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Fluticasone Furoate

Intranasal Use in Allergic Rhinitis

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Contents

Abstract

▲ Fluticasone furoate nasal spray is a new topical intranasal corticosteroid with enhanced affinity for the glucocorticoid receptor and low systemic exposure, which was recently approved in the US for the treatment of seasonal or perennial allergic rhinitis in adults and in children aged ≥2 years.

▲ Fluticasone furoate nasal spray employs a novel delivery device with a unique side-actuated design, a short nozzle and a new trigger mechanism designed for ease of use.

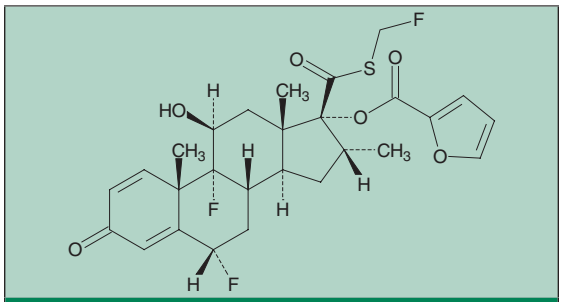
▲ In well controlled clinical trials, intranasal fluticasone furoate 110μg once daily for 2 weeks in adults and adolescents with seasonal allergic rhinitis reduced nasal and ocular symptoms, and improved health-related quality of life to a significantly greater extent than placebo.

▲ Similarly, treatment with intranasal fluticasone furoate 110μg once daily for 4–6 weeks in adults and adolescents with perennial allergic rhinitis was superior to placebo in reducing nasal symptoms and with respect to overall response to therapy.

▲ In children aged 6–11 years, fluticasone furoate nasal spray was shown to be effective in reducing the nasal symptoms of seasonal and perennial allergic rhinitis following treatment for 2 and 4 weeks, respectively.

▲ Fluticasone furoate nasal spray was well tolerated in adults, adolescents and children aged 2–11 years, with an overall incidence of adverse events similar to that with placebo.

Features and properties of fluticasone furoate (GW685698X; Veramyst™; Avamys™)	
Indication	
Seasonal or perennial allergic rhinitis	
Mechanism of action	
Glucocorticoid receptor agonist producing anti-inflammatory activity	
Dosage and administration	
Recommended starting dose in adults and adolescents	110μg
Recommended starting dose in children	55μg
Route	Intranasal (topical spray)
Frequency	Once daily
Pharmacokinetic profile (single- or multiple-dose intranasal, oral or intravenous administration in healthy male or female adult volunteers)	
Absolute bioavailability (880μg intranasally 8-hourly for 10 doses)	0.5%
Oral bioavailability (2mg single oral dose)	1.26%
Elimination half-life (single intravenous dose)	15.1h
Most common adverse events (incidence >1% in adults/adolescents or >3% in children, and with a higher frequency than with placebo)	
Headache, epistaxis, nasopharyngitis, pyrexia, pharyngolaryngeal pain, nasal ulceration, cough, back pain	



Fluticasone furoate

Allergic rhinitis is a very common disease affecting up to 30% of the general population.[1,2] Of the two most common forms, seasonal allergic rhinitis (hayfever) is usually caused by allergy to airborne plant pollens, while perennial allergic rhinitis is generally caused by allergy to house dust mites, animal dander or mould spores.[1,3] Allergic rhinitis is now more commonly classified as intermittent or persistent, rather than seasonal or perennial.[4] Allergic rhinitis is not a life-threatening disease, but it can dramatically reduce patients' quality of life, and may have an impact on patients' careers and reduce academic performance in students.[1,3,5] It is frequently associated with, and may lead to, more severe disease, such as asthma or otitis media.[2,3,6] Nasal symptoms (rhinorrhoea, blockage, itching and sneezing) are often accompanied by symptoms involving the eyes (allergic conjunctivitis), throat and ears.[2]

Intranasal corticosteroids provide potent anti-inflammatory activity locally at the nasal mucosa, while limiting systemic corticosteroid exposure.[1,6] They are the preferred first-line agents for controlling the nasal symptoms of persistent or moderate to severe intermittent allergic rhinitis,[7] especially where nasal obstruction is the main symptom.[1,6]

Fluticasone furoate (GW685698X) is a new topical corticosteroid with high affinity for the glucocorticoid receptor, which is being developed as a nasal spray (Veramyst™; Avamys™)[1] for the treatment of seasonal and perennial allergic rhinitis. This article reviews the pharmacological properties, therapeutic efficacy and tolerability of fluticasone furoate nasal spray in adults and children with seasonal or perennial allergic rhinitis.

