How not to take a photo
Role of Intranasal corticosteroids in paediatrics: revisited

Dr. Eric Muchangi
MBChB, MPH
Outline of Presentation

– Definition
– Epidemiology and Burden of Disease
– Classification
– Symptoms and Physical features
– Principles of Management
– FFNS Clinical data
– Summary
Definition of Allergic Rhinitis

“Rhinitis is defined as an inflammation of the lining of the nose and is characterised by nasal symptoms including anterior or posterior rhinorrhea, sneezing, nasal blockage and/or itching of the nose… It is often associated with ocular symptoms.”¹

*BRIA = Allergic Rhinitis and its Impact on Asthma

Prior to the ARIA classification, the traditional definition of AR was:

- **Seasonal Allergic Rhinitis (SAR)** – allergy caused by seasonal allergens (sometimes referred to as outdoor allergens, e.g. grass and tree pollen)
- **Perennial Allergic Rhinitis (PAR)** – allergy caused by perennial allergens (sometimes referred to as indoor allergens, e.g. dust mites, pet dander)
Clinical Management Review

**Current and Future Directions in Pediatric Allergic Rhinitis**

Deborah Gentile, MD*, Ashton Bartholow, BS*, Erkka Valovirta, MD, PhD¹, Glenis Scadding, MD², and David Skoner, MD³. *Pittsburgh, Pa, Turku, Finland; and London, United Kingdom*
Overview of prevalence and burden of Allergic Rhinitis

- Allergic rhinitis (AR) is a highly prevalent, chronic disease, with rates of up to 40% in some populations such as US.
- The prevalence is increasing in many "westernized" countries including developing countries.
- 80% of patients develop symptoms of AR before 20 years, of these 40% are symptomatic by 6 years.

Gentile et al. J Allergy Clin Immunol 2013;
• Paucity of paediatric data, especially in developing countries.

**Paediatric Allergies in America National Survey**

- Screened 35757 households age 4-17 yrs
- 13% of children had HCP diagnosed AR
- 61% had AR by 6 yrs
- Most diagnosed by paediatricians, SPT or blood test no routinely done – Under reporting.

• Co morbidities and complications: Asthma, sinusitis, OME, Orthodontic malocclusion, habitual snoring, Impaired sleep, irritability, behaviour problems and mood disorders.

Gentile et al. J Allergy Clin Immunol 2013;
Prevalence of symptoms and burden of allergic rhinoconjunctivitis in Africa
ISAAC Study I & III

- Phase I involved 6 African countries, 1995
- Phase III involved 16 countries, 2001-2
- Variation in the prevalence of AR - (7.2 – 27.3%)
Prevalence of symptoms of Allergic Rhinoconjunctivitis in Kenya

AR is the commonest atopic disease world wide, epidemiology not known
One questionnaire based study documented\(^1\)

Gathiru, C. 2014\(^1\)
Point prevalence of AR among KMTC students – 13%
81% of respondents had daily life affected.
Sneezing most common symptom – 83.6%

ISAAC 1 study 1995\(^2\)
Allergic Rhinitis prevalence last 12 months
Age group: 13-14 yrs
Nairobi – 25.0%
Eldoret – 14.9%

ISAAC 3 study 2002\(^2\)
Allergic rhinitis prevalence last 12 months
Age group: 13-14 yrs
Nairobi – 19.8%
Eldoret – 22.4%
Symptoms of Allergic Rhinitis

• In AR, the immediate reaction resulting from IgE-mediated mast cell degranulation and mediator release is rapid and leads to:
  – Sneezing
  – Rhinorrhoea
  – Itch
  – Nasal blockage
late-phase reaction involves inflammation, with an eosinophilic infiltrate. Symptoms are:

- Chronic obstruction
- Hyposmia
- Post-nasal mucous discharge
- Nasal hyper-reactivity
• Allergic asthma and allergic rhinitis are often considered clinical manifestations of the same condition, the chronic allergic respiratory syndrome
• The ‘one airway’ hypothesis has been proposed suggesting that the upper and lower airways do not function as anatomically or functionally distinct areas.
• Epidemiologic surveys have shown that allergic rhinitis and asthma commonly coexist and that patients with nasal allergy demonstrate nonspecific bronchial hyper-responsiveness in the absence of overt asthma [33].
• Bronchial inflammation can result from nasal allergen challenge in patients with AR in the absence of obvious asthma
• As well, patients with asthma can have eosinophilic infiltration of their nasal mucosa without reporting symptoms of rhinitis
In the past, allergic rhinitis was considered to be a disorder localized to the nose and nasal passages, but current evidence indicates that it may represent a component of systemic airway disease involving the entire respiratory tract.

There are a number of physiological, functional and immunological relationships between the upper (nose, nasal cavity, paranasal sinuses, pharynx and larynx) and lower (trachea, bronchial tubes, bronchioles and lungs) respiratory tracts.

For example, both tracts contain a ciliated epithelium consisting of goblet cells that secrete mucous, which serves to filter the incoming air and protect structures within the airways.

The submucosa of both the upper and lower airways includes a collection of blood vessels, mucous glands, supporting cells, nerves and inflammatory cells.

Evidence suggests that allergen provocation of the upper airways not only leads to a local inflammatory response, but also to inflammatory processes in the lower airways,

Supported by the fact that rhinitis and asthma frequently coexist.

