NHS
Vale of York
Clinical Commissioning Group

COMMISSIONING POLICY RECOMMENDATION
TREATMENT ADVISORY GROUP
FLUTICASONE/VILANTEROL COMBINATION INHALER - COPD
Policy agreed by Vale of York CCG (*date*)

Drug, Treatment, Device name
Fluticasone furoate/vilanterol 92/22mcg (Relvar GSK)
Licensed indication
Relvar Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.
Device cost (at recommended dose)

Dose	**Product device and dose frequency**	**Medium strength**	**High strength**
30	Fluticasone/vilanterol (Relvar dry powder) One dose ONCE daily	92/22mcg £27.80	184/22mcg -**Not licensed for COPD.**
60	Fluticasone/ salmeterol (Seretide Accuhaler) One dose TWICE daily		500/50mcg £40.92
120	Fluticasone/ salmeterol (Seretide MDI) TWICE daily		250/25mcg (Unlicensed) £59.48
see strength	Budesonide/ formoterol (Symbicort dry powder inhaler) One dose TWICE daily	200/6mcg £38 (120 dose)	400/12mcg £38 (60 dose)

Resource impact on population
There will no significant resource impact.
Recommendation to not commission
When is funding appropriate?
Relvar dry powder inhalersare not recommended as a treatment option in COPD due to the lack of comparative data against standard licensed inhaler treatments for COPD. There are emerging safety concerns relating to increased risk of pneumonia and non-traumatic fractures. CCGs may wish to consider the possible savings if used instead of Seretide or Symbicort for this indication however, they should also be aware of the lack of dose equivalence of fluticasone furoate to fluticasone propionate
Clinical and cost effectiveness evidence

NICE clinical guideline 101: Chronic Obstructive Pulmonary Disease
http://www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf
Classification of severity of airflow obstruction in COPD according to the NICE clinical guideline is shown in the table below:

Post-bronchodilator FEV_1/FVC	FEV_1 % predicted	Post-bronchodilator
<0.7	≥80%	Stage 1: Mild[a]
<0.7	**50–79%**	**Stage 2: Moderate**
<0.7	30–49%	Stage 3: Severe
<0.7	<30%	Stage 4: Very severe[b]

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expired volume in 1 second; FVC, forced vital capacity.

[a] Symptoms should be present to diagnose COPD in people with mild airflow obstruction.

[b] Or FEV_1 <50% with respiratory failure.

Table 1 NICE classification of severity of airflow obstruction in COPD

The NICE clinical guideline defines COPD as follows:

- Airflow obstruction is defined as a reduced FEV_1/FVC ratio (where FEV_1 is forced expired volume in 1 second and FVC is forced vital capacity), such that FEV_1/FVC is less than 0.7.
- If FEV_1 is 80% predicted normal or more, a diagnosis of COPD should be made only in the presence of respiratory symptoms, for example, breathlessness or cough.

The guideline recommends the following inhaled treatments for managing stable COPD. The list is not comprehensive but does include the key recommendations that relate to this evidence summary and the likely place in therapy of fluticasone furoate/vilanterol.

- Short-acting bronchodilators, as necessary, should be the initial empirical treatment for the relief of breathlessness and exercise limitation.
- In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed, offer the following as maintenance therapy:
    - if FEV_1 is 50% predicted or more: either a long-acting $beta_2$ agonist (LABA) or a long-acting muscarinic antagonist (LAMA)
    - if FEV_1 is less than 50% predicted: either a LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA.
- In people with stable COPD and an FEV_1 of 50% predicted or more who remain breathless or have exacerbations despite maintenance therapy with a LABA:
    - consider a LABA with an ICS in a combination inhaler
    - consider a LAMA in addition to a LABA where an ICS is declined or not tolerated.
- Offer a LAMA in addition to a LABA with an ICS to people with COPD who remain breathless

or have exacerbations despite taking a LABA with an ICS, irrespective of their FEV_1.