1. Device Design Characteristics

- The nasal spray delivery device for use with fluticasone furoate has a unique side-actuated design and a short nozzle that together minimise movement of the nozzle in the nose during actuation and make it easier for care-givers to administer the medication (see figure 1).[8]
- A new trigger mechanism minimises potential variation in the dose delivered (27.5μg per actuation for the standard strength preparation)[9] and the pressure required to actuate the trigger (20–40N) makes the device suitable for use in young children aged 2 years and in the elderly.[8]
- The device delivers a low volume (50μL) of the aqueous formulation as a fine mist, which minimises the amount of liquid available to run down the back of the patient's throat or drip from the nostrils.[8]

2. Pharmacodynamic Profile

- Fluticasone furoate is a synthetic, lipophilic, trifluorinated glucocorticoid receptor agonist containing a 17α-furoate ester.[10] Its exact mechanism of action in allergic rhinitis is unknown, but is believed to relate to the potent anti-inflammatory activities of the corticosteroid.
- *In vitro* binding studies demonstrated that fluticasone furoate rapidly associated with the glucocorticoid receptor from human lung tissue and dissociated slowly compared with dexamethasone, and had higher receptor affinity than other commonly used corticosteroids.[10] The equilibrium dissociation constant (K_d) of fluticasone furoate was 0.3 nmol/L compared with 8.8 nmol/L for dexamethasone. The relative receptor affinity (RRA) of fluticasone furoate was 2989 (with reference to dexamethasone [RRA = 100]) compared with RRA values of 2244, 1775, 1345, 1212 and 855 for mometasone furoate, fluticasone propionate, beclomethasone-17-mono-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

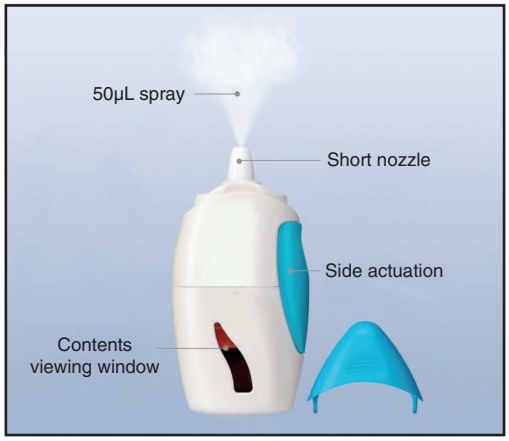


Fig. 1. Design characteristics of the fluticasone furoate nasal spray device.

propionate, ciclesonide active principle and budesonide, respectively.[10]

- Fluticasone furoate displayed greater potency than other corticosteroids in inhibiting tumour necrosis factor (TNF)-induced, nuclear factor κB-mediated alkaline phosphatase release from human lung epithelial cells (50% inhibitory concentration [IC_{50}] of 25 pmol/L vs 33 pmol/L for fluticasone propionate, 40 pmol/L for mometasone furoate and 185 pmol/L for budesonide and ciclesonide active principle).[11] It was also more potent in inhibiting lipopolysaccharide-induced TNF release from peripheral blood mononuclear cells (IC_{50} = 0.15 nmol/L) than fluticasone propionate (0.24 nmol/L), ciclesonide active principle (4.1 nmol/L) and budesonide (5.6 nmol/L).[11]

- Fluticasone furoate was ≈10-fold more potent than either fluticasone propionate or mometasone furoate in preventing damage to cultured human lung epithelial cells induced by elastase and was approximately 2- to 22-fold more potent than fluticasone propionate, mometasone furoate or budesonide in preventing mechanical damage to these cells.[12]

- In a rat model of allergen (ovalbumin)-induced lung inflammation, fluticasone furoate completely prevented lung eosinophilia at an intra-tracheal dose of 100μg and displayed numerically greater anti-inflammatory potency than fluticasone propionate.[12]

- Fluticasone furoate induced faster translocation of the glucocorticoid receptor into the nucleus of cultured monkey COS-1 cells than did fluticasone propionate.[12] Fluticasone furoate displayed high selectivity for the glucocorticoid receptor *in vitro*; the effect of fluticasone furoate on the human glucocorticoid receptor-mediated nuclear factor-κB pathway was 38-fold more potent than activation of the progesterone receptor, 794-fold more potent than its effect on the mineralocorticoid receptor and >300 000-fold greater than its effect on the androgen or estrogen receptor.[12]

- In adult male patients with seasonal allergic rhinitis (n = 59), treatment with intranasal fluticasone furoate 200μg once daily for 8 days outside the grass pollen season significantly ($p < 0.05$) reduced the nasal and ocular symptoms of rhinitis compared with placebo after challenge with grass pollen for 4 hours conducted at two timepoints after the last dose (1–5 hours and 22–26 hours).[13] Relative to placebo, total nasal symptom scores were reduced by 4.14 points at 1–5 hours and 3.63 points at 22–26 hours in recipients of fluticasone furoate.[13]