Therefore, allergic rhinitis and asthma appear to represent a combined airway inflammatory disease, and this needs to be considered to ensure the optimal assessment and management of patients with allergic rhinitis.
In susceptible individuals, inhaled allergens stimulate production of IgE.

This allergen specific IgE binds to mast cells in the nasal mucosa and when the allergen is next inhaled, the mast cells are stimulated to produce inflammatory mediators, such as histamine.

These inflammatory mediators induce the symptoms associated with allergic rhinitis.

Pathogenesis of allergic rhinitis

- In susceptible individuals, when an allergen is inhaled it induces an immune response leading to allergic sensitisation, characterised by the production of specific IgE directed against the allergen. This specific IgE coats the surface of mast cells in the nasal mucosa, and when the specific allergen is again inhaled into the nose, it binds to this IgE on mast cells, leading to the immediate release of the immune mediators, including histamine. These mast cells also quickly synthesise other mediators, including leukotrienes and prostaglandin D2 which induce inflammation and the characteristic symptoms of allergic rhinitis.

- In addition, mucous glands are stimulated to increase secretions, vascular permeability is increased and vasodilation occurs, leading to congestion and increased nasal pressure.

- Sensory nerves are also stimulated, leading to sneezing and itching.

- These events can occur in minutes and this is termed the early, or immediate, phase of the reaction. In the following 4–8 hours these mediators continue to interact and recruit other inflammatory cells to the mucosa, which prolongs the inflammation and is termed the late-phase response. The symptoms of the late-phase response tend to be similar to that encountered in the early phase, but with less sneezing and itching and more congestion and mucus production; this late phase may persist for hours or days.

- The inflammatory response can also cause systemic effects, such as fatigue, sleepiness, and a general feeling of being unwell.

Causes and triggers of allergic rhinitis

- Allergic rhinitis is a multifactorial disease induced by gene-environment interactions
- Allergic rhinitis is caused by both indoor and outdoor inhaled allergens

**Common indoor allergens**
- Dust mites
- Insects
- Moulds
- Animal danders, although uncommon in the MEA region

**Common outdoor allergens**
- Pollens
- Moulds
- Sand and dust storms

**Occupational agents** (cause rhinitis by allergic and non-allergic mechanisms)
- Flour, grain and wood dust
- Organic compounds: isocyanates, glutaraldehydes, anhydrides
- Solder, resins and glues
- Latex
- Metal salts
- Natural gases (e.g., methane from oil refineries)

Skoner, D.P. *J Allergy Clin Immunol* 2001;108:S2-8., NUMBER 1
Classification of allergic rhinitis*

**Intermittent**
- Symptoms present for <4 days per week
  - OR
  - Symptoms present for <4 consecutive weeks

  **Mild**
  - Normal sleep
  - Normal daily activities, and
  - Normal work/school
  - No troublesome symptoms

  **Moderate-Severe**
  - Abnormal sleep, or
  - Impairment of daily activities, or
  - Problems at work/school
  - Troublesome symptoms

**Persistent**
- Symptoms present for >4 days per week
  - AND
  - Symptoms present for >4 consecutive weeks

  **Mild**
  - Normal sleep
  - Normal daily activities, and
  - Normal work/school
  - No troublesome symptoms

  **Moderate-Severe**
  - Abnormal sleep, or
  - Impairment of daily activities, or
  - Problems at work/school
  - Troublesome symptoms

Physical features of allergic rhinitis

• Patients presenting with allergic rhinitis often display the following:
  – Red puffy faces (with reddened, watery eyes in the case of allergic rhino-conjunctivitis)
  – Pale nasal turbinates
  – Blush discolouration of lower eyelids (‘allergic shiners’)
  – Slightly puffy lower eyelids and semilunar lines or folds below the inferior eyelid (‘Dennie-Morgan folds’)
  – Swollen, red and shiny nose, from constant rubbing
  – A horizontal creasing over the nasal tip, often seen in children
    • Caused by habitual rubbing of the nose due to constant irritation (nasal or allergic salute)

Examples of physical features of allergic rhinitis

Blush discolouration of lower eyelids (‘allergic shiners’)

Semilunar lines or folds below the inferior eyelid (‘Dennie-Morgan folds’)

A horizontal creasing over the nasal tip – caused by rubbing/allergic salute
The allergic Salute

Frequent upward rubbing of the nose (either with the index finger or hand) to relieve itching
Nasal symptom burden among Primary Care Practitioners (PCPs)

• Common symptoms in PCPs before taking medication

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of PCPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezing</td>
<td>72%</td>
</tr>
<tr>
<td>Runny nose</td>
<td>66%</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>59%</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>58%</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>45%</td>
</tr>
<tr>
<td>Itchy palate</td>
<td>39%</td>
</tr>
<tr>
<td>Cough</td>
<td>33%</td>
</tr>
</tbody>
</table>

Base: AR sufferers (n=600)

Principles of Management

Aims of Management

– Optimize therapeutic outcomes
– Improve symptoms
– Improve Health Related QOL

Treatment Guidelines

• Guideline directed management shown to improve treatment outcomes e.g.
  – ARIA 2010
  – UK guidelines
  – European Academy for Allergy and Clinical Immunology (EAACI)
  – American Academy for Allergy and Clinical Immunology (AAACI)
  – World Allergy Organization
Treatment strategies

- The management of allergic rhinitis consists of the following 4 major treatment strategies:¹,²
- Education
- Environmental control measures and allergen avoidance:
  - These include keeping exposure to allergens such as pollen, dust mites, and mould to a minimum
- Pharmacotherapy:
  - Intranasal corticosteroids are the most efficacious medication available for the treatment of allergic and non-allergic rhinitis. Patients are also often successfully treated with oral antihistamines, decongestants, or both
- Immunotherapy:
  - This treatment may be considered more strongly with severe disease, poor response to other management options, and the presence of comorbid conditions or complications
  - Immunotherapy is often combined with pharmacotherapy and environmental control


EA/AR/0001/15
Treatment algorithm
Point of Action for each drug group

Fig. 1. Point-of-action for each drug group.