- Consider a LABA with an ICS in a combination inhaler in addition to a LAMA for people with stable COPD who remain breathless or have exacerbations despite maintenance therapy with a LAMA, irrespective of their FEV_1.
- The choice of drug(s) should take into account the person's symptomatic response and preference, and the drug's potential to reduce exacerbations, its side effects and cost.

ESNM21: Chronic pulmonary disease: fluticasone furoate plus vilanterol. NICE June 2013
http://publications.nice.org.uk/esnm21-chronic-obstructive-pulmonary-disease-fluticasone-furoate-plus-vilanterol-esnm21
Summary table of evidence extracted from the above article

Effectiveness	**Safety**
• No published studies comparing fluticasone furoate/vilanterol with other ICS/LABA combination inhalers licensed for use in COPD. • Fluticasone furoate/vilanterol 100/25 micrograms reduced the mean yearly rate of moderate and severe exacerbations, but not exacerbations requiring admission to hospital, compared with vilanterol 25 micrograms alone. • Fluticasone furoate/vilanterol 100/25 micrograms improved trough FEV_1 after 24 weeks' treatment compared with placebo but not compared with vilanterol alone.	• No statistical analysis of safety data from studies is available. • Local corticosteroid effects, pneumonia (including requiring admission to hospital) and non-traumatic fractures were seen more frequently with fluticasone furoate/vilanterol 100/25 micrograms than with vilanterol alone.
Patient factors	**Cost**
• Administration is once-daily using a multi-dose dry powder inhalation device (the Ellipta device). The 2 combination inhalers in the same class currently licensed for use in COPD are for twice-daily use.	• £27.80 per month

This article indicates that currently, published efficacy and safety data for fluticasone

furoate/vilanterol are limited to short term, placebo-controlled trials with disease-orientated primary outcomes and 1 study of the effect of fluticasone furoate/vilanterol on rates of moderate and severe exacerbations compared with vilanterol alone. These trials provide no information on the effectiveness of fluticasone furoate/vilanterol compared with available licensed inhaled therapy for COPD.

At the time of publication, NICE reported that the exact dose equivalence between fluticasone furoate and fluticasone propionate (the currently licensed fluticasone salt) is not known (GlaxoSmithKline: personal communication May 2013).

Clinical evidence

Dransfield MT et al
Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials
The Lancet Respiratory Medicine, Volume 1, Issue 3, Pages 210 - 223, May 2013
http://www.thelancet.com/journals/lanres/article/PIIS2213-2600(13)70040-7/abstract

Design: 2 simultaneous, replicate, 52-week, randomised, double-blind, parallel group studies. Each had a 4-week open-label run-in period using combination fluticasone propionate/salmeterol 250/50 micrograms twice daily. The method of allocation described suggests that this was concealed.

Population: 1622 adults in study 1 and 1633 adults in study 2. Study 1 involved 167 sites in 15 countries and study 2 involved 183 sites in 15 countries. Participants were 40 years or older (mean 64 years) with COPD (post-bronchodilator FEV1 70% predicted or less, mean range 44.3% to 46.4%, and FEV1/FVC [forced vital capacity] ratio 0.7 or less), a history of at least 1 COPD exacerbation in the previous year that needed systemic or oral corticosteroids, antibiotics or admission to hospital, and a smoking history of 10 or more pack-years.

Intervention and comparison: participants were randomised in approximately equal numbers to 4 treatments, taken once daily using the Ellipta inhaler:

- fluticasone furoate 50 micrograms (emitted dose 44 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
- fluticasone furoate 100 micrograms (emitted dose 92 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
- fluticasone furoate 200 micrograms (emitted dose 184 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
- vilanterol 25 micrograms (emitted dose 22 micrograms).

Outcome: The primary efficacy end point was the yearly rate of moderate and severe COPD exacerbations. Moderate exacerbations were defined as worsening symptoms of COPD needing treatment with oral corticosteroids and/or antibiotics. Severe exacerbations were defined as those that needed hospital admission. Secondary and additional end points included the time to first moderate or severe exacerbation, yearly rate of severe exacerbations, the number of night-time awakenings due to symptoms, and dyspnoea score. Specific safety end points included haematological and clinical measurements, incidence of bone fractures and clinically diagnosed

pneumonia. The 2 studies were analysed separately and in a predefined pooled analysis, based on the intention-to-treat population. Results of this pooled analysis are summarised in table 2.

