100): atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles, palpitations, and hypersensitivity reactions including rash. Rare (≥1/10,000 to <1/1,000): anaphylaxis, angioedema, and urticaria. Glaucoma, vision blurred, intraocular pressure increased and paradoxical bronchospasm. See SmPC for other adverse reactions. Legal category: POM. Presentation and Basic NHS cost: Anoro® Ellipta®, 1 inhaler x 30 doses. Anoro® Ellipta® 55/22 mcg - £32.50. Marketing authorisation (MA) no. 55/22 mcg 1x30 doses [EU/1/14/898/002]; MA holder: Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK. Last date of revision: Jan 2017. UK/UCV/0095/15(2). Anoro® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. All rights reserved. Anoro® was developed in collaboration with Innoviva Inc.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441
Relvar ▼ Ellipta (fluticasone furoate/vilanterol [as trifenatate]) Prescribing information

(Please consult the full Summary of Product Characteristics (SmPC) before prescribing)

Relvar ▼ Ellipta (fluticasone furoate/vilanterol [as trifenatate])

**Indication:** Each single inhalation of fluticasone furoate (FF) 100 micrograms (mcg) and vilanterol (VI) 25 mcg provides a delivered dose of 92 mcg FF and 22 mcg VI. Each single inhalation of FF 200 mcg and VI 25 mcg provides a delivered dose of 184 mcg of FF and 22 mcg of VI.

**Indications:** Asthma: Regular treatment of asthma in patients ≥12 years not adequately controlled on inhaled corticosteroids (ICS) and "as needed" short-acting inhaled ß₂-agonists, where a long-acting ß₂-agonist (LABA) and ICS combination is appropriate. COPD: Symptomatic treatment of adults with COPD with a FEV₁ <70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy.

**Dosage and administration:** Inhalation only. Asthma: Adults and adolescents ≥12 years: one inhalation once daily of Relvar 92/22 mcg for patients who require a low to mid dose of ICS in combination with a LABA. If patients are inadequately controlled then the dose can be increased to one inhalation once daily Relvar 184/22 mcg. Relvar 184/22 mcg can also be considered for patients who require a higher dose of ICS in combination with a LABA. Regularly review patients and reduce dose to lowest that maintains effective symptom control. COPD: one inhalation once daily of Relvar 92/22 mcg. Relvar 184/22 mcg is not indicated for patients with COPD.

**Contraindications:**
- Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate & magnesium stearate).
- Precautions:
  - Pulmonary tuberculosis, severe cardiovascular disorders or heart rhythm abnormalities, thryotoxicosis, uncorrected hypokalaemia, patients predisposed to low levels of serum potassium, chronic or untreated infections, diabetes mellitus, paradoxical bronchospasm.
  - In patients with moderate to severe hepatic impairment 92/22 mcg of VI.
  - Concomitant administration of other sympathomimetic medicinal products may potentiate the adverse reactions of FF/VI.

**Side effects:**
- Very Common (≥1/10):
  - Blurred vision.
- Common (≥1/100 to <1/10):
  - Nasopharyngitis.
- Uncommon (≥1/1000 to <1/100):
  - Headache, nasopharyngitis.

**Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard.**

Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

Relvar Ellipta ▼ Ellipta® was developed in collaboration with Innoviva Inc.

Zinc code: UK/INC/0005/14(12)
Date of preparation: September 2017
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Anoro Ellipta and Relvar Ellipta were developed in collaboration with Innoviva Inc