Corticosteroids block the action of inflammatory mediators early in the allergic response.

Mast cell stabilizers inhibit the degranulation of sensitized mast cells, thereby inhibiting release of histamine and other inflammatory mediators.

Antihistamines block H₁-receptors.

Anticholinergic agents block the effect of acetylcholine, which causes watery secretion from nasal glands and vasodilation of blood vessels serving the glands.

Exposure to allergens triggers the release of multiple inflammatory mediators.

Immunotherapy gradually raises patient tolerance to the allergens.

Monoclonal IgE antibody inhibits binding of IgE to receptors on surface of basophils and mast cells.

Anti-leukotriene agents either block leukotriene synthesis or block their receptors.

Decongestants (α-adrenergic agonists) act on α-adrenergic receptors in the nasal mucosa, producing vasoconstriction and shrinkage of swollen mucosa.
## Effect of Therapies on Rhinitis Symptoms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sneezing</th>
<th>Rhinorrhoea</th>
<th>Nasal Obstruction</th>
<th>Nasal Itching</th>
<th>Ocular Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>INS</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>OAH</td>
<td>+++</td>
<td>+++</td>
<td>0 to +</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Intranasal decongestant</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intranasal chromone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LTRA</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

0 = no effect, +++ = maximum effect, LTRA, leukotriene receptor antagonist; OAH, oral antihistamine

Why Intranasal Steroids?

• **Mainstay of treatment for Allergic Rhinitis**
  – Allows delivery of high therapeutic concentration directly on the site of disease
  – Incremental benefit in symptom reduction with continual use
  – Prolonged duration of action
  – Acceptable safety profile for modest to severe Allergic rhinitis
  – Potent anti-inflammatory properties
  – Newer molecules have low systemic bioavailability
  – Most effective in controlling late phase mediators.
Characteristics of an ideal Steroid

• High Lipophilicity; Increases deposition in lung tissue, slow release from drug lipid compartment, Increases affinity for GCR, Increased GCR occupancy

• Low Systemic Bioavailability

• High Glucocorticoid receptor affinity and selectivity

• High anti-Inflammatory potency

• Fast and virtually complete first pass metabolism to completely inactive metabolite

• Greater anti-Inflammatory potency

• Rapid receptor association and slow dissociation leading to fast effect and long half life

Malcom Johnson PHD Middlesex, United Kingdom, J. Allergy Cin Immunol Vol101 1996
FDA Approves Once-Daily Veramyst (fluticasone furoate) Nasal Spray for Treatment of Seasonal and Year-Round Allergy Symptoms in Adults and Children as Young as Two Years
ARIA recommendations for intranasal glucocorticosteroids for treatment of AR1
• ARIA recommend intranasal glucocorticosteroids for treatment of AR in adults1
• ARIA suggest intranasal corticosteroids in children with AR1
Molecular characteristics of fluticasone furoate nasal spray – an enhanced affinity steroid
Fluticasone furoate: an enhanced-affinity glucocorticoid

Fluticasone furoate: a combination of the fluticasone backbone and a 17-α furoate ester

Furoate ester group

Fluticasone backbone

Enhanced glucocorticoid affinity and greater selectivity (the clinical significance of this is unknown)

FF is a distinct drug molecule and not a salt or a pro-drug of fluticasone


Copyright authorisation to reproduce this figure is required
Avamys enhances affinity by making effective contact with the glucocorticoid receptor*1-3

Biggadike K et al. Ann Allergy Asthma Immunol 2007;98:A91–A92
2. Biggadike K et al. EAACI 2006, Abstract 783
Affinity for the glucocorticoid receptor

FF has the highest Glucocorticoid Receptor affinity compared with other currently available Intranasal corticosteroids

Bioavailability of currently used Intranasal corticosteroids

Steroid Lipophilicity

Relationship between the relative receptor affinities (RRA) of glucocorticoids and their lipophilicity expressed as relative retention times (k'). The reference glucocorticoid was dexamethasone for RRA and dexamethasone-21-isonicotinate for k'. Coefficient ...
Steroid tissue retention

Retention of glucocorticoids in a human respiratory epithelial tissue monolayer (mean ± SD, n = 3). Difference vs. FF (t-test): *P < 0.05 and **P < 0.01.

