New drugs

Fluticasone furoate with vilanterol

Approved indications: asthma, chronic obstructive pulmonary disease

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100/25 microgram, 200/25 microgram powder for inhalation

Australian Medicines Handbook section 19.1

In asthma a long-acting beta agonist can be added to treatment if an inhaled corticosteroid is insufficient to control the patient's symptoms. Inhaled corticosteroids can be added to long-acting beta agonists to try and reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD). Fluticasone propionate is already available in combination with salmeterol for both conditions, so the combination of fluticasone furoate with vilanterol trifenatate is just another option for delivering a corticosteroid and a long-acting beta agonist by inhalation. These combinations have anti-inflammatory effects and relax bronchial smooth muscle.

A specific device is needed to inhale the powder formulation. Following inhalation, some of the dose is absorbed through the lung into the systemic circulation. The subsequent metabolism of both drugs includes cytochrome P450 (CYP) 3A4. Vilanterol has a half-life of 2.5 hours with most of its metabolites being excreted in the urine, while fluticasone has an elimination half-life of 24 hours with most of its metabolites being excreted in faeces. No dose reduction is needed in renal impairment, but in moderate or severe hepatic impairment the maximum dose is limited to fluticasone furoate 100 microgram and vilanterol 25 microgram.

Efficacy

There have been multiple studies of the combination in more than 17 000 patients. These have established the usual dose of fluticasone furoate/vilanterol to be 100/25 microgram once daily. Some patients with asthma will need 200/25 microgram, but this dose is not indicated in patients with COPD.

Asthma

The efficacy of the combination was compared with fluticasone products in patients with persistent asthma. These patients were at least 12 years old and had a forced expiratory volume in one second (FEV_1) that was 40–90% of the predicted value. Following a run-in period, 197 patients were randomised to use the combination (200/25 microgram daily), 194 inhaled fluticasone furoate (200 microgram daily) and 195 inhaled fluticasone propionate (500 microgram twice daily). The mean pre-dose (trough) FEV_1 at baseline was 2.153 L. After 24 weeks this had improved by 394 mL with the combination, by 201 mL with fluticasone furoate and by 183 mL with fluticasone propionate. The combination of fluticasone furoate and vilanterol therefore had a significantly greater effect on lung function than fluticasone alone.[1]

Another trial studied the effect of the combination on exacerbations of asthma. The 2020 adolescents and adults in the study had FEV_1 values that were 50–90% of their predicted value, and a history of at least one exacerbation in the previous year. They were randomised to receive fluticasone furoate/vilanterol 100/25 microgram or fluticasone furoate 100 microgram daily. At least one severe exacerbation occurred in 340 patients. At one year, the risk of having an exacerbation was reduced by 20% in the patients inhaling the combination.[2]

The combination of fluticasone furoate and vilanterol (100/25 microgram) has been compared with the combination of fluticasone propionate and salmeterol (250/50 microgram). After a run-in period, 806 patients, with FEV_1 40–85% of the predicted value, were randomised to inhale the drugs for 24 weeks. The mean FEV_1 increased by 341 mL with the vilanterol combination and by 377 mL with the salmeterol combination. This difference is not statistically significant and there was also no difference in asthma control or exacerbations.[3]

Chronic obstructive pulmonary disease

Two placebo-controlled, parallel group trials studied different doses of fluticasone furoate and vilanterol in patients with COPD. These patients were at least 40 years old, had a smoking history of at least 10 pack-years and an FEV_1 that was 70% or less than the predicted value after using a bronchodilator. In addition to the different doses of the combination, both trials had arms which included fluticasone furoate alone and vilanterol alone.[4,5]

The first trial randomised 1030 patients. After 24 weeks the mean trough FEV_1 had increased by 33 mL with fluticasone furoate and by 67 mL with vilanterol, compared to placebo. The 100/25 microgram combination increased trough FEV_1

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

by 115 mL more than placebo. This combination also significantly increased the mean FEV_1 in the four hours following the inhalation (see Table).[4]