- Treatment for 6 weeks with fluticasone furoate nasal spray 110μg once daily had no effect on the hypothalamic-pituitary-adrenal axis in children (aged 2–11 years)[14] or adolescents and adults (aged 12–65 years)[15] with perennial allergic rhinitis. Mean serum cortisol ratios from baseline at 6 weeks (i.e. week 6 **:** baseline values) were similar between recipients of fluticasone furoate and placebo (0.94–0.97 vs 0.98–0.99).[14,15] The treatment ratios (active **:** placebo) were 0.97 for children[14] and 0.98 for adolescents/adults[15] compared with 0.49 for a control adult subgroup administered prednisone 10 mg/day for the last 7 days.[15]

- Fluticasone furoate nasal spray 110μg once daily for 2 weeks was noninferior to placebo with respect to effects on lower-leg growth rate assessed by knemometry in children (aged 6–11 years) with allergic rhinitis (n = 58).[16] Mean lower-leg growth rates in recipients of fluticasone furoate and placebo were 0.40 and 0.42 mm/week in the per-protocol

population (n = 53). The treatment difference was −0.016 mm/week with a 95% confidence interval of −0.13 to +0.10, the lower bound of which was within the prespecified noninferiority margin of −0.20 mm/week.[16]

3. Pharmacokinetic Profile

The pharmacokinetic properties of fluticasone furoate have been determined in healthy male and female adults, aged 19–56 years, after single- and multiple-dose intranasal administration, and single-dose oral or intravenous administration.[17,18]

Absorption and Distribution

- Following single-dose administration of intranasal fluticasone furoate 55–880μg or multiple-dose administration of intranasal fluticasone furoate 220 or 880μg once daily for 7 days in healthy male volunteers (n = 24), aged 21–45 years, plasma drug concentrations were below the lower limit of quantification (10 pg/mL) in most samples.[17] In the few plasma samples with quantifiable levels of fluticasone furoate, the concentration was <30 pg/mL.
- In patients with seasonal allergic rhinitis treated with fluticasone furoate nasal spray 55–440μg once daily for 2 weeks (n = 502), 12% of patients had quantifiable plasma concentrations of fluticasone furoate (>10 pg/mL); usually not exceeding three times the lower limit of quantification.[19] Only 2% of samples from patients receiving the 110μg dose had quantifiable plasma drug concentrations, compared with 15% of samples from patients receiving the 440μg dose.[19]
- *In vitro*, fluticasone furoate was 99.4% bound to plasma protein.[11]
- After administration of intranasal fluticasone furoate 880μg every 8 hours for 10 doses in healthy male and female adult volunteers (n = 16), the average absolute bioavailability was low at 0.5%.[17]
- The oral bioavailability of fluticasone furoate following a single 2000μg oral dose was also low at 1.26%.[17] Comparison of plasma radioactivity after oral and intravenous administration of ^{14}C-fluticasone furoate demonstrated that ≥30% of the 2000μg oral dose was absorbed, indicating extensive first-pass metabolism of the absorbed drug.[17]

Metabolism and Elimination

- Fluticasone furoate is excreted mainly in the faeces, with only minor amounts (1–3% of the total dose) in the urine, following oral or intravenous administration of ^{14}C-radiolabelled drug.[18] Clearance of fluticasone furoate is primarily by metabolism, since there was little unchanged drug in the faeces.[18] The average elimination half-life after intravenous administration was 15.1 hours.[9]
- The principle route of metabolism of fluticasone furoate is hydrolysis in the liver by the cytochrome P450 isozyme (CYP) 3A4 to the 17β-carboxylic acid metabolite (M10),[9] which displayed ≈10 000-fold lower glucocorticoid receptor agonist potency than fluticasone furoate *in vitro*.[18] Minor metabolites (M32 and M26) may also exist, but generation of fluticasone by loss of the furoate moiety does not appear to occur.[18]

4. Therapeutic Efficacy

There are eight published clinical trials on the use of fluticasone furoate nasal spray in the treatment of allergic rhinitis. Five trials assessed patients with seasonal allergic rhinitis (four in adults and adolescents [aged ≥12 years][19-22] and one in children [aged 2–11 years][23]) and three trials assessed patients with perennial allergic rhinitis (two in adults/adolescents[24,25] and one in children[26]). Three of the trials are fully published,[19,20,22] while preliminary results for the others are available in abstracts/posters from scientific meetings.[21,23-26]

The clinical trials were randomised, double-blind, placebo-controlled, parallel-group trials of 2,[19-23] 4,[24] 6[25] or 12[26] weeks' duration. Study medication (fluticasone furoate and/or placebo) was routinely administered as two sprays in each nostril once daily in the morning.[19,20]

The primary efficacy endpoint in all trials was the least squares mean change from baseline in daily reflective total nasal symptom score (rTNSS)[19-26] over the entire treatment period,[19-25] except for in

the 12-week trial in children with perennial allergic rhinitis where efficacy was evaluated over the first 4 weeks of therapy in the sub-population of patients aged 6–11 years.[26] The rTNSS was the sum of four nasal symptoms: congestion, itching, rhinorrhoea and sneezing, each assessed on a 4-point scale (0 = none; 3 = severe).