### Onset of Action

<table>
<thead>
<tr>
<th>INS</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone Diproprionate</td>
<td>Within 3 days</td>
</tr>
<tr>
<td>Budesonide</td>
<td>In 24 hrs</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>4 - 7 days</td>
</tr>
<tr>
<td>Fluticasone Propionate</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Within 12 hrs</td>
</tr>
<tr>
<td><strong>Fluticasone furoate</strong></td>
<td>8 hrs</td>
</tr>
</tbody>
</table>

Anolik, R.  *Journal of Asthma and Allergy* 2010 387–99
Fluticasone Furoate (Avamys) Treatment in Paediatric patients
Mode of action

- FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity
- The precise mechanism through which FF affects rhinitis symptoms is not known
- Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation
Mode of Action (Inflammatory cascade)

- Binding of INS to the glucocorticoid receptor downregulates the inflammatory cascade\textsuperscript{2,3}
- Downregulation of the inflammatory cascade reduces symptoms\textsuperscript{2,3}

\textsuperscript{1} Scadding et al. Clin Exp Allergy 2008; 38: 19–42
\textsuperscript{3} Greiner AN et al. Lancet 2011; 378: 2112–22

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Anti-inflammatory activity

- FF may reduce nasal mucosa inflammation by inhibiting the secretion of cytokines such as GM-CSF, IL-6 and IL-8 from nasal epithelial cells.
- FF may reduce upper eosinophilic inflammation through the decrease of eosinophil survival induced by the nasal mucosa epithelial cell secretions.

Roca-Ferrer et al. JACI 2013. abstract 408
Effect of FF on cytokine secretion from human nasal epithelial cells

Epithelial cells were incubated with culture media (white bars), FBS at 10% (black lines) or FBS at 10% plus FF (gray bars) for 24 h.

FF caused a dose-related inhibitory effect on GM-CSF (a), IL-6 (b) and IL-8 (c) release induced by FBS.

Roca-Ferrer et al. JACI 2013. abstract 408

Copyright authorisation to reproduce this figure is required.
FFNS is postulated to work on ocular symptoms via a neuronal reflex mechanism

1. FF has enhanced affinity for the glucocorticoid receptor

2. This may produce a greater inhibitory effect on the naso-ocular reflex mechanism

3. The release of mediators that cause ocular symptoms is reduced

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Summary

- FFNS inhibits the release of inflammatory mediators leading to reduced nasal inflammation which relieves nasal symptoms
- FFNS also reduces eye symptoms such as itchy, watery or red eyes
- FFNS may reduce nasal mucosa inflammation by inhibiting the secretion of cytokines such as GM-CSF, IL-6 and IL-8 from nasal epithelial cells
- FFNS may reduce upper eosinophilic inflammation through the decrease of eosinophil survival induced by the nasal mucosa epithelial cell secretions
• Fluticasone furoate nasal spray clinical efficacy

Paediatric studies
Prescribing Information
(Please amend as per your local license)

Adults and adolescents (aged > 12 years)

- Treatment of the nasal symptoms and ocular symptoms of seasonal allergic rhinitis
- Treatment of the nasal symptoms of perennial allergic rhinitis
- The recommended starting dosage is 2 sprays (27.5 µg of FF per spray) in each nostril once daily (total daily dose, 110 µg)
- Once adequate control of symptoms is achieved, dose reduction to one spray in each nostril once daily (total daily dose, 55 µg) may be effective for maintenance
Children (2 to 11 years)

- Treatment of the nasal symptoms of seasonal and perennial allergic rhinitis
- The recommended starting dosage is 1 spray (27.5 µg of FF per spray) in each nostril once daily (total daily dose, 55 µg)
- Patients not adequately responding to 1 spray in each nostril once daily (total daily dose, 55 µg) may use 2 sprays in each nostril once daily (total daily dose, 110 µg). Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril once daily (total daily dose, 55 µg) is recommended
- There are no data to recommend use of intranasal FF for the treatment of SAR or PAR in children under 2 years of age
Standardised study design of Phase III efficacy studies

Symptoms collected throughout treatment period

- **Primary endpoint:** Mean change from baseline in daily rTNSS
- **Key secondary endpoints:**
  - Mean change from baseline in AM pre-dose iTNSS
  - Mean change from baseline in daily rTOSS
  - Overall evaluation of treatment effect
- Mean changes assessed over the entire treatment period, except in Global Paediatric PAR study (first 4 weeks of the 12-week treatment period)

Symptom scoring for all efficacy studies (Phase II/III)

• Symptoms were scored twice daily:

• Total nasal symptom score (TNSS)
  – Nasal symptoms: rhinorrhoea, congestion, sneezing, itching
  – Maximum TNSS = 12

• Total ocular symptom score (TOSS)
  – Ocular symptoms: watering, itching, redness
  – Maximum TOSS = 9

• Reflective (r) vs instantaneous (i)
  – AM and PM reflective – “how have you felt over the past 12 hours?”
    • rTNSS and rTOSS
    • AM and PM scores ‘averaged’ to calculate daily rTNSS and rTOSS
  – AM pre-dose instantaneous “how do you feel now?” – iTNSS and iTOSS

FFNS provides relief from nasal symptoms in adults with SAR (daily reflective TNSS)

### Mean change from baseline rTNSS

<table>
<thead>
<tr>
<th></th>
<th>European Grass (SAR)</th>
<th>US Ragweed (SAR)</th>
<th>US Mountain Cedar (SAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean daily rTNSS</td>
<td>FFNS 110 µg</td>
<td>Placebo</td>
<td>FFNS 110 µg</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td>8.4</td>
<td>9.6</td>
</tr>
<tr>
<td>LS mean change from baseline over 2-week treatment period (* difference FFNS vs placebo)</td>
<td>-4.94 (*P&lt;0.001)</td>
<td>-3.18 (*P&lt;0.001)</td>
<td>-3.55 (*P&lt;0.001)</td>
</tr>
<tr>
<td>Patients, n</td>
<td>141</td>
<td>144</td>
<td>151</td>
</tr>
</tbody>
</table>

