BEDFORDSHIRE AND LUTON JOINT PRESCRIBING COMMITTEE (JPC)

18TH September 2019
Revision date: September 2021

Bulletin 279: Umeclidinium / Vilanterol (Anora®Ellipta®) for the treatment of COPD

JPC Recommendation:

- The committee agreed to add Umeclidinium **/** Vilanterol (Anora®Ellipta®) to the formulary within it's licensed indication as a 2nd choice LAMA / LABA option for the treatment of COPD.

Bedfordshire CCG
Luton CCG

New Medicine Review Bulletin

Choice of combination Long Acting Muscarinic Agent (LAMA) and Long Acting Beta Agonist (LABA) inhaler for Chronic Obstructive Pulmonary Disease (COPD)

Medicine	Umeclidinium/ vilanterol 55/22 micrograms inhalation powder (Anoro® Ellipta®)
Document status	Final
Date of last revision	August 2019, Approved September 2019
Proposed Sector of prescribing	Primary and secondary care
Introduction Summary Key points Evidence level	Umeclidinium/ vilanterol 55/22 micrograms inhalation powder (Anoro® Ellipta®) was launched in July 2014 and is a fixed dose combination inhaler containing a long-acting muscarinic antagonist (LAMA) and a long-acting beta agonist (LABA). There are currently 4 LABA/LAMA combination inhalers licensed for the maintenance treatment of patients with chronic obstructive pulmonary disease. Currently the formulary and COPD guidelines include tiotropium/olodaterol (Spiolto® Respimat®), aclidinium/formoterol (Duaklir® Genuair®) and glycopyrronium/indacterol (Ultibro® Breezhaler®) but not umeclidinium/vilanterol (Anoro® Ellipta®) Clinical experience from Dr Bagmane at Bedford Hospital suggests once daily preparations are better at supporting patients that struggle to comply with twice daily.
The intervention Mechanism of action	Inhaled long-acting muscarinic antagonist (LAMA) bronchodilator and long-acting beta agonist (LABA) bronchodilator. A combination inhaler containing fixed doses of umeclidinium and vilanterol in a multi dose dry powder inhaler device, the Ellipta®. Bronchodilators have a direct relaxation effect on airway smooth muscle cells. Whilst both drugs are bronchodilators, they act upon different receptors in the lungs and so have different mechanisms of action. Anoro® is provided in the Ellipta device which is also available to deliver LAMA (Incruse®), ICS/LABA (Relvar®) and ICS/LAMA/LABA (Trelegy®) enabling device continuity for a patient throughout they COPD maintenance therapy.
Licensed indication	Anoro® Ellipta® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Formulation/Available Products	1. Aclidinium and formoterol fumarate dihydrate (Duaklir® Genuair®) 340 micrograms /12 micrograms inhalation powder.

	 2. Glycopyrronium and indacaterol (Ultibro® Breezhaler) 85 micrograms/43 micrograms, inhalation powder hard capsules.  3. Tiotropium and Olodaterol (Spiolto Respimat®) 2.5 micrograms/2.5 micrograms solution for inhalation.  4. Umeclidinium and vilanterol (Anoro® Ellipta®) 55 micrograms/22 micrograms inhalation powder, pre-dispensed. 
Usual dosage	One inhalation of Anoro® Ellipta® 55/22 micrograms once daily.
Treatment alternatives/ place in therapy	The Bedfordshire and Luton COPD and ACO Guidelines recommend offering a LAMA/LABA if the patients symptoms persist despite using a salbutamol (or an alternative SABA) and if the MRC is 3 or above and the CAT is 10 or above.
Future alternatives	