Secondary endpoints commonly included: least squares mean changes from baseline in morning, predose, instantaneous total nasal symptom score (iTNSS), daily reflective total ocular symptom score (rTOSS) and morning, predose, instantaneous total ocular symptom score (iTOSS), and subject-rated overall response to therapy on a 7-point scale (significantly/moderately/mildly improved, no change or mildly/moderately/significantly worse). Ocular symptom scores were the sum of three symptoms: eye itching/burning, tearing/watering and redness, each assessed on a 4-point scale (0 = none; 3 = severe).

Seasonal Allergic Rhinitis

Of the four controlled trials in adults and adolescents with seasonal allergic rhinitis, the specific pollen allergies required of the enrolled patient populations were mountain cedar pollen (two studies),[19,21] ragweed pollen[20] and grass pollen.[22] The specific pollen allergy of patients in the study in children was not stated.[23]

The trials in patients with seasonal allergic rhinitis were each of 2 weeks' duration and consisted of a dose-ranging study (fluticasone furoate 55, 110, 220 and 440μg once daily vs placebo; n = 641) in adults and adolescents,[19] three comparisons (n = 299,[20] 302[21] and 285[22]) of fluticasone furoate 110μg once daily versus placebo in adults/adolescents, and a comparison of fluticasone furoate 55 and 110μg once daily versus placebo in children (n = 554).[23]

Where stated,[19,20,22] patients were required to have a documented history of seasonal allergic rhinitis, with seasonal allergy symptoms during the previous two pollen allergy seasons and a positive skin prick test (wheal ≥3mm larger than the diluent control) to the specific allergen, or a positive *in vitro* test for specific IgE,[22] within 12 months of enrolment in the studies. The trials were conducted in the peak pollen season and only patients with moderate to severe nasal symptoms (rTNSS [and iTNSS in two studies][19,22] ≥6 and reflective nasal congestion score ≥2), and ocular symptoms in two studies (rTOSS ≥4),[20,22] during the last 4 days of the screening period were eligible for randomisation.[19,20,22]

All four studies in adults and adolescents with seasonal allergic rhinitis[19-22] assessed the effect of therapy on health-related quality of life (HR-QOL) using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) consisting of 28 items (grouped into seven domains) each scored from 0 to 6 where higher scores represent greater impairment of HR-QOL.[27-29] One study also used the Nocturnal RQLQ (NRQLQ), consisting of 16 items grouped into four domains, to assess the effect of nocturnal allergic rhinitis symptoms on HR-QOL.[30]

Adults and Adolescents

- In a dose-ranging study in patients with seasonal allergy to mountain cedar pollen, fluticasone furoate 55–440μg once daily for 2 weeks significantly reduced daily rTNSS, iTNSS (indicating 24-hour duration of efficacy) and rTOSS compared with placebo (figure 2).[19]
- Likewise, significant ($p < 0.001$) improvements with fluticasone furoate compared with placebo were seen for individual nasal symptom scores, morning and evening rTNSS and overall response to therapy.[19] Significant improvement was reported by 16%, 28%, 23% and 26% of patients receiving fluticasone furoate 55, 110, 220 and 440μg, respectively, compared with 8% of placebo recipients. All doses other than the 55μg dose were significantly ($p < 0.05$) better than placebo in reducing morning, predose iTOSS.[19]
- Overall, the 110μg dose provided the optimal benefit-risk ratio of the four doses assessed and was selected for further study in phase III trials.[19]
- Fluticasone furoate nasal spray 110μg once daily for 2 weeks was superior to placebo in reducing daily rTNSS (primary endpoint) in each of three randomised, double-blind trials in adults and adolescents with seasonal allergic rhinitis caused by rag-