**Significant and consistent improvement of nasal symptoms**

**FFNS demonstrates 24-hour efficacy**  
(Am pre-dose iTNSS)

### Graphs
- **Grass**
- **Ragweed**
- **Mountain Cedar**

### Table: Change from Baseline in AM pre-dose iTNSS

<table>
<thead>
<tr>
<th></th>
<th>European Grass (SAR)</th>
<th>US Ragweed (SAR)</th>
<th>US Mountain Cedar (SAR)</th>
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<tbody>
<tr>
<td>Baseline mean daily iTNSS</td>
<td>FFNS 110 µg</td>
<td>Placebo</td>
<td>FFNS 110 µg</td>
</tr>
<tr>
<td>8.1</td>
<td>8.3</td>
<td>9.4</td>
<td>9.3</td>
</tr>
<tr>
<td>LS mean change from baseline over 2-week treatment period (± difference FFNS vs placebo)</td>
<td>-4.5 (P&lt;0.001)</td>
<td>-2.6</td>
<td>-2.90 (P&lt;0.001)</td>
</tr>
<tr>
<td>Patients, n</td>
<td>141</td>
<td>144</td>
<td>151</td>
</tr>
</tbody>
</table>

24-hour efficacy allows once-daily dosing

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**FFNS provides relief from ocular symptoms in adult patients with SAR (daily reflective TOSS)**

<table>
<thead>
<tr>
<th>European Grass (SAR)</th>
<th>US Ragweed (SAR)</th>
<th>US Mountain Cedar (SAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline mean daily rTOSS</strong></td>
<td><strong>LS mean change from baseline over 2-week treatment period</strong> (*P&lt;0.001)</td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>FFNS 110 µg</td>
<td>5.4</td>
<td>-3.00 (P&lt;0.001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.3</td>
<td>-2.26</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>141</td>
<td>144</td>
<td>151</td>
</tr>
</tbody>
</table>

**Proven and consistent efficacy for ocular symptoms**


Copyright authorisation to reproduce this figure is required.
FFNS improves individual nasal symptoms in adult patients with SAR

Mean change from baseline in total and individual reflective and instantaneous nasal symptoms (14 day treatment period)

* P<0.001

Fokkens et al. Allergy 2007; 62(9): 1078-1084

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Analysis of ocular efficacy in SAR across Intranasal corticosteroids

• Data was included from patients with SAR treated with INS which assessed ocular efficacy as part of the study protocol, either as a primary or secondary endpoint, or as a contributory component of a non-nasal symptom score (which included three ocular symptoms)

• A total of 35 studies were included for analysis

• All studies were double blind (with one exception), randomised, placebo-controlled trials of at least 2 weeks duration;10 also had an active comparator arm (either another INS or an antihistamine)

Analysis of ocular efficacy in SAR across Intranasal corticosteroids

• Assessments employed included:
  – days without symptoms
  – total ocular symptom scores (TOSS)
  – instantaneous TOSS (iTOSS)
  – reflective TOSS (rTOSS)
  – or non-nasal symptoms (eye itching, eye tearing, eye redness, ear/palate itching) scores measured using either a four-point categorical scale, a visual analogue scale (VAS) ranging from 0 (no symptoms) to 100 (most severe symptoms), or a seven-point scale (0 = none, 6 = incapacitated)

• Eye symptoms were rated by physicians or patients using diary cards, and included itching, burning, irritation, tearing, watering, redness, and puffiness

Consistency of ocular efficacy in SAR across Intranasal corticosteroids


Copyright authorisation to reproduce this figure is required.
Consistent efficacy in seven individual nasal and ocular symptoms in SAR

Integrated analysis from 4 studies; treatment period 14 days

Proven and consistent efficacy across all seven nasal and ocular symptoms


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FFNS provides relief from nasal symptoms in adults with PAR

![Graph showing mean change from baseline in daily rTNSS for North American (PAR), Global (PAR), and Global (PAR) groups.]

<table>
<thead>
<tr>
<th></th>
<th>North American (PAR)</th>
<th>Global (PAR)</th>
<th>Global (PAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean daily rTNSS</td>
<td>FFNS 110 µg</td>
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<td>LS mean change from baseline over 2-week treatment period (* difference FFNS vs placebo)</td>
<td>-2.78 (*P&lt;0.005)</td>
<td>-2.08</td>
<td>-3.95 (*P&lt;0.001)</td>
</tr>
<tr>
<td>Patients, n</td>
<td>149</td>
<td>153</td>
<td>151</td>
</tr>
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</table>

Significant and consistent improvement of nasal symptoms

An integrated analysis of the efficacy of FFNS versus placebo on the nasal symptoms of PAR

• An integrated analysis of 3 studies was performed to determine whether the beneficial effects of FFNS consistently improved individual nasal symptoms of PAR

• The three studies were randomised, double blind, placebo-controlled, parallel-group, multicentre trials of similar study design; two were of 4 weeks duration and one of 6 weeks duration

• Comparisons were made between FFNS and placebo on the mean change from baseline over weeks 1-4

An integrated analysis of the efficacy of FFNS versus placebo on the nasal symptoms of PAR

- FFNS110µg once daily effectively relieved all nasal symptoms of PAR including nasal congestion over a 24-hour period.
- The analysis showed that treatment with FFNS consistently relieved all nasal symptoms of PAR.
- A significant improvement in all symptom domains of the TNSS was seen at every week. The efficacy was shown to be sustained over 24 hours which is important to decrease the morning peak symptoms.
- The reduction in nasal blockage is important for subjects with PAR because it affects their sleep and quality of life.

