NHS
Vale of York
Clinical Commissioning Group

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

Drug, Treatment, Device name

Fluticasone furoate/vilanterol 92/22mcg and 184/22mcgs (Relvar GSK)

Licensed indication

Is indicated for adults and children 12 years and over as regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate:

- For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist. **Or**
- For patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist as single separate inhalers.

Cost per device (at recommended dose)

Dose	120 dose MDI	Low strength	Medium strength	High strength
30 1 OD	Fluticasone/vilanterol (Relvar dry powder)	Not available	92/22mcg £27.80	184/22mcg £38.87
120 2 BD	Fluticasone/ formoterol (Flutiform MDI)	50/5mcg £18.00	125/5mcg £29.26	250/10mcg £45.56
120 2 BD	Beclomethasone/ formoterol (Fostair MDI)	Not available	100/6mcg £29.32	Not available
120 2 BD	Fluticasone/ salmeterol (Seretide MDI)	50/25mcg £18	125/25mcg £35	250/25mcg £59.48
60 1 BD	Budesonide/ formoterol (Symbicort dry powder inhaler)	100/6mcg £33	200/6mcg £38	400/12mcg £38

Price taken from BNF online (Accessed 24/02/14)

Resource impact on population

There will no significant resource impact. Comparative costs are provided as a graphical representation on page 11.

Recommendation To be agreed following consultation

When is funding appropriate?

Fluticasone/vilanterol dry powder is not recommended as a treatment option when a LABA/ICS is indicated for the treatment of asthma until further data is available relating to efficacy and safety.

Clinical and cost effectiveness evidence

NICE TA 138: inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over. March 2008
http://publications.nice.org.uk/inhaled-corticosteroids-for-the-treatment-of-chronic-asthma-in-adults-and-in-children-aged-12-years-ta138/guidance

- For adults and children aged 12 years and older with chronic asthma in whom treatment with an inhaled corticosteroid (ICS) is considered appropriate, the least costly product that is suitable for an individual, within its marketing authorisation, is recommended.
- For adults and children aged 12 years and older with chronic asthma in whom treatment with an ICS and long-acting beta-2 agonist (LABA) is considered appropriate, the following apply.
  - The use of a combination device within its marketing authorisation is recommended as an option.
  - The decision to use a combination device or the two agents in separate devices should be made on an individual basis, taking into consideration therapeutic need and the likelihood of treatment adherence.
  - If a combination device is chosen then the least costly device that is suitable for the individual is recommended.

BTS and SIGN: British guideline on the management of asthma. May 2008 (revised 2011).
http://www.sign.ac.uk/pdf/qrg101.pdf

These guidelines advocate a stepwise approach to the management of asthma. For children over 5 years and adults, an ICS and LABA is considered at step 3 following failure to manage the condition with ICS and SABA. However, before starting a new drug or stepping up treatment, adherence with existing therapies, inhaler technique, and appropriate elimination of trigger factors should be confirmed.
It states that in efficacy studies, where there is generally good compliance, there is no difference in efficacy in giving inhaled steroid and a LABA in combination or in separate inhalers. In clinical practice, however it is generally considered that combination inhalers aid compliance and also have the advantage of guaranteeing that the long-acting B_2 agonist is not taken without the inhaled steroids.

RDTC New drug evaluation: Fluticasone furoate + vilanterol: for the treatment of Asthma
http://rdtc.nhs.uk/sites/default/files/publications/nde_131_relvar_0.pdf
Fluticasone furoate/vilanterol (Relvar®q, GSK) is a fixed dose combination of a corticosteroid and a long-acting beta-agonist available in two strengths and administered once-daily via a dry powder inhaler for treatment of asthma in adults and adolescents. The combination has been shown to be superior to fluticasone furoate alone. Limited data suggest that fluticasone furoate/vilanterol 92/22 once daily has comparable efficacy to fluticasone propionate/salmeterol 250/50 twice daily, and that adverse effects for both strengths may be comparable to those seen with fluticasone propionate 500mcg twice

daily. Once daily administration may be attractive to many patients, but clinical relevance has not been demonstrated. Fluticasone furoate/vilanterol has no other proven advantages over alternatives and there are no safety data beyond 52 weeks. Until more data are available, fluticasone furoate/vilanterol should not be routinely preferred to other more established combination inhalers for asthma.