Table 2 Summary of the pooled analysis

	Fluticasone furoate/vilanterol once daily (micrograms)			**Vilanterol 25 micrograms on daily**
	50/25	**100/25**	**200/25**	
Efficacy (ITT population)	n=820	n=806	n=811	n=818
Primary outcome				
Moderate and severe exacerbations; LS mean yearly rate	0.93	0.81	0.85	1.11
LS mean yearly RR for moderate and severe exacerbations (95% CI) compared with vilanterol alone	0.8 (0.7 to 1.0), p=0.014	0.7 (0.6 to 0.8), p<0.0001	0.8 (0.7 to 0.9), p=0.0003	–
Selected secondary and additional outcomes				
Time to first moderate or severe exacerbation: HR (95% CI) compared with vilanterol alone	0.9 (0.8 to 1.0), p=0.114	0.8 (0.7 to 0.9), p=0.0002	0.8 (0.7 to 0.9), p=0.0001	–
Severe exacerbation LS mean yearly rate	0.08	0.09	0.08	0.10
LS mean yearly RR for severe exacerbations (95% CI) compared with vilanterol alone	0.8 (0.6 to 1.2), p=0.313	0.9 (0.6 to 1.4), p=0.695	0.8 (0.5 to 1.2), p=0.280	–
Night-time awakenings, LS mean difference (95% CI) from vilanterol alone	−0.06 (−0.10 to −0.01), p=0.011	−0.08 (−0.12 to −0.03), p=0.001	−0.07 (−0.12 to −0.03), p=0.002	–
Dyspnoea score[a]: LS mean difference (95% CI) from vilanterol alone	−0.08 (−0.12 to −0.03), p=0.0006	−0.09 (−0.014 to −0.05), p<0.0001	−0.11 (−0.16 to −0.07), p<0.0001	–
Safety (ITT population)	n=820	n=806	n=811	n=818
Adverse events leading to discontinuation or withdrawal[b]	6.5% (53/820)	7.7% (62/806)	7.5% (61/811)	5.5% (45/818)

Local corticosteroid effects[b]	17.3% (142/820)	15.0% (121/806)	17.3% (140/811)	11.7% (96/818)
Pneumonia[b]	5.9% (48/820)	6.3% (51/806)	6.8% (55/811)	3.3% (27/818)
Bone disorders (including fractures)[b]	2.9% (24/820)	3.3% (27/806)	2.6% (21/811)	1.1% (9/818)

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intention-to-treat; LS, least squares; RR, rate ratio.

[a] Dyspnoea was scored on a scale of −2 to +2, with −2 indicating 'much less than usual' and +2 indicating 'much more than usual'.

[b] No statistical analysis of safety outcomes was presented.

Kerwin KM et al.
A randomised trial of fluticasone furoate/vilanterol (50/25 µg; 100/25 µg) on lung function in COPD
Respiratory Medicine (2013) 107, 560-569

Design: 24-week double-blind, placebo-controlled RCT. The method of allocation described suggests that this was concealed.

Population: 1030 adults in 9 countries aged at 40 years or older (mean 63 years) with COPD (post bronchodilator FEV1 70% predicted or less, mean range 46.9–49.9%, and FEV1/FVC ratio 0.7 or less), a smoking history of at least 10 pack-years, and a score of at least 2 on the Modified Medical Research Council Dyspnoea Scale. No previous history of COPD exacerbations was needed but about a quarter of participants had had at least 1 moderate exacerbation of COPD (needing treatment with oral corticosteroids and/or antibiotics but not hospital admission) and about 7% had had at least 1 severe exacerbation (needing hospital admission) in the year before trial entry.