Integrated analysis in adults with PAR

Mean change from baseline in daily rTNSS

Mean change from baseline in reflective individual nasal symptom scores

Mean change from baseline in AM pre-dose instantaneous score


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Long term efficacy in PAR

Mean Change from Baseline in Daily rTNSS over the 12 month Treatment Period

Rosenblut et al. Allergy 2007;62: 1071-1077

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Allergic Rhinitis in the Elderly

- Allergic rhinitis is becoming increasingly common in elderly patients
- Although the incidence of allergic rhinitis generally decreases with age, national data recently have shown that this condition has become more common among individuals aged 65–74 years old when compared with those aged 18–44 years old (8.8% versus 7.0%, respectively)
- The recognition and treatment of allergic rhinitis in the elderly has also assumed greater importance, because this is the fastest-growing population in many countries
- The importance of treating allergic rhinitis in the elderly is further underscored by the fact that this condition increases the risk for asthma, which is associated with higher rates of morbidity and mortality in the elderly than in younger patients

Slavin et al. Allergy Asthma Proc 2010; 31:179-184
FFNS provides relief from nasal symptoms in elderly adults (≥ 65 years) with PAR

![Graph showing mean change from baseline in individual daily reflective scores for congestion, rhinorrhea, sneezing, and itching. FFNS compared to placebo with p-values provided for each symptom.]

- Congestion: p=0.0053
- Rhinorrhea: p=0.0076
- Sneezing: p=0.0802
- Itching: p=0.0138

N=44
FFNS improves nasal symptoms in children with SAR

Mean change from baseline in mean daily rTNSS over 2-weeks in patients aged 6–11 yr

Consistent improvement of nasal symptoms


Copyright authorisation to reproduce this figure is required
FFNS improves nasal symptoms in children with PAR

Consistent improvement of nasal symptoms


Copyright authorisation to reproduce this figure is required

p=0.003, Avamys 55 μg vs placebo.
No significant difference between Avamys 110 μg vs placebo.
Summary

- FFNS produces significant and consistent improvement of nasal and ocular symptoms in SAR
- FFNS improves individual nasal symptoms in adult patients with SAR
- FFNS has consistent ocular efficacy in SAR compared to other INS
- FFNS has proven and consistent efficacy across all seven nasal and ocular symptoms in SAR
- 24-hour efficacy allows once daily dosing
- FFNS produces significant and consistent improvement of nasal symptoms in PAR
- FFNS effectively relieved all nasal symptoms of PAR including nasal congestion over a 24-hour period
- Long term efficacy of FFNS has been demonstrated in PAR
Quality of Life
Quality of Life assessment in clinical trials with FFNS

- The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was developed to measure the functional problems (physical, emotional, social and occupational) that are most troublesome to adults with AR.
- It has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose/eye symptoms, practical problems and emotional function).
- Patients recall how bothered they have been by their AR during the previous week and to respond to each question on a 7-point scale (0 = not impaired at all to 6 = severely impaired).
- The overall RQLQ score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains.
- A reduction in score of ≥0.5 is considered a minimal important difference (MID).

FFNS improves health-related QoL in adults with SAR

Least Square Mean Change From Baseline for FFNS vs Placebo in RQLQ Domains and Overall RQLQ Score

ACT = Activity  
SLP = Sleep  
EMT = Emotional problems  
PRAC = Practical problems  
NOSE = Nasal symptoms  
EYE = Ocular symptoms  
OTHER = Non hayfever symptoms

Fokkens et al. Abstract and poster at 63rd AAAAI 2007
FFNS improves health-related QoL in adults with SAR (European Grass study)

**P=0.001; *P<0.05

Change from baseline in RQLQ score

Overall Activities Sleep Non-nose symptoms Practical problems Nose symptoms Eye symptoms Emotional problems

**P=0.001; *P<0.05


Copyright authorisation to reproduce this figure is required
FFNS improves health-related QoL in adults with PAR

Vasar M et al. *Allergy Asthma Proc* 2008;29:313–21

Copyright authorisation to reproduce this figure is required
FFNS provides relief from nasal symptoms in elderly adults (≥ 65 years) with PAR

Mean Change from Baseline in RQLQ

<table>
<thead>
<tr>
<th>Age &lt; 65 years</th>
<th>Age ≥ 65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>FFNS</td>
</tr>
</tbody>
</table>

Mean change from baseline in RQLQ

Lee et al. ACAAI 2010

Copyright authorisation to reproduce this figure is required
Sleep and Quality of Life

• Lack of sleep is very common in AR, with nasal congestion being a key cause¹
• In a survey, 68% of respondents with PAR and 48% with SAR reported that their condition interfered with sleep¹
• An epidemiological survey showed that sleep quality was worse in patients with moderate to severe and particularly in severe AR²
• The effects of lack of sleep are fatigue and decrease in a patient’s QoL¹
• The importance of sleep impairment is recognised by the ARIA guidelines in which the presence of sleep disturbance is one of the factors that reclassified the severity of AR from mild to moderate-severe³

FFNS and Sleep

- Two studies looked at FFNS vs the oral antihistamine Fexofenadine for nighttime symptoms of SAR
- Each morning, patients completed a validated nighttime symptoms questionnaire comprised of three items:
  - How difficult was it to get to sleep last night because of your nose symptoms? (rated on a scale from 0 [not at all difficult] to 3 [very difficult])
  - How many times did your nose symptoms wake you up last night? (rated on a scale from 0 [not at all] to 3 [I feel like I was awake all night])
  - How severe was your stuffy nose when you woke up? (rated on a scale from 0 [none] to 3 [severe])
- The sum of scores comprises the nighttime symptoms score, which has been shown to be a clinically meaningful measure of nighttime sleep disturbance in AR

FFNS and Sleep

- FFNS was significantly more effective than Fexofenadine and placebo with respect to mean change from baseline in the nighttime symptoms scores over the 2 week treatment period.