National guidance	NICE guidance (NG115) on Chronic Obstructive Pulmonary Disease recommends the use of LAMA/LABAs for the management of COPD in patients who do not have asthmatic features/features suggesting steroid responsiveness. BTS GOLD guidelines (2019) recommend a LAMA/LABA for patients with persistent exacerbations or dyspnoea on long acting bronchodilator monotherapy Neither guidance makes a recommendation about which LAMA/LABA should be chosen but suggest that treatment should be individualised
Local Guidance	The Bedfordshire and Luton COPD and ACO Guidelines recommend offering a LAMA/LABA combination inhaler if the patients symptoms persist despite using a salbutamol (or an alternative SABA) and if the MRC is 3 and above, and the CAT is 10 or above. Or in patients experiencing persistent breathlessness or exacerbations on LAMA inhaler. Spiolto Respimat (tiotropium/olodaterol) is currently the first choice of LAMA/LABA on the joint formulary for COPD.
Evidence for use	Since the JPC last reviewed the inclusion of umeclidinium/vilanterol on the formulary there have been comparison studies published. • Feldman et al (2017) compared umeclidinium/vilanterol with tiotropium/olodaterol in a 12 week open label randomised controlled study with FEV_1 as the primary outcome. This is the first direct comparison of two once-daily fixed-dose LAMA/LABA combinations, superiority was observed for the primary end point of trough FEV1 at week 8 with umeclidinium/vilanterol compared with tiotropium/olodaterol in patients with symptomatic COPD. Both treatments had similar safety profiles. Previous review for the JPC reported the following evidence (taken from SMC assessment): The main evidence supporting the marketing authorisation is from four phase III multicentre, randomised, double-blind, studies, three active-controlled and one placebo-controlled. The active-controlled studies, DB2113360, DB2113374 and ZEP117115, were similar in design although they included different treatment groups. All four studies recruited patients ≥40 years old, with a diagnosis of COPD treated in an outpatient setting, ≥10 pack-year smoking history, post-salbutamol forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio of <0.70, post-salbutamol FEV1≤70% predicted normal and ≥2 on the Modified Medical Research Council Dyspnoea Scale (mMRC). In the three active-controlled studies, after a 7 to 10 day run-in period, patients were randomised equally to receive 24 weeks of allocated study treatment. All three studies had an umeclidinium/vilanterol 55/22 micrograms group and a tiotropium 10 micrograms group (delivered dose); DB2113360 and DB2113374 also had an umeclidinium/vilanterol 113/22 micrograms group; in addition, DB2113360 had a vilanterol 22 micrograms monotherapy group and DB2113374 had a umeclidinium 113 micrograms monotherapy group. All study treatments were administered once daily. Tiotropium was administered via a HandiHaler® device and the other treatments via a novel dry powder inhaler. Matching placebos were used to maintain blinding. Permitted concomitant medication comprised inhaled salbutamol as required for rescue and inhaled corticosteroids (ICS) at a stable dose of ≤1000

