fluticasone furoate, 27.5 micrograms /actuation nasal spray (Avamys®) No. (544/09)

GlaxoSmithKline

06 March 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fluticasone furoate (Avamys®) is accepted for use within NHS Scotland for the treatment of the symptoms of allergic rhinitis in adults, adolescents (12 years and over) and children (6 to 11 years).

Evidence to support its efficacy comes from a number of comparator- and placebo-controlled studies conducted in adults and children with seasonal and perennial allergic rhinitis.

Prescribers should be aware that the recommended doses of fluticasone furoate are not equivalent, on a microgram per microgram basis, to other fluticasone nasal sprays currently available.

Other intranasal steroids are available at a lower cost.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of the symptoms of allergic rhinitis in adults, adolescents (12 years and over) and children (6 to 11 years).

Dosing information

Adults and Adolescents (12 years and over)

The recommended starting dose is two spray actuations (27.5micrograms of fluticasone furoate per spray actuation) in each nostril once daily (total daily dose, 110micrograms). Once adequate control of symptoms is achieved, dose reduction to one spray actuation in each nostril (total daily dose 55micrograms) may be effective for maintenance.

Children (6 to 11 years of age)

The recommended starting dose is one spray actuation (27.5micrograms of fluticasone furoate per spray actuation) in each nostril once daily. Patients not adequately responding to one spray actuation in each nostril once daily may use two spray actuations in each nostril once daily. Once adequate control of symptoms is achieved, dose reduction to one spray actuation in each nostril once daily is recommended.

Product availability date

29 January 2009

Summary of evidence on comparative efficacy

Fluticasone furoate is a highly selective intranasal steroid available as an aqueous suspension for the treatment of allergic rhinitis. Although structurally related to fluticasone propionate it has different pharmacology. Efficacy data were provided from 15 randomised double-blind studies. Nine efficacy studies recruited adult patients with seasonal allergic rhinitis (SAR), of which six were placebo-controlled (two with an active control arm), and three had active comparators (two versus an oral antihistamine and one versus fluticasone propionate nasal spray [FPNS]). Four efficacy studies (one of which included an active comparator arm, mometasone furoate) recruited adult patients with perennial allergic rhinitis (PAR). Paediatric data were provided from one placebo-controlled trial in SAR and one in PAR. All included patients allocated to fluticasone furoate nasal spray (FFNS) at licensed doses.

All patients were required to have a documented history of SAR or PAR, based on clinical history of nasal allergy symptoms and immunological evidence, to have adequate exposure to relevant antigen(s) and to be symptomatic at the time of randomisation according to symptom-score criteria which differed between studies. The primary efficacy outcome was based on patients' assessment of nasal symptoms in all studies comparing change from baseline between treatment arms. Ocular symptoms and disease-specific quality of life measures were also assessed in most studies.

One active-comparator study randomised adult SAR patients to FFNS 110micrograms daily or matching placebo and to FPNS 100micrograms twice daily or matching placebo for two weeks. The design was double-blind for the active-placebo comparisons but allocation between the active treatment arms was blinded to investigators only (because of practical dosing concerns). The primary outcome was change from baseline in a Total Nasal Symptom Score defined as the sum of three individual 4-point symptom scores for sneezing, rhinorrhoea and nasal congestion (3TNSS). Each was scored from 0 = no symptom to 3 = severe, giving a maximum score of 9. Most other trials used a four-item score (4TNSS)

which also assessed nasal itching and gave a maximum score of 12. As in other trials the primary assessment of TNSS was reflective (rTNSS - reflecting symptoms over the previous 12 hours) rather than instantaneous (iTNSS - at the time of assessment).

In the active-comparator trial non-inferiority would be concluded if the upper limit of the 97.5% one-sided confidence interval in the per-protocol population did not exceed 0.75 for the difference in change from baseline in r3TNSS comparing FFNS and FPNS. The adjusted mean reduction from baseline was 1.06 for FPNS and 1.23 for FFNS representing a difference of 0.173 (95% confidence intervals: -0.51 to 0.17), verifying the non-inferiority of FFNS. No baseline values were given. A significant reduction from placebo was observed at day 1 with FFNS and at day 2 with FPNS. Changes in 4TNSS were similar to those in 3TNSS. No outcomes relating to ocular symptoms or quality of life were reported in this trial.