- FFNS was shown to improve quality of life related to sleep - the nocturnal Rhinoconjunctiviis Quality of life Questionnaire (NRQLQ)

- FFNS was shown to last for 24 hours compared to fexofenadine

- FFNS improved nasal congestion, the most bothersome symptom of AR and the symptoms thought to be the main cause of sleep impairment

Summary

• FFNS improves health-related QoL in adults with SAR and PAR

• FFNS improves health-related QoL in elderly adults (≥ 65 years) with PAR

• Lack of sleep is very common in AR, with nasal congestion being a key cause

• FFNS was shown to improve quality of life related to sleep
  - the nocturnal Rhinoconjunctiviis Quality of life Questionnaire (NRQLQ)
Safety and tolerability

Paediatric studies
Side effects of Intranasal steroids

• The most common local AEs associated with INSs are:
  – Epistaxis
  – Throat irritation and nasal dryness
  – Burning
  – Stinging

• Systemic side effects can include:
  – Effects on the HPA axis
  – Effects on Statural Growth in Children
  – Effects on Bone Density
  – Ocular effects

Serum cortisol levels in adults

- Serum cortisol weighted mean (ratio from baseline)

<table>
<thead>
<tr>
<th>Treatment comparison</th>
<th>Least square mean</th>
<th>Treatment ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>FFNS 110 µg vs placebo</td>
<td>0.97</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Prednisone vs placebo</td>
<td>0.49</td>
<td>0.99</td>
<td>0.49</td>
</tr>
</tbody>
</table>

## Incidence of Epistaxis in 3 adult studies in PAR

### Incidence of adverse events in ≥ 3% of patients in each individual study

<table>
<thead>
<tr>
<th>Study</th>
<th>FFNS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>**US PAR (4 week study)**1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasal septum ulceration</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>**Global PAR (6 week study)**2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Nasal septum ulceration</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>**Global PAR (4 week study)**3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Epistaxis rates are consistent with those reported for other Intranasal corticosteroids

- Epistaxis has been shown to occur more frequently in FFNS recipients than in placebo recipients; however, the observed incidence was consistent with that reported in the literature for other INS.

Epistaxis rates in clinical trials 6–12 months

<table>
<thead>
<tr>
<th>Study duration</th>
<th>MF %</th>
<th>BDP %</th>
<th>TAA %</th>
<th>FP %</th>
<th>FF %</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months(^1,2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(blood in the nasal mucosa)</td>
<td></td>
<td>9 (9)</td>
<td></td>
<td>8-15 (2-9)</td>
<td></td>
<td>8 (1-2)</td>
</tr>
<tr>
<td>12 months(^3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>3 months(^4,5)</td>
<td>17-19</td>
<td>23</td>
<td></td>
<td>17</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>12 months(^6)*</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

*Duration of treatment not specified but includes 513 patients treated for ≥ 1 year

FFNS is not associated with an increased incidence of ocular AEs

There was no difference between FFNS and placebo on ocular safety in patients ≥12 years after 2 years of continuous treatment

<table>
<thead>
<tr>
<th>Time to first Intraocular pressure event (ITT)</th>
<th>FFNS N=367</th>
<th>Placebo N=181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative % with event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 36</td>
<td>0.32</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 52</td>
<td>0.71</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 64</td>
<td>1.12</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 76</td>
<td>1.98</td>
<td>0.00</td>
</tr>
<tr>
<td>Week 88</td>
<td>1.98</td>
<td>0.84</td>
</tr>
<tr>
<td>Week 104</td>
<td>2.96</td>
<td>0.84</td>
</tr>
<tr>
<td>P value vs placebo</td>
<td>0.34</td>
<td></td>
</tr>
</tbody>
</table>

Laforce et al. Ann Allergy Asthma Immunol 2013:111; 45-50
Long term safety of FFNS (incidence of ocular AEs)

Change from Baseline in Intraocular Pressure over 12 months

Rosenblut et al. Allergy 2007;62: 1071-1077

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Growth in paediatrics

• General limitations of the studies investigating the effect of INS on growth up until 2006 were that they used a variety of methods and study designs and that the results could not adequately define the effect on growth.

• Recognising this in 2007 the FDA produced guidance for industry on the conduct of such studies to improve the way the impact of particular corticosteroid treatments on growth is assessed.

• GSK undertook a study of the effect of FFNS on growth velocity as part of a post-licence commitment to the FDA.

• This is the first INS study to be conducted to the full requirements of the FDA guidance and therefore represents a precise description of the effect of FFNS on growth velocity.