	micrograms/day of fluticasone propionate or equivalent from 30 days prior to screening onward. The primary outcome was trough (pre-dose) FEV1 at week 24, analysed using a mixed model repeated measures analysis, in the intention to treat (ITT) population (all randomised patients who had received at least one dose of study drug). Study DB2113360 excluded twenty patients recruited by one investigator from the ITT population. In studies DB2113360 and DB2113374, a step-down closed testing procedure, to account for multiplicity, tested the higher (unlicensed) dose of umeclidinium/vilanterol first. In both studies these criteria were satisfied and the primary endpoints of umeclidinium/vilanterol 55/22 micrograms versus comparators could be tested. Results for the licensed dose only of umeclidinium / vilanterol are reported in Table 1. There was a significant improvement for umeclidinium/vilanterol 55/22 micrograms over tiotropium in the secondary endpoint of change from baseline in weighted mean FEV1 (0 to 6 hours post dose); the least squares [LS] mean between-treatment difference at 24 weeks was 0.074L (95% CI: 0.022 to 0.125), 0.096L (95% CI: 0.050 to 0.142) and 0.105L (95% CI: 0.071 to 0.140) in studies DB2113360, DB2113374 and ZEP117115, respectively, p≤0.005 for all comparisons. There was a significantly greater reduction in rescue medication use (mean number of puffs per day of salbutamol) between umeclidinium/vilanterol 55/22 micrograms and tiotropium after 24 weeks in studies DB2113360, and ZEP117115: LS mean difference between treatments of -0.7 (95% CI: -1.2 to -0.1) p=0.022, and -0.5 (95% CI: -0.7 to -0.2) p<0.001, but not in study DB2113374: -0.6 (95% CI:-1.2 to 0.0). The effect of treatment on breathlessness was evaluated using the interviewer-administered Transition Dyspnoea Index (TDI), which measures change from baseline in the patient's dyspnoea, by scoring three categories (functional impairment, magnitude of task, and magnitude of effort). A 1-unit change in TDI focal score is considered to be the minimal clinically important improvement from baseline. There was no significant difference in TDI focal score at Week 24 between umeclidinium/vilanterol and tiotropium in studies DB2113360 or DB2113374; treatment difference: -0.1 (95% CI: -0.7 to 0.5), p=0.721 and 0.2 (95% CI: -0.5 to 0.9), p=0.548, respectively. ZEP117115 did not assess this outcome. The St. George's Respiratory Questionnaire (SGRQ) was used to assess specific disease-related quality of life. Reduction in score indicates improvement and a decrease of at least 4 points is considered to be clinically relevant. There was no significant difference after 24 weeks in total SGRQ score for umeclidinium/vilanterol 55/22 micrograms versus tiotropium in studies DB2113360 and DB2113374: -6.87 versus -7.62; and -9.95 versus -9.78, respectively; in ZEP117115 the treatment difference was statistically but not clinically significant: -2.1 (95% CI: -3.61 to -0.59) p=0.006. A randomised, double-blind, placebo-controlled study, DB2113373, had the same inclusion criteria, primary outcome, primary analysis method, population, inhaler devices, rescue treatment and concomitant medication as the active-controlled studies. After a 7 to 14 day run-in period, 1,532 patients were randomised 3:3:3:2 to receive 24 weeks treatment with once daily inhalations of umeclidinium/vilanterol 55/22 micrograms, umeclidinium 55 micrograms, vilanterol 22 micrograms, or placebo. There was a significant improvement in the primary outcome of trough FEV1 at week 24 for umeclidinium/vilanterol 55/22 micrograms versus placebo: LS mean difference 0.167L (95% CI: 0.128 to 0.207), p<0.001. Statistically significant improvements versus placebo were also seen for each monocomponent.

<table>
<tr><td></td><td></td></tr>
<tr><td>Safety*</td><td>The most frequently reported adverse reaction with umeclidinium/vilanterol was nasopharyngitis. Other common side effects include constipation, dry mouth, cough, headache, urinary tract infections, sinusitis, pharyngitis, upper respiratory tract infection and oropharyngeal pain. Administration of umeclidinium/vilanterol may produce paradoxical bronchospasm that may be life-threatening. Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects.

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists and sympathomimetics, including umeclidinium/vilanterol. Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium/vilanterol should be used with caution in patients with severe cardiovascular disease.

Umeclidinium/vilanterol should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists.

The safety profile of ANORO ELLIPTA is based on safety experience with umeclidinium/vilanterol and the individual components from the clinical development program comprising of 6,855 patients with COPD and from spontaneous reporting. The clinical development programme included 2,354 patients who received umeclidinium/vilanterol once daily in the Phase III clinical studies of 24 weeks or more, of whom 1,296 patients received the recommended dose of 55/22 micrograms in 24-week studies, 832 patients received a higher dose of 113/22 micrograms in 24-week studies and 226 patients received 113/22 micrograms in a 12-month study.</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Costs
Tariff status
Activity costs</td><td>
<table>
<tr><th>Drug & Dosage</th><th>30 day cost/per patient</th><th>Annual Cost per patient</th></tr>
<tr><td>Anoro Ellipta® (umeclidinium/ vilanterol)</td><td>£32.50</td><td>£390</td></tr>
<tr><td>Ultibro® Breezhaler® (indacaterol / glycopyrronium)</td><td>£32.50</td><td>£390</td></tr>
<tr><td>Duaklir® Genuair® (aclidinium / formoterol)</td><td>£32.50</td><td>£390</td></tr>
<tr><td>Spiolto® Respimat® (Tiotropium /olodaterol)</td><td>£32.50</td><td>£390</td></tr>
</table>