Intervention and comparison: participants were randomised in approximately equal numbers to 5 treatments, taken once daily in the morning using a dry powder inhaler:

- fluticasone furoate 50 micrograms (emitted dose 44 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
- fluticasone furoate 100 micrograms (emitted dose 92 micrograms) plus vilanterol 25 micrograms (emitted dose 22 micrograms)
- fluticasone furoate 100 micrograms (emitted dose 92 micrograms)
- vilanterol 25 micrograms (emitted dose 22 micrograms)
- placebo.

Outcomes: there were 2 co-primary outcomes: weighted mean FEV1 (0–4 hours post-dose) on day 168, and the change from baseline in trough FEV1 (23–24 hours post-dose) on day 169.The primary

analysis was based on the intention-to-treat population split into 2 levels pre-specified by the authors to avoid spurious statistically significant findings arising through chance, given the number of possible comparisons:

The level 1 analysis consisted of 6 key comparisons of the co-primary end points for fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms.

The authors specified that only if all comparisons reached statistical significance at level 1 would they move on to level 2 analyses, which included comparison with fluticasone furoate/vilanterol 50/25 micrograms. The level 1 analysis did not meet the pre-defined criteria and so no formal statistical testing was performed at level 2.

Secondary and additional outcomes included changes in dyspnoea score, night-time awakenings and other symptom-related end points but the statistical hierarchy used in the analysis meant that no statistical significance can be inferred from the results for these outcomes.

Results: Fluticasone furoate/vilanterol 100/25 micrograms was statistically significantly superior to placebo in improving post-dose weighted mean FEV1 (173 ml, 95% CI 123 to 224 ml, p<0.001) and trough FEV1 (115 ml, 95% CI 60 to 169 ml, p<0.001) after 24 weeks' treatment. However, there was no statistically significant difference in trough FEV1 between fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms (48 ml, 95% CI -6.0 to 102ml, p=0.082).
The same percentage of patients receiving fluticasone furoate/vilanterol 100/25 micrograms and placebo had an adverse event leading to discontinuation or withdrawal from the study (9%). Pneumonia occurred in 2% of the fluticasone furoate/vilanterol 100/25 microgram group compared with 1% of the placebo group.

Agusti et al
A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD.
Eur Resp Journal; 10 Oct 2013 (Abstract)

Fluticasone furoate/vilanterol trifenatate (FF/VI) is a once-daily (OD) inhaled corticosteroid/long-acting β2-agonist combination in development for chronic obstructive pulmonary disease (COPD) treatment. We compared the efficacy and safety of FF/VI versus fluticasone propionate/salmeterol (FP/SAL) twice-daily (BD) over 12 weeks.

Moderate to very severe COPD patients received FF/VI 100/25 µg OD in the morning (N=266) or FP/SAL 500/50 µg BD (N=262). Primary endpoint: change from baseline in 0–24 h weighted mean forced expiratory volume in 1 s (wmFEV1) at 12 weeks. Additional endpoints included: time to 100 mL improvement from baseline on day 1; change from baseline in St George's Respiratory Questionnaire (SGRQ). Safety was also assessed.

wmFEV1 (mean, 130 mL) was greater and time to 100mL improvement shorter (median, 16min) with FF/VI than FP/SAL (mean [wm], 108mL; median, 28min). Health status (SGRQ total score)

improved in both groups (FF/VI, –4.3 units; FP/SAL, –3.0 units). Differences between treatments were not statistically significant. Six patients in the FF/VI (2%) and 3 in the FP/SAL (1%) arm experienced serious adverse events, none of which were considered to be drug-related.

Improvements in lung function and health status were not significantly different between FF/VI 100/25 µg OD and FP/SAL 500/50 µg BD; there was no apparent differentiation between the safety profiles of either therapy.