Growth in paediatrics

The study demonstrated that growth velocity is lower in children receiving FFNS 110mcg daily for one year compared with placebo (LS means 5.46 cm/yr and 5.19cm/yr for placebo and FFNS, respectively), and the mean treatment difference is -0.270 cm per year [95% CI -0.48 to -0.06]¹

The design of this study is unprecedented mainly with regards to the large sample size (n=474)¹

Indirect comparison with other growth studies with other INS treatments cannot be made

¹ Lee et al. J Allergy Clin Immunol Pract. 2014;2(4):421-7; ² Avamys UK GDS; ³ Flixonase UK GDS; ⁴ Nasonex UK SMPC
### Growth velocity (cm/year) measured by stadiometry

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>FFNS (N=217)</th>
<th>Placebo (N=218)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female, n</strong></td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>6.08 (1.22)</td>
<td>6.16 (1.22)</td>
</tr>
<tr>
<td>Treatment mean (SD)</td>
<td>5.54 (1.44)</td>
<td>5.88 (1.19)</td>
</tr>
<tr>
<td>Change (SD)</td>
<td>-0.54 (1.61)</td>
<td>-0.28 (1.73)</td>
</tr>
<tr>
<td><strong>Male, n</strong></td>
<td>149</td>
<td>151</td>
</tr>
<tr>
<td>Baseline mean (SD)</td>
<td>5.87 (1.26)</td>
<td>5.89 (1.21)</td>
</tr>
<tr>
<td>Treatment mean (SD)</td>
<td>5.34 (1.05)</td>
<td>5.60 (1.24)</td>
</tr>
<tr>
<td>Change (SD)</td>
<td>-0.53 (1.51)</td>
<td>-0.29 (1.49)</td>
</tr>
</tbody>
</table>

**FFNS over 52 weeks in pre-pubescent children resulted in a 0.27cm reduction in growth velocity compared with placebo**

Paediatric safety

- Pooled analysis of adverse events with an incidence of ≥3% and more common than placebo (6–11 year age group) (3 studies)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=330)</th>
<th>FFNS 55µg (n=295)</th>
<th>FFNS 110µg (n=321)</th>
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</thead>
<tbody>
<tr>
<td>Most common (occurring ≥ 3%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Headache</td>
<td>27 (8)</td>
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<td>28 (9)</td>
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<td>14 (4)</td>
<td>13 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (2)</td>
<td>8 (3)</td>
<td>10 (3)</td>
</tr>
</tbody>
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FFNS 55mcg: 2-week SAR study and 6 week PAR study; FFNS 110mcg:2-week SAR study, 12-week and 6-week PAR study

FFNS has a favorable safety and tolerability profile in patients aged 6–11 years with PAR or SAR

• Avamys device and patient
• preference study
Delivery system is designed to meet the needs of patients

Easy to use device

- **Patient-friendly spray**
  - Less aftertaste and less smell\(^1\)
  - Less drip down the nose or throat\(^1\)
  - Half the spray volume of other intranasal steroids\(^2-4\)
  - Fine mist spray\(^4\)
  - A consistent amount each time\(^3\)

- **Nozzle is short** and ergonomically designed\(^3\)
  - Comfortable for patients\(^3\)

- **Side actuation**
  - Easy to grip\(^5\)
  - Easy for carers to administer medication\(^3,5\)

- **Viewing window**
  - See how much is left\(^5\)

---

5. Godfrey et al. JACI 2007 S230
Patient preference study: single dose study design

- Randomised, multicentre, double-blind, single-dose, crossover study

![Flowchart showing patient preference study design](chart.png)
Sensory attributes of fluticasone furoate nasal spray vs fluticasone propionate nasal spray: patient preferences

- No statistically significant preferences between FFNS and FPNS for attributes related to the medication being soothing, irritating or making patients sneeze

Patients favoured FFNS over FPNS with regards to most sensory attributes


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• Summary

• AR is a global burden and is prevalent throughout Latin-America and Asia-Pacific1

• AR significantly impacts patient quality of life2

• Co-morbidities are highly prevalent with AR
  – The presence of AR often precedes the development of asthma3,4

• A number of treatment guidelines exist, with the ARIA guidelines being the most robust5

• The three main classes of treatment recommended for AR are:5
  – H1 antihistamines
  – Leukotrienes
  – Intranasal glucocorticosteroids

• Avamys is an effective and well tolerated treatment for adults and children with AR6,13
No change in Nasal biopsies after 12 months treatment

Epithelial thickness (mm) at baseline and week 52 (adult PAR)

Each point on the graph represents data from an individual study participant.


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Following 12 months of treatment, there was greater reduction in sub-epithelial inflammatory cell infiltration with FFNS as compared to MFNS. Similar to MFNS, FFNS showed no evidence of mucosal atrophy.

Summary

• A number of treatment guidelines exist, with the ARIA guidelines being the most robust.

• FFNS has a favourable tolerability profile in paediatric subjects two years of age and older with SAR and/or PAR over 2- to 6-week treatment periods.

• Growth should be monitored in paediatrics.
Consistent efficacy in seven individual nasal and ocular symptoms in SAR

Integrated analysis from 4 studies; treatment period 14 days

Nasal itching  Sneeze  Congestion  Rhinorrhea  Eye itching/burning  Eye tearing/watering  Eye redness

Mean change from baseline in daily rTNSS

-0.93  -0.98  -0.93  -0.93  -0.79  -0.8  -0.74

* * * * * *

FFNS  Placebo

*p<0