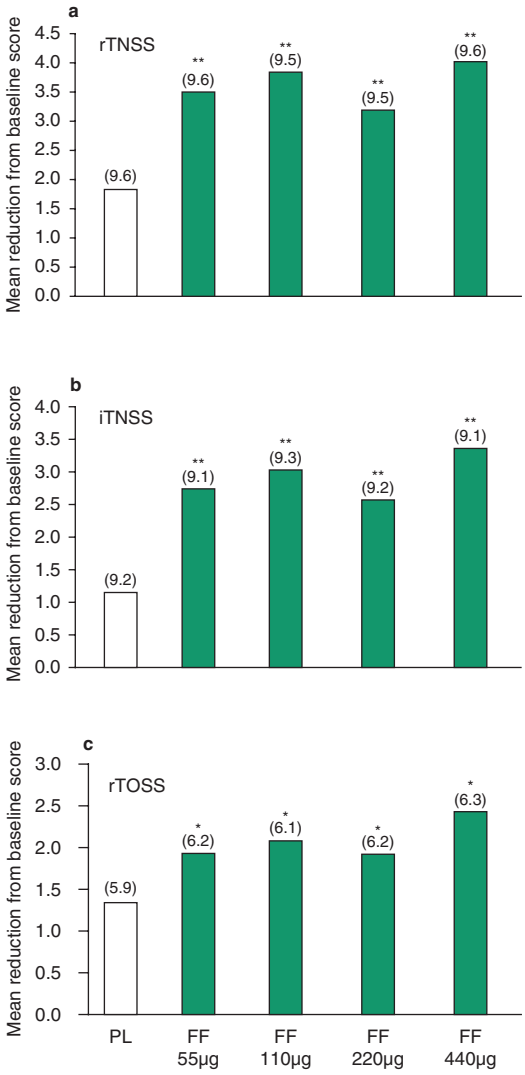


Fig. 2. Dose-ranging efficacy of fluticasone furoate (FF) nasal spray in the treatment of adults and adolescents with seasonal allergic rhinitis. Mean reductions from baseline in (**a**) daily reflective total nasal symptom score (rTNSS; primary endpoint), (**b**) morning, predose, instantaneous total nasal symptom score (iTNSS) and (**c**) daily reflective total ocular symptom score (rTOSS) in a randomised, double-blind study, in which patients (aged ≥12 years) with seasonal allergy to mountain cedar pollen and moderate to severe symptoms received intranasal FF 55 (n = 127), 110 (n = 127), 220 (n = 129) or 440µg (n = 130) once daily or placebo (PL) [n = 128] for 2 weeks during the peak pollen season.[19] Numbers in parentheses above the bars refer to the mean values at baseline. * $p \leq 0.013$, ** $p < 0.001$ vs PL.

weed pollen,[20] grass pollen[22] or mountain cedar pollen[21] (figure 3).

- Fluticasone furoate 110µg once daily was also superior to placebo in all three trials with respect to reductions in iTNSS (figure 3), rTOSS (figure 3) and overall response to therapy (all $p < 0.001$).[20-22]
- The proportions of patients receiving fluticasone furoate 110µg versus placebo who reported significant or moderate improvement after treatment were 42% versus 21% in the ragweed pollen allergy trial[20] and 67% versus 39% in the grass pollen allergy trial.[22] Fluticasone furoate 110µg was also superior to placebo for morning, predose iTOSS in the mountain cedar pollen ($p < 0.01$)[31] and grass pollen ($p < 0.001$)[22] allergy studies.
- With regard to onset of action, a statistically significant difference between fluticasone furoate 110µg and placebo in morning, predose iTNSS was first seen at 8 hours after the first dose in two studies (both $p < 0.05$)[19,20] and after 24 hours ($p < 0.001$) in another.[22]

Health-Related Quality of Life

- In all four trials assessing HR-QOL, fluticasone furoate consistently produced statistically significant ($p < 0.05$–0.001) and clinically meaningful improvements (≥0.5 reduction in global RQLQ score over placebo) in global RQLQ[22,27-29] and NRQLQ[30] scores compared with placebo.
- Compared with placebo, all fluticasone furoate treatment groups in all four studies also had significantly ($p < 0.05$–0.01) improved RQLQ or NRQLQ scores for each of the individual domains,[22,27-30] except for eye symptoms in two studies[28,32] and non-hayfever symptoms in one study.[22]
- In the dose-ranging study, the mean placebo-corrected changes from baseline in global RQLQ score were −0.82, −1.00, −0.85 and −1.00 for fluticasone furoate 55, 110, 220 and 440µg, respectively (all $p < 0.001$),[27] while those for the global NRQLQ score were −0.68, −0.95, −0.76 and −0.98, respectively (all $p < 0.001$).[30]
- In the three trials comparing intranasal fluticasone furoate 110µg once daily with placebo for 2 weeks, the mean placebo-corrected changes from