N.B. Doses are for general comparison and do not imply therapeutic equivalence</td></tr>
<tr><td>Cost effectiveness (if available)</td><td>Information taken from SMC submission in 2015
The submitting company presented a cost-minimisation analysis comparing umeclidinium/ vilanterol for adult patients with COPD eligible for treatment with tiotropium monotherapy or tiotropium in combination with a LABA with the following comparators:
• Tiotropium monotherapy</td></tr>
</table>

- Tiotropium plus indacaterol
- Tiotropium plus formoterol
- Tiotropium plus salmeterol.

A cost-utility analysis was also provided comparing umeclidinium/vilanterol with tiotropium monotherapy and tiotropium plus indacaterol. However, SMC clinical expert responses indicate that tiotropium plus formoterol and tiotropium plus salmeterol are the key comparators and therefore the cost-minimisation analysis was considered to be the relevant analysis.

A five year time horizon was used and the analysis was carried out from an NHS Scotland perspective.

The data to support the comparable efficacy between umeclidinium/vilanterol and tiotropium plus indacaterol, tiotropium plus formoterol and tiotropium plus salmeterol were based on indirect treatment comparisons which showed there to be no significant differences between any of the treatments. A Bayesian NMA comparing umeclidinium/vilanterol with tiotropium plus formoterol was also presented, with placebo as the common comparator. The results showed comparable efficacy between umeclidinium/vilanterol and tiotropium plus formoterol for SGRQ total score at 24 weeks. The data to support the comparable efficacy between umeclidinium/vilanterol and tiotropium monotherapy were based on an integrated NMA of the three 24-week studies, for the calculation of the primary outcome (% predicted FEV1).

The analysis compared the drug acquisition costs only and after the first year they were discounted at 3.5% in line with normal convention in economic evaluations.

The main economic results show that umeclidinium/vilanterol is cost saving compared to tiotropium monotherapy, tiotropium plus indacaterol, tiotropium plus salmeterol and tiotropium plus formoterol. The results also show that umeclidinium/vilanterol is cost saving compared to the weighted cost of the comparator treatments which is calculated using Scottish sales data and assumes the LABA market share is consistent when used in combination with tiotropium. The tiotropium plus LABA weighted cost is based on market shares of 84.3%, 10.6% and 5.1% for tiotropium plus salmeterol, tiotropium plus formoterol and tiotropium plus indacaterol respectively.

Comparator treatments	Comparator drug costs		**Cumulative savings with Umeclidinium/vilanterol**	
	Year 1	Year 5	Year 1	Year 5
Tiotropium (Spiriva)	£407.58	£1,904.67	£12.17	£56.86
Tiotropium plus Indacaterol (Spiriva plus Onbrez Breezhaler)	£763.58	£3,568.27	£368.16	£1,720.46
Tiotropium plus Salmeterol (Weighted Cost)	£763.14	£3,566.24	£367.73	£1,718.42
Tiotropium plus Formoterol (Weighted Cost)	£664.38	£3,104.69	£268.96	£1,256.88
Tiotropium plus LABA (Weighted Cost)	£752.74	£3,517.62	£357.32	£1,669.81

The results are based on indirect comparisons that had some limitations, but despite these, the economic case has been demonstrated.