Points for consideration

- Kerwin *et al* demonstrated that fluticasone furoate/ vilanterol 100/25mcg has beneficial effects on lung function as measured by trough FEV1 in people with COPD compared with placebo, when used up to 24 weeks. There was no statistically significant difference in trough FEV1 between fluticasone furoate/vilanterol 100/25 micrograms and vilanterol 25 micrograms. It should be noted that the lower limit in the confidence interval of trough FEV1 is less than the 100 ml difference in FEV1 considered in the full NICE guideline on COPD to be the minimum clinically important difference. Dransfield et al demonstrated that fluticasone/ vilanterol 100/25mcg reduces the yearly rate of moderate to severe exacerbations compared to vilanterol 25mcg alone and the time to first moderate or severe exacerbation, but not the rate of exacerbations requiring admission to hospital.
- There is limited evidence comparing with available licensed inhaled therapy for COPD.
- Statistical analysis of safety data was not presented in any of the studies included in the NICE review, which limits the conclusions that can be drawn. Local corticosteroid effects, pneumonia (including pneumonia requiring admission to hospital) and non-traumatic fractures were seen more frequently with fluticasone furoate/vilanterol 100/25 micrograms than with vilanterol alone.
- Once daily administration may be attractive to many patients, but clinical relevance has not been demonstrated.
- The device is contained within a sealed foil pouch, once opened, the shelf life is 6 weeks, which increases the risk of patients using “expired” inhaler.
- Relvar is significantly cheaper than both Symbicort and Seretide inhalers.

Health gains

This is a once daily product and the available evidence indicates that the new combination product reduces yearly moderate –severe exacerbations of COPD, however, there was no reduction in hospital admissions.

Patient safety / pharmacovigilance

- Clinical study data has highlighted some emerging safety concerns with this product relating to
- Pneumonia (including hospital admission) and fractures which were reported more frequently with the combination product than vilanterol alone. Additionally concerns have been raised by clinical pharmacists (reporting in the Pharmaceutical Journal 19/02/14) to the fact that the licensed strengths of Relvar Ellipta (92µg/22µg and 184µg/22µg) are equivalent to medium to high doses of fluticasone propionate (500µg and 1,000µg, respectively). Importantly, steroid doses of this new combination product are not equivalent to fluticasone propionate, which potentially

introduces a risk of prescribing error.
When to stop treatment
• Adverse effects • Deterioration in COPD control
Who prescribes?
Relvar can be prescribed by hospital specialist, GPs or non-medical prescribers. It is suitable for initiation in primary or secondary care if a positive decision to commission the treatment is made and it is included in any local treatment pathway(s)
Stakeholder views
Equity of access

SPECIFICATION DATE, REVIEW DATE, AND LEAD NAME/JOB TITLE	
Origin Date: February 2014	Originator:
TAG Review Date:	Sue Watts/ Chris Ranson
TAG Recommendation Date: February 2014	

Impact on individual clinical commissioning groups

Prescribing data for alternative LABA/ICS combination inhalers for the time period of January'13 – December'13
Please note these inhalers will be used for both asthma and COPD.

Inhaler	CCG									
	ERY		HRW		HaRD		Hull		NEL	
	Items	Cost	Items	Cost	Items	Cost	Items	Cost	Items	Cost
Symbicort 200/6 Turbo	13586	£552975.96	9167	£363041.98	7597	£353115.18	23781	£968278.96	4352	£183500.82
Symbicort 400/12mcg Turbo	8232	£351375.74	7114	£318298.80	2980	£144222.35	8049	£364998.03	2511	£118122.18
Seretide Accuhaler 500/50mcg	13,554	£540,902.35	2,134	£89,970.41	2,454	£102,137.43	7,970	£329,834.22	8,913	£366,183.14

Inhaler	CCG							
	NL		SR		York		AWC	
	Items	Cost	Items	Cost	Items	Cost	Items	Cost
Symbicort 200/6 Turbo	7062	£264419.18	2436	£104135.04	10691	£525730.95	4831	£231043.44
Symbicort 400/12mcg Turbo	5905	£236374.50	1370	£63122.30	5466	£277034.07	3548	£184193.21
Seretide Accuhaler 500/50mcg	5,037	£196,806.11	1,590	£65,405.78	5,125	£231,826.22	5,889	£291,382.81