Two active-controlled SAR trials showed significantly greater reductions in reflective and instantaneous nasal symptom scores for FFNS compared with oral fexofenadine 180mg once daily as well as greater improvements in overall scores from the Rhinitis Quality of Life Questionnaire and ocular symptom scores. FFNS was also significantly superior to placebo for these measures across a range of trials.

In PAR, one open-label, active-controlled 52-week study was primarily a safety trial investigating the nasal morphology and cytology of patients receiving FFNS 110micrograms daily and mometasone furoate nasal spray (MFNS) 200micrograms daily. Daily rTNSS (assessed primarily as a measure of compliance) was reduced with FFNS by 3.6 from a baseline of 6.2 and with MFNS by 3.8 from a baseline of 6.6 representing a treatment difference of 0.2. No other efficacy or quality of life outcomes were reported.

In two patient-preference studies with the same design a significantly greater proportion of patients with SAR expressed preference for FFNS than for FPNS for the primary endpoint of scent/odour sensory attribute as well as for secondary endpoints of leaking out of nose/down throat, gentleness of mist, and reduced aftertaste. For both studies there were no significant differences between FFNS and FPNS for delivery of consistent amount of medication and comfort of the nose tip.

Two placebo-controlled studies were conducted in children less than 12 years of age. In a two-week study including patients with SAR there was a significant difference for FFNS 110micrograms daily but not FFNS 55micrograms daily versus placebo for the primary endpoint of rTNSS. In a 12-week study of PAR patients, both FFNS 55micrograms daily and FFNS 110micrograms daily were significantly superior to placebo for iTNSS. For the primary outcome, rTNSS, the difference was significant for 55micrograms daily but not 110micrograms daily. There were no significant differences for ocular symptoms in the study of SAR patients.

Summary of evidence on comparative safety

In the comparative open-label safety study in patients with PAR described previously, the overall incidence of adverse events (AEs) was comparable between FFNS and MFNS. The most common AEs reported during the treatment period were pharynolaryngeal pain, epistaxis, nasopharyngitis and headache. Most of the incidences of these events were mild to moderate in intensity and had recovered or resolved by end of treatment. In one subject in the MFNS group, nasopharyngitis was of severe intensity.

In the comparative trial versus FPNS in patients with SAR, all AEs occurred with a similar incidence in the treatment and placebo groups and were mild or moderate in intensity.

In an integrated safety analysis of six trials in SAR/PAR, AEs that occurred more commonly in the FFNS 110micrograms group than in the placebo group were headache, epistaxis, pharyngolaryngeal pain, back pain and nasal septum ulceration. However, the difference in the incidence of these events between FFNS 110micrograms group and placebo was 2% or less for each of these individual adverse events.

In three pooled paediatric studies the majority of AEs were mild to moderate in intensity. Pyrexia was reported more frequently in the FFNS groups than with placebo. There were no reports of severe epistaxis.

Two clinical studies assessed hypothalamic-pituitary-adrenal (HPA) axis function over six weeks and suggested a very low potential for AEs related to HPA axis function with FFNS.

Summary of clinical effectiveness issues

The comparative study of FFNS versus FPNS in SAR was conducted in Japanese patients in the cedar pollen season. The primary analysis of the trial was a non-inferiority analysis and the EMEA notes that non-inferiority trials are not possible in SAR/PAR due to lack of sensitivity in outcome measures. In PAR, the comparative study versus MFNS was primarily a safety study and was not designed to detect treatment differences in efficacy outcomes. FFNS has been studied at starting doses but not at the lower maintenance doses. These factors may influence the generalisability of these studies.

It should be noted that the EMEA's European Public Assessment Report of fluticasone furoate does not present evidence from any head to head or active comparator efficacy trials, suggesting that the efficacy of FFNS was concluded on the basis of placebo-controlled trials. The EMEA comments that treatment effects relating to nasal symptoms in SAR were in the range expected with marketed products that are effective for allergic rhinitis and that those relating to ocular symptoms were in the range expected for oral antihistamines used in clinical practice. In PAR, the nasal treatment effects were considered within the range expected for an intranasal corticosteroid currently used in clinical practice.

Summary of comparative health economic evidence

The economic evaluation was a simple cost-minimisation analysis comparing fluticasone furoate nasal spray and beclometasone dipropionate, fluticasone propionate and mometasone furoate - the three most frequently used intranasal steroid products for allergic rhinitis in Scotland. An assumption was made of equal clinical efficacy based on comparative trials for fluticasone furoate versus fluticasone propionate in adult SAR and mometasone furoate in adult PAR, and an indirect comparison based on a systematic review of the comparator intranasal steroids. A comparison of drug cost based on 30-day maintenance therapy once symptoms were controlled estimated a cost per patient of £3.22 for fluticasone furoate compared to £1.73, £4.38, and £3.36 for beclometasone dipropionate, fluticasone propionate and mometasone furoate respectively. Displacing each of the comparators proportionate to their use in Scotland was estimated to result in minor cost savings.