The second trial randomised 1224 patients. Compared to placebo, the trough FEV_1 increased by 44 mL with fluticasone furoate, 100 mL with vilanterol and by 144 mL with the 100/25 microgram combination. After 24 weeks this combination had also increased the mean FEV_1 in the four hours following the inhalation (see Table).[5]

Another two trials in similar groups of patients assessed the effect of vilanterol 25 microgram and different doses of the combination on exacerbations. These patients had a history of at least one exacerbation in the previous year. The first study randomised 1622 patients and the second study randomised 1633. A pooled analysis after one year showed that 48.9% of the patients taking vilanterol and 41.9% of those taking the 100/25 microgram combination had an exacerbation. This combination also significantly reduced the rate of moderate and severe exacerbations.[6]

Safety

In addition to data from the clinical trials, the safety of fluticasone furoate and vilanterol has been investigated in safety studies. One study followed 503 patients with asthma for a year. One hundred patients took fluticasone propionate and the remainder took the 100/25 or 200/25 microgram combination. The most frequent adverse effects in all groups were headache, upper respiratory tract infection and nasopharyngitis.[7] This reflects the observations seen in the clinical trials in asthma and COPD. Oral candidiasis was the most frequent treatment-related adverse effect. A few cases of dysphonia and extrasystoles were seen with the combination, but not with fluticasone propionate.[7] Inhaling a beta agonist can increase the pulse rate.

Combinations containing fluticasone furoate initially had less effect than fluticasone propionate on 24-hour urinary cortisol, but by 52 weeks there was no significant difference between the treatments.[7] In patients with COPD there were more fractures with the combination than in patients taking vilanterol alone. There were also more cases of pneumonia, some of which were fatal. The incidence of pneumonia was 6–7% with the combination compared to 3% in patients taking vilanterol alone.[6] In the trial which compared the combination to fluticasone propionate/salmeterol there was no significant difference in adverse effects.[3]

Conclusion

The studies show that the combination of fluticasone furoate and vilanterol has more effect on lung function than its individual components given alone. These differences were not always statistically significant. While the combination reduces exacerbations, the absolute reduction is small. In asthma the rate of severe exacerbations was

Table **Efficacy of fluticasone furoate/vilanterol combination in COPD**

	Fluticasone furoate 100 microgram	Vilanterol 25 microgram	Fluticasone furoate/vilanterol 100/25 microgram
Study 1 [4]			
Number of patients	206	205	206
Baseline trough FEV_1	1.166 L	1.285 L	1.246 L
Change compared to placebo at 24 weeks			
trough FEV_1	33 mL	67 mL	115 mL
mean FEV_1 (0–4 hours post-dose)	53 mL	103 mL	173 mL
Study 2 [5]			
Number of patients	204	203	204
Baseline trough FEV_1	1.412 L	1.371 L	1.357 L
Change compared to placebo at 24 weeks			
trough FEV_1	44 mL	100 mL	144 mL
mean FEV_1 (0–4 hours post-dose)	46 mL	185 mL	214 mL

FEV_1 forced expiratory volume in one second

0.14/patient/year with 100/25 microgram, compared with 0.19/patient/year with fluticasone furoate 100 microgram.[2] In COPD the rate of severe exacerbations was 0.09/year with the combination and 0.1/year with vilanterol 25 microgram.[6]

At the time of writing, neither fluticasone furoate nor vilanterol was available separately in Australia. This means that patients cannot have their doses individually titrated and then be changed to the combination. It would be inappropriate to start treating asthma or COPD with this combination. This means patients who are prescribed the combination are likely to be switching from other drugs. The comparative study in asthma suggests that fluticasone furoate/vilanterol 100/25 microgram once daily is similar to fluticasone propionate/salmeterol 250/50 microgram twice daily.[3] A once-daily dose may help some patients adhere to their treatment. The fluticasone furoate/vilanterol combination is not indicated for treating acute symptoms, so patients will still need a short-acting beta agonist. It is also not approved for treating asthma in children less than 12 years old.

T manufacturer provided the product information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)