Clinical Evidence
Bateman ED et al.
Once-daily fluticasone furoate (FF)/ vilanterol reduces risk of severe exacerbations in asthma versus FF alone.
Thorax 2013; 0:1-8
http://www.ncbi.nlm.nih.gov/pubmed/24253831

Objective: To evaluate the effect of the addition of a LABA, vilanterol, to a once daily ICS, fluticasone furoate, on the risk of severe asthma exacerbations in patients with uncontrolled asthma.

Methods: Patients aged≥ 12 years were eligible if they had a history of asthma defined as ≥ 1 year prior to screening , were using ICS at a dose of ≥ 200ug/day FP or equivalent or ICS/LABA at a dose of 200/100-500/100ug FP/salmeterol or equivalent for≥ 12 weeks prior to screening, and had ≥ 1 asthma exacerbation requiring systemic steroids and/or hospital/A+E admission in the previous year. Eligible patients had a best pre-bronchodilator forced expiratory volume in 1s (FEV1) of 50-90% predicted normal screening, and could demonstrate ≥12% and ≥200ml reversibility with inhaled salbutamol. This was a phase III randomised, multicentre, double-blind. Parallel-group study and patients were randomised to either FF/VI 92/22mcg (1 puff daily) or FF 100mcg (1 puff daily) for a minimum of 24 weeks and up to 78 weeks. The study was designed to finish after 330 events (patient's first on treatment severe exacerbation).

Primary outcome: Time to first severe asthma exacerbation.
Secondary end points: Rate of severe asthma exacerbations per patient per year and change in trough evening forced expiratory volume in 1s from baseline.

Results
2019 patients were randomised and included in the study.
The adjusted probability of experiencing a severe asthma exacerbation by 52 weeks was 15.9% (95% CI 13.5% to 18.2%) in the FF 100µg group and 12.8% (95% CI 10.7% to 14.9%) in the FF/ VI 100/25µg group. The HR for FF/VI 100/25µg vs FF 100µg was 0.795 (95% CI 0.642 to 0.985, p=0.036, adjusted for the interim analysis), representing a 20% risk reduction.
The rate of severe asthma exacerbations per patient per year was significantly lower in the FF/VI 100/25µg group than in the FF 100µg group (0.14 vs 0.19), a reduction in rate of 25% (95% CI 5% to 40%; p=0.014).
Trough FEV1 increased over the treatment period in both the FF and FF/VI treatment groups. FF/VI demonstrated statistically significant improvements over FF in trough FEV1, with adjusted mean changes of 83–95 mL (p<0.001).
Both treatments were well tolerated with similar rates of treatment related adverse events

and on-treatment serious adverse events.

O'Byrne PM et al.
Once-daily fluticasone furoate alone or combined with vilanterol in persistent asthma.
Eur Respir J. 2013 Oct 17.p1-16
http://www.ncbi.nlm.nih.gov/pubmed/24136330

Objective: Study objectives were to compare the efficacy and safety of once-daily FF/VI with FF alone and twice-daily fluticasone propionate (FP) in patients ≥12 years of age with moderate-to-severe persistent asthma**.**

Methods
The study enrolled asthma patients aged ≥12 years with documented use of ICS, with or without LABA, for ≥12 weeks with stable ICS dose (FP 500µg twice daily [or equivalent], or mid-dose ICS/LABA [FP/salmeterol 250/50µg twice daily or equivalent]) for ≥4 weeks. Eligible patients were required to demonstrate an evening pre-bronchodilator forced expiratory volume in 1 s (FEV1) of 40–90% of predicted normal and FEV1 reversibility of ≥12% and ≥200mL on inhalation of salbutamol. Patients were ineligible if they had a history of life-threatening asthma in the previous 10 years, an asthma exacerbation requiring overnight hospitalisation or emergency room attendance within 6 months of screening, and/or an asthma exacerbation requiring oral corticosteroids within 12 weeks of screening.
At randomisation, all eligible patients were required to have recorded asthma symptoms (equating to a score of ≥3 on the asthma symptom scale) and/or daily albuterol/salbutamol use on ≥4 of the 7 preceding days.
This phase III, randomised, multicentre, double-blind, double-dummy, parallel-group study. Patients were randomised (1:1:1) to FF/VI 200/25µg (representing an emitted dose of 184/22µg), FF 200µg once daily in the evening, or FP 500µg twice daily (morning and evening) for 24 weeks.
Primary outcomes: mean change from baseline in pre-dose (trough) FEV1 and weighted mean (wm) FEV1 (0–24h post-dose) after 24 weeks of treatment.
Secondary outcomes: mean change from baseline in the percentage of rescue-free 24-h 7 periods during the 24-week treatment period (a nominated powered endpoint), change from baseline in the percentage of symptom-free 24-h periods during the 24-week treatment period, and change from baseline in Total Asthma Quality of Life Questionnaire (AQLQ+12) score after 12 and 24 weeks of treatment.