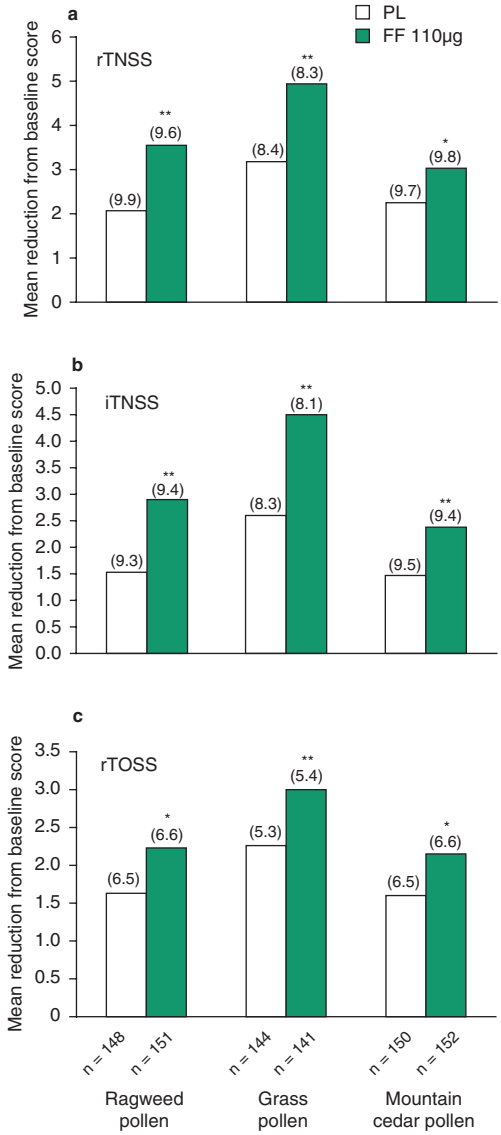


Fig. 3. Efficacy of fluticasone furoate (FF) nasal spray 110µg once daily in adults and adolescents with seasonal allergic rhinitis. Mean reductions from baseline in (**a**) daily reflective total nasal symptom score (rTNSS; primary endpoint), (**b**) morning, predose, instantaneous total nasal symptom score (iTNSS) and (**c**) daily reflective total ocular symptom score (rTOSS) in three randomised, double-blind trials comparing intranasal FF 110µg once daily with placebo (PL) for 2 weeks in patients (aged ≥12 years) with seasonal allergy to ragweed pollen,[20] grass pollen[22] or mountain cedar pollen.[21,31] Numbers in parentheses above the bars refer to the mean values at baseline. * $p < 0.01$, ** $p \leq 0.001$ vs PL.

baseline in global RQLQ score were −0.599,[28] −0.688[29] and −0.70[22] (all $p < 0.001$).

Children

- Treatment with fluticasone furoate nasal spray 110µg, but not 55µg, once daily for 2 weeks in children with seasonal allergic rhinitis produced significantly ($p < 0.05$) greater reductions in rTNSS (primary endpoint) than placebo for the cohort aged 6–11 years (primary efficacy population; n = 448) [figure 4] and the full intent-to-treat (ITT) population (aged 2–11 years; n = 554).[23,33] The placebo-corrected mean changes from baseline in daily rTNSS with fluticasone furoate 110µg were −0.616 ($p = 0.025$) for the cohort aged 6–11 years and −0.609 ($p = 0.012$) for the entire ITT population.[23,33]
- Similarly, fluticasone furoate 110µg, but not 55µg, once daily significantly reduced morning, predose iTNSS compared with placebo in both the cohort aged 6–11 years (−2.80 vs −2.13; $p = 0.015$) and the full ITT population (−2.87 vs −2.23;

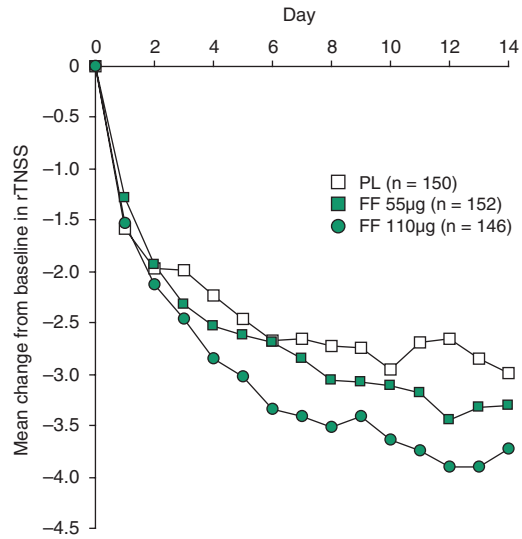


Fig. 4. Efficacy of fluticasone furoate (FF) nasal spray in children with seasonal allergic rhinitis. Mean change from baseline in daily reflective total nasal symptom score (rTNSS; primary endpoint) in children aged 6–11 years (primary efficacy population) during treatment for 2 weeks with intranasal FF 55µg, FF 110µg or placebo (PL) once daily in a randomised, double-blind, parallel-group trial.[33] Mean rTNSS values at baseline were 8.6, 8.5 and 8.4 for FF 55µg, FF 110µg and PL, respectively.

p = 0.008), indicating a 24-hour duration of action.[33] Improvements in the overall response to therapy were also significantly (p < 0.001) greater in fluticasone furoate 110µg recipients than in placebo recipients for both study populations.[33]