Potential number of patients in Bedfordshire and Luton **Impact per 100,000 population** **Affordability considerations**	COPD prevalence is estimated at 2-4% but the diagnosed prevalence is about 1.5% (1,500 per 100,000) which increases to 10% in men aged over 75. (14) An average GP practice of 6,600 patients is likely to have about 100 patients on its COPD disease register. This equates to approximately 6,100 and 3,000 patients with COPD in Bedfordshire and Luton respectively.
Decisions from other bodies **Comments sought from –**	SMC and AWMSG have approved umeclidinium/vilanterol for maintenance treatment in patients with COPD. Milton Keynes Formulary has approved umeclidinium/vilanterol for prescribing, Cambridgeshire and Peterborough formulary have it listed as non-formulary.
Evidence strengths and limitations	

PAC New Drug Template – Adapted from East Anglia Medicines Information, NHS Suffolk, NHS Cambridgeshire and NHS Derby templates

**Consult Summary of Prescribing Characteristics for full prescribing detail.*

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

Appendix 1- Search Strategy

Anoro Ellipta (umeclidinium 55micrograms/vilanterol 22micrograms) Summary of Product Characteristics. Accessed via www.medicines.org.uk on 15th August 2019.

BTS GOLD strategy for chronic obstructive pulmonary disease. December 2018, accessed via www.guidelines.org.uk

Drug Tariff, NHSBSA, August 2019 accessed via www.nhsbsa.nhs.uk

Feldman G et al., Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study. Adv Ther (2017) 34:2518–2533

NICE Guidelines (NG115) Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Updated July 2019, accessed via www.nice.org.uk

Scottish Medicines Consortium. Umeclidinium/vilanterol (Anoro) detailed advice, January 2015. Accessed via www.scottishmedicines.org.uk

Treatment assessed (September 2019): Choice of combination Long Acting Muscarinic Agent (LAMA) and Long Acting Beta Agonist (LABA) inhaler for Chronic Obstructive Pulmonary Disease (COPD)
JPC Recommendation • The committee agreed to add Umeclidinium **/** Vilanterol (Anora®Ellipta®)to the formulary as a 2nd choice LAMA / LABA option for the treatment of COPD.
1) Clinical Effectiveness The evidence base shows that all the LABA/LAMA inhalers are effective bronchodilators which produce clinically significant improvements in lung function (FEV1).
2) Cost Effectiveness The Scottish Medicines Consortium has provided health economic analysis in their reports on umeclidinium/vilanterol. The results are based on indirect comparisons that had some limitations, but despite these, the economic case has been demonstrated.
3) Equity & Equality Impact Assessment* No impact envisioned
4) Needs of the community COPD prevalence locally is increasing and underdiagnosed.
5) Need for healthcare (incorporates patient choice and exceptional need) The choice of treatment for a person with COPD depends on drug efficacy, tolerability to treatment, possible adverse events and the suitability of different inhaler devices to the person. Inhaled long-acting bronchodilators have an important role to play in managing COPD.
6) Policy drivers NICE Clinical Guideline NG115 on COPD Bedfordshire and Luton COPD and ACO Guidelines
7) Disinvestment Potential for disinvestment in LABA/LAMA inhalers not recommended for use by the JPC.

The JPC agreed the following sections within the PCT Ethical and Commissioning Framework were not relevant to JPC discussions: Health Outcomes, Access, and Affordability.

***Equality Impact Assessment for BCCG only**

Where the implementation of the decision of the Bedfordshire and Luton Joint Prescribing Committee (JPC) may impact on one or more equality group differently to others, BCCG will require an equality impact assessment to be completed. The guidance on this can be found in the attached document. Please summarise the equality impact in the in the Equity & Equality Impact Assessment box above.

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Protected Characteristics (under the Equality Act):-

Age; Disability; Gender reassignment; Marriage & Civil Partnership (in employment only); Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual orientation; carers; other identified groups.

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*