Results
587 patients were randomised into the study.
Both trough FEV1 and 24-hour weighted mean FEV1 increased to a greater extent from baseline with fluticasone furoate/ vilanterol 184/22 compared with fluticasone propionate (FP) 500 micrograms twice daily via Accuhaler® or separate fluticasone furoate (FF) 184 micrograms once daily.

Difference (N = 587)	Trough FEV1 (95% CI)	24hour wmFEV1 (95% CI)
vs. FF	193 (108 - 277)	136 (1 - 270)
vs. FP	210 (127 - 294)	206 (73 - 339)

The percentage of rescue-free 24-h periods increased over the study with all therapies. The difference in improvement was significant for the comparison of FF/VI with FF, but not for FF/VI compared with FP. The number of additional rescue-free 24-h periods per week compared with baseline was 2.7 with FF/VI, 1.9 with FF, and 2.2 with FP.
On-treatment AEs were similar across treatment groups (46–50%). Nasopharyngitis (13–20%) and headache (6–8%) occurred most frequently. More patients withdrew from the study due to an Adverse Event in the FF/VI group (7 [4%]), compared with FF (3 [2%]) and FP (2 [1%]). The incidence of treatment-related AEs was greater with FF/VI (9%) and FP (8%) than FF (4%).

Woodcock A et al
Efficacy and safety of fluticasone furoate/ vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: A randomized trial.
Chest 2013;144:1222-29.

Objective: The aim of this study was to compare the efficacy of FF/VI with fluticasone propionate (FP)/salmeterol (SAL) in patients with persistent asthma uncontrolled on a medium dose of ICS.

Methods:
Patients aged 12 years with asthma were eligible if they could demonstrate a 12% and 200-mL reversibility of FEV 1 following albuterol inhalation at screening and had a best evening FEV 1 of 40% to 85% of the predicted normal value at screening and at randomization. 11 Before screening, patients had been taking ICS for 12 weeks, with a stable medium dose of ICS (FP 250 mg bid or equivalent) for 4 weeks.
This phase 3, multicenter, randomized, double-blind, doubledummy, parallel group study. Patients were randomised (1:1) to either FF/VI 100/25 m g (emitted dose, 92/22 m g) once daily in the evening, administered through an ELLIPTA dry powder inhaler (GlaxoSmithKline), or FP/SAL 250/50 m g bid (morning and evening) through DISKUS/ACCUHALER (GlaxoSmithKline) for 24 weeks.

Primary outcome: The primary efficacy measure was 0- to 24-h serial weighted mean (wm) FEV1 after 24 weeks of treatment.
Secondary outcomes: Individual serial FEV 1 assessments at week 24 (FEV 1 at each time point on day 168), time to onset of bronchodilator effect (the time point when FEV 1 first exceeded the 12% and 200-mL increase over baseline [taken from serial measurements]) at randomization visit only, 0- to 4-h serial wmFEV 1 postdose at the randomization visit

and at week 24, percentage of patients experiencing a 12% and 200-mL increase from baseline in FEV 1 at 12 and 24 h at week 24, and change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV 1 at week 24.

Results:

In a randomized, double-blind, double-dummy, parallel group study, 806 patients received FF/VI (100/25 mg, n 5 403) once daily in the evening delivered through ELLIPTA (GlaxoSmithKline) dry powder inhaler, or FP/SAL (250/50 mg, n 5 403) through DISKUS/ACCUHALER (GlaxoSmithKline).

Improvements from baseline in 0- to 24-h wmFEV1 were observed with both FF/VI (341 mL) and FP/SAL (377 mL); **the adjusted mean treatment difference was not statistically significant** (-37 mL; 95% CI, -88 to 15, P = 0.162). There were no differences between 0- to 4-h serial wmFEV1, trough FEV1, and asthma control and quality-of-life questionnaire scores. There was no difference in reported exacerbations between treatments. Both treatments were well tolerated, with no clinically relevant effect on urinary cortisol excretion or vital signs and no treatment-related serious adverse events.

Busse W et al

Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2 agonist vilanterol administered once daily for 52 weeks in patients >=12 years old with asthma: a randomised trial.