Perennial Allergic Rhinitis

The three clinical trials in patients with perennial allergic rhinitis consisted of two comparisons of intranasal fluticasone furoate 110µg once daily with placebo for either 4 (n = 302)[24] or 6 weeks (n = 302)[25] in adults and adolescents, and a comparison of intranasal fluticasone furoate 55 and 110µg once daily with placebo for 4 weeks in children (n = 550).[26]

Adults and Adolescents

- Treatment of adult and adolescent patients with perennial allergic rhinitis for either 4[24] or 6 weeks[25] with fluticasone furoate nasal spray 110µg once daily produced significantly greater mean reductions from baseline than placebo in rTNSS and iTNSS (figure 5). In the 6-week study, a statistically significant difference between fluticasone furoate (n = 151) and placebo (n = 151) was first noted at 24 hours after the first dose for iTNSS and after 2 days for rTNSS.[25]
- In the 6-week study, fluticasone furoate 110µg also produced significantly greater mean reductions from baseline than placebo for rTOSS (figure 5) and iTOSS (−1.76 vs −1.26; p = 0.007).[25]
- The overall response to therapy rating was significantly higher with fluticasone furoate than placebo after both 4 (p < 0.01)[24] and 6 weeks (p < 0.001).[25] The proportions of patients with significant or moderate improvement after treatment with fluticasone furoate versus placebo were 44% versus 33% at 4 weeks[24] and 62% versus 39% at 6 weeks.[25]

Children

- For the primary endpoint in the treatment of children with perennial allergic rhinitis (rTNSS after 4 weeks in those aged 6–11 years [n = 431]), fluticasone furoate 55µg once daily produced significantly (p = 0.003) greater improvement from baseline than placebo, but the improvement with the 110µg once-daily dosage did not differ significantly from that with placebo (figure 6).[26]

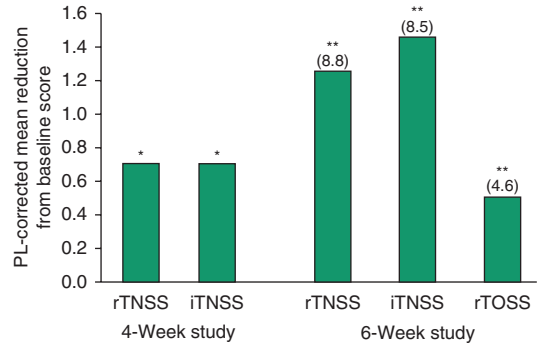


Fig. 5. Efficacy of fluticasone furoate (FF) nasal spray in adults and adolescents with perennial allergic rhinitis. Placebo (PL)-corrected mean reductions from baseline in daily reflective total nasal symptom score (rTNSS; primary endpoint) and morning, predose, instantaneous total nasal symptom score (iTNSS) [plus daily reflective total ocular symptom score (rTOSS) in one study] in two randomised, double-blind trials (both n = 302) in which adults and adolescents (aged ≥12 years) received intranasal FF 110µg once daily or PL for 4[24] or 6[25] weeks. Numbers in parentheses above the bars refer to the mean values at baseline (where available). * p < 0.01, ** p < 0.001 vs PL.

- In the full ITT population (aged 2–11 years; n = 550), both fluticasone furoate 55µg (−4.17 vs −3.36; p < 0.001) and 110µg (−3.83 vs −3.36; p = 0.031) produced significantly greater reductions from baseline in rTNSS than placebo.[26]
- Both fluticasone furoate 55 and 110µg once daily were superior (p < 0.01) to placebo with respect to reductions from baseline in morning, predose iTNSS in both the cohort aged 6–11 years (−3.62 and −3.52 vs −2.87) and the full ITT population (−3.62 and −3.44 vs −2.81), although the reductions with fluticasone furoate 55µg were numerically higher than those with fluticasone furoate 110µg in each population.[26]

5. Tolerability

- Fluticasone furoate nasal spray was well tolerated in clinical trials. In a pooled analysis of six clinical trials in adults and adolescents, and three in children receiving fluticasone furoate 55µg (n = 369) or 110µg (n = 1194), or placebo (n = 1203) for 2–12 weeks, the overall incidence of adverse