The economic analysis was simple and transparent. However, this was associated with some limitations. The evidence supporting the assumption of equal clinical efficacy was limited in children and in comparisons with beclometasone dipropionate. In addition, the comparative clinical evidence for fluticasone furoate was based on the higher starting drug

doses used to alleviate symptoms and so there was no direct evidence supporting an assumption of equal efficacy in lower dose maintenance therapy, which was the focus of the economic analysis. The cost comparison did not take account of the costs of the higher initial recommended doses for each intranasal steroid, or possible differences in doses associated with SAR and PAR or between adults/adolescents and children. However, it is unlikely these considerations would significantly impact on the relative costs of fluticasone furoate and the comparator drug therapy.

Accepting the assumption of equal efficacy, the base case and sensitivity analysis demonstrated that fluticasone furoate could result in modest drug cost savings compared to fluticasone propionate and mometasone furoate, but higher costs than beclometasone dipropionate.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Alternative nasal preparations include other corticosteroid nasal sprays (e.g. beclometasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate and triamcinolone acetonide), antihistamine nasal spray (azelastine) or sodium cromoglicate.

Cost of relevant comparators

Drug	Dose regimen (for adults)	Cost per 28 days (£)
Fluticasone furoate nasal spray (Avamys®)	**Two sprays (55micrograms) into each nostril daily**	**6**
Sodium cromoglicate 4% (Rynacrom®)*	One spray into each nostril daily 2 to 4 times daily	18 per 22ml*
Sodium cromoglicate 2% (Vividrin®)*	One spray into each nostril daily 4 to 6 times daily	10 per 15ml*
Fluticasone propionate nasal spray (Flixonase®)	Two sprays (100micrograms) into each nostril daily	9
Azelastine nasal spray (Rhinolast®)	One spray (140micrograms) into each nostril twice daily	8
Triamcinolone acetonide nasal spray (Nasacort®)	Two sprays (110micrograms) into each nostril daily	7
Fluticasone propionate nasal spray (Nasofan®)	Two sprays (100micrograms) into each nostril daily	7
Mometasone furoate nasal spray (Nasonex®)	Two sprays (100micrograms) into each nostril daily	6
Flunisolide nasal spray (Syntaris®)	Two sprays (50micrograms) into each nostril twice daily	5
Budesonide nasal	Two sprays (128micrograms) into each	4

spray (Rhinocort®)	nostril daily	
Budesonide nasal spray	Two sprays (200micrograms) into each nostril daily	3
Beclometasone dipropionate nasal spray	Two sprays (100micrograms) into each nostril twice daily	2

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 07 January 2009 and based on the adult starting doses. * Costs for sodium cromoglicate are quoted for one spray unit. Budesonide is not licensed for children < 12 years.

Additional information: budget impact

The manufacturer estimated net savings of £402 in year one based on 2,963 patients with allergic rhinitis being treated with fluticasone furoate nasal spray, rising to net savings of £1,660 in year five based on 12,780 patients being treated. The budget impact estimates are based on an estimated total eligible population of 81,000 patients currently treated with an intranasal steroid and fluticasone furoate displacing 3% and 6% of the current market share of beclometasone dipropionate, fluticasone propionate and mometasone furoate in 2009 in PAR and SAR respectively (rising to 11% and 27% respectively in 2013). If only fluticasone propionate and mometasone furoate are displaced the estimated savings are £15K in year one, rising to £60K in year five.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 13 February 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Okubu K, Nakashima MD, Miyake N et al. Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis. Allergy and asthma proceedings 2008; Accepted for publication.

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Meltzer EO, Lee J, Tripathy I et al. Efficacy and safety of once daily fluticasone furoate nasal spray in children with seasonal allergic rhinitis treated for 2 wk. Pediatr Allergy Immunol 2008.

Maspero JF, Rosenblut A, Finn A et al. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. Otolaryngol Head Neck Surg 2008; 138(1):30-37.

The European Medicines Agency (EMEA) European Public Assessment Report. Fluticasone furoate (Avamys®). 2008, EMEA H-770-en6. www.emea.europa.eu