Thorax. 2013 Jun;68(6):513-20

http://www.ncbi.nlm.nih.gov/pubmed/23440247

OBJECTIVE: To assess the safety and tolerability of FF/VI over 52 weeks in patients with asthma.

METHODS: Patients (aged ≥12 years; on inhaled corticosteroid) were randomised (2:2:1) to FF/VI 100/25 µg or FF/VI 200/25 µg once daily in the evening, or fluticasone propionate (FP) 500 µg twice daily. Safety evaluations included adverse events (AEs), non-fasting glucose, potassium, 24-h urinary cortisol excretion, ophthalmic assessments, heart rate and pulse rate.

RESULTS: On-treatment AEs were similar across groups (FF/VI 66-69%; 73% FP). Oral candidiasis/oropharyngeal candidiasis was more common with FF/VI (6-7%) than FP (3%). Twelve serious AEs were reported; one (worsening hepatitis B on FP) was considered drug related. Statistically significant cortisol suppression was seen with FP compared with both FF/VI groups at Weeks 12 and 28 (ratios [95% CI] to FP ranged from 1.43 [1.11 to 1.84] to 1.67 [1.34 to 2.08]; p≤0.006), but not at Week 52 (ratios to FP were 1.05 [0.83 to 1.33] for FF/VI 100/25 µg and 1.09 [0.87 to 1.38] for FF/VI 200/25 µg). No clinically important changes in non-fasting glucose, potassium, QT interval corrected using Fridericia's formula (QTc[F]) or ophthalmic assessments were reported. Pulse rate (10 min post dose [Tmax], Week 52) was significantly increased with FF/VI versus FP (3.4 bpm, 95% CI 1.3 to 5.6; p=0.002 [FF/VI 100/25 µg]; 3.4 bpm, 95% CI 1.2 to 5.6; p=0.003 [FF/VI 200/25 µg]). Mean heart rate (24-h Holter monitoring) decreased from screening values in all groups (0.2-1.1 bpm FF/VI vs 5 bpm FP; Week 52).

Points for consideration

- Clinical trials have shown fluticasone furoate/ vilanterol to be superior fluticasone

furoate alone, which may be anticipated given comparison only with a steroid formulation.

- There is limited data to show that this new combination is noninferior to fluticasone propionate/salmeterol.
- Prescribers should be aware that in patients with asthma, potency of the new steroid product is NOT EQUIVALENT to fluticasone propionate, which presents a risk of error if introducing a new product to the current formulary.

Dose of fluticasone furoate	Approximate EQUIVALENT fluticasone propionate dose
100 micrograms ONCE daily	250 micrograms TWICE daily
200 micrograms ONCE daily	500 micrograms TWICE daily

- There is no low-dose inhaled corticosteroid version available and the 92µg/22µg strength, marketed as "low to mid dose of inhaled corticosteroid" is actually at the top of the dose-response curve in asthma. Consequently Relvar Ellipta is not appropriate for patients at Step 3 of the British Thoracic Society and Scottish Intercollegiate Guidelines Network asthma guidelines.
- Concerns have been flagged up by the UK Clinical Pharmacy Association Respiratory group that the blue cover on the inhaler and the brand name sounds similar to "reliever". This could cause patients mistakenly to use Relvar Ellipta on an "as needed" basis rather than regularly just once a day.
- The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the indication for asthma.
- Adverse effects of both strengths may be comparable to those seen with fluticasone propionate 500mcg twice daily. It should be noted that the comparator is a very high dose of ICS which is not commonly used in UK practice.
- There are currently four other ICS/LABA combination products available (Seretide, Symbicort, Fostair and Flutiform) which provide a range of doses and delivery device options. At present there is limited comparative data comparing Relvar to these therefore it is not possible to confirm any differences in efficacy and safety.
- Price comparisons for Relvar compared to alternatives is difficult as relative potency and dose equivalence has not been fully established (see cost comparison table at end of document)
- The device is contained within a sealed foil pouch, once opened, the shelf life is 6 weeks, which practically may pose a risk of patients using an "expired"inhaler
- Relvar is the only ICS/LABA combination licensed for once daily use. This may be attractive to some patients but there is no evidence that demonstrates improved clinical outcomes.
- Relvar is licensed for both asthma and COPD. This specification considers the evidence for asthma only.