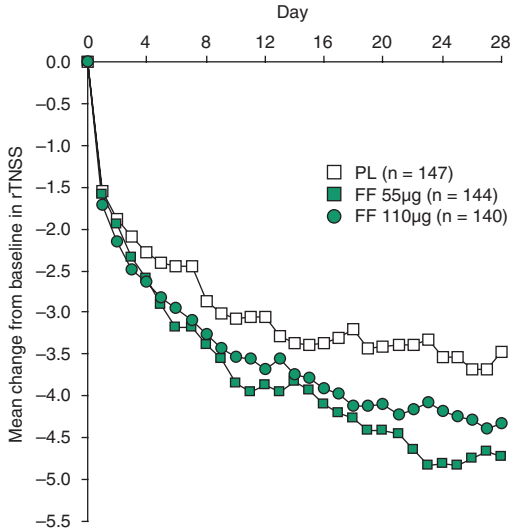


Fig. 6. Efficacy of fluticasone furoate (FF) nasal spray in children with perennial allergic rhinitis. Mean change from baseline in daily reflective total nasal symptom score (rTNSS; primary endpoint) in children aged 6–11 years (primary efficacy population) during treatment for 4 weeks with intranasal FF 55µg, FF 110µg or placebo (PL) once daily in a 12-week, randomised, double-blind, parallel-group trial.[26] Mean rTNSS values at baseline were 8.5, 8.6 and 8.5 for FF 55µg, FF 110µg and PL, respectively.

events with intranasal fluticasone furoate was similar to that with placebo.[9]

- Adverse events occurring in adults and adolescents with an incidence >1% and more frequently in those receiving fluticasone furoate 110µg (n = 768) than in placebo recipients (n = 774) were headache (9% vs 7%), epistaxis (6% vs 4%), pharyngolaryngeal pain (2% vs 1%), nasal ulceration (1% vs <1%) and back pain (1% vs <1%).[9] Fewer than 3% of adults and adolescents withdrew from therapy as a result of adverse events and the rate of withdrawal with fluticasone furoate was similar to or less than that with placebo.[9]

- Similarly, in children aged 2–11 years receiving fluticasone furoate 55 or 110µg once daily or placebo for 2–12 weeks, the adverse events occurring with an incidence >3% and more commonly in at least one dosage group of fluticasone furoate recipients (n = 795) than in placebo recipients (n = 429) were headache (7.7% vs 7.2%), nasopharyngitis (5.2% vs 4.9%), epistaxis (4.3% vs 4.4%), pyrexia (4.5% vs 1.6%), pharyngolaryngeal pain (3.5% vs 3.3%) and cough (3.5% vs 2.8%).[9]

- Fluticasone furoate nasal spray was likewise well tolerated during long-term treatment. In adult and adolescent patients treated with intranasal fluticasone furoate 110µg (n = 605) or placebo (n = 201) for 12 months, epistaxis was the only adverse event occurring more frequently in fluticasone furoate than placebo recipients (20% vs 8%).[9,34] All placebo recipients reporting epistaxis experienced episodes of mild intensity only.[34] Among fluticasone furoate recipients reporting epistaxis, 67%, 32% and 1% of patients reported episodes with a maximum intensity of mild, moderate and severe, respectively.[34]

- Short-term treatment with fluticasone furoate nasal spray did not significantly alter 24-hour urinary cortisol levels[19] and there was no evidence during long-term therapy of adverse events suggestive of clinically relevant systemic corticosteroid exposure.[34]

6. Dosage and Administration

The recommended starting dosage of fluticasone furoate nasal spray in adults and adolescents aged ≥12 years with seasonal or perennial allergic rhinitis is 110µg once daily administered as two sprays (27.5 µg/spray) in each nostril.[9] The dosage should be titrated to the minimal effective dosage (e.g. 55µg once daily) in order to reduce the possibility of adverse events.

The recommended starting dosage in children aged 2–11 years is 55µg (one spray in each nostril) once daily, although nonresponders to 55µg may use 110µg once daily until symptoms have been controlled and then reduce the dosage to 55µg once daily.[9]

Caution is necessary if coadministered with potent CYP3A4 inhibitors, such as ketoconazole, and coadministration with the potent CYP3A4 inhibitor ritonavir should be avoided since the increased exposure to fluticasone furoate may increase the risk of systemic adverse effects.[9]

Local prescribing information should be consulted for detailed dosage and administration infor-

mation, including warnings, precautions and use in special patient populations.

7. Fluticasone Furoate: Current Status of Intranasal Use in Allergic Rhinitis

Fluticasone furoate nasal spray was approved by the US FDA in April 2007 for the treatment of seasonal or perennial allergic rhinitis in adults and children aged ≥2 years. An application for marketing approval has also been submitted in the EU.

Fluticasone furoate nasal spray is a new, enhanced-affinity, topical corticosteroid employing a unique side-actuated delivery device designed for ease of use. Intranasal fluticasone furoate has shown clinical efficacy in a number of randomised, double-blind, placebo-controlled trials in children, adolescents and adults with either seasonal or perennial allergic rhinitis. In adults and adolescents, it has also shown efficacy in reducing the ocular symptoms of allergic rhinitis in addition to the nasal symptoms. Fluticasone furoate nasal spray was well tolerated in adults, adolescents and children aged ≥2 years, with an overall incidence of adverse events similar to that with placebo.

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