Health gains	
Equivalent gains expected to the separate reference corticosteroid and long-acting beta2-agonist as it has demonstrated clinical non-inferiority to combination product.	
Patient safety / pharmacovigilance	
• FEV 1 • Asthma exacerbations • Adverse effects	
When to stop treatment	
• Adverse effects • Deterioration in asthma 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 where a positive recommendation is made to commission the treatment	
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 current alternative LABA/ICS combination inhalers prescribed for the time period of January'13 – December'13
Please note these inhalers will be used for both asthma and COPD.

	CCG									
Inhaler	**ERY**		**HRW**		**HaRD**		**Hull**		**NEL**	
	Items	**Cost**	**Items**	**Cost**	**Items**	**Cost**	**Items**	**Cost**	**Items**	**Cost**
Flutiform 50/5mcg	46	£764.73	7	£116.31	14	£232.63	35	£581.88	31	£515.56
Flutiform 125/5mcg	1085	£29,637.89	49	£1,404.71	102	£2,944.85	216	£6,052.91	91	£2,513.23
Flutiform 250/5mcg	1120	£47,956.36	68	£2,901.99	79	£3,533.13	150	£6,520.17	16	£673.13
Symbicort 100/6mcg Turbo	2238	£77589.83	624	£21271.18	743	£30016.16	2706	£91251.19	642	£21334.33
Symbicort 200/6mcg Turbo	13586	£552975.96	9167	£363041.98	7597	£353115.18	23781	£968278.96	4352	£183500.82
Symbicort 400/12mcg Turbo	8232	£351375.74	7114	£318298.8	2980	£144222.35	8049	£364998.03	2511	£118122.18
Fostair 100/6mcg	10,893	£323,469.12	891	£26,262.82	581	£18,954.82	6,006	£183,951.25	2731	£82,483.46
Seretide MDI 50/25mcg	3,765	£71,830.85	973	£17,591.32	1112	£23,144.00	3,883	£77,074.43	2307	£44,831.23
Seretide MDI 125/25mcg	10,791	£390,686.86	2818	£103,522.88	5,512	£228,964.28	9,646	£359,606.43	6111	£232,277.91
Seretide MDI 250/25mcg	13,943	£827,586.24	4,030	£250,333.59	7,023	£459,535.62	13,477	£843,000.43	7,016	£437,650.17
Seretide Accuhaler 100/50mcg	2,960	£59,090.92	343	£6,799.66	753	£15,146.86	2732	£54,808.04	1577	£29,699.07
Seretide Accuhaler 250/50mcg	4,975	£192,182.48	802	£32,771.84	1788	£70,717.61	1,981	£212,466.47	3053	£113,458.53
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
Flutiform 50/5mcg	6	£99.76	11	£199.45	18	£299.36	0	£0.00
Flutiform 125/5mcg	169	£4,782.29	167	£4,511.68	59	£1,756.56	6	£270
Flutiform 250/5mcg	382	£17,162.95	153	£6,688.44	79	£3,365.73	26	£1,304.22
Symbicort 100/6mcg Turbo	1104	£35657.21	505	£19499.72	1622	£64940.34	677	£28555.96
Symbicort 200/6mcg Turbo	7062	£264419.18	2436	£104135.04	10691	£525730.95	4831	£231043.44
Symbicort 400/12mcg Turbo	5905	£236374.5	1370	£63122.3	5466	£277034.07	3548	£184193.21
Fostair 100/6mcg	3913	£109,338.25	580	£18,546.82	2,922	£100,342.59	436	£19,089.55
Seretide MDI 50/25mcg	2102	£37,116.08	1042	£19,718.65	3,012	£62,399.94	2502	£58,841.88
Seretide MDI 125/25mcg	6,376	£217,505.82	4,346	£155,980.25	9,960	£423,898.86	5,849	£249,819.28
Seretide MDI 250/25mcg	12,089	£694,908.63	8,012	£504,454.16	18,232	£1,303,757.95	9,748	£692,420.18
Seretide Accuhaler 100/50mcg	1,973	£36,131.78	643	£11,606.06	1390	£30,975.76	1348	£33,153.25
Seretide Accuhaler 250/50mcg	3,636	£129,550.97	1473	£55,268.02	3,031	£138,012.05	2,604	£115,906.85
Seretide Accuhaler 500/50mcg	5,037	£196,806.11	1,590	£65,405.78	5,125	£231,826.22	5,889	£291,382.81

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Annual data providing comparative costs of asthma inhaler choices – source Regional Drug & Therapeutics New Drug Evaluation fluticasone furoate + vilanterol No.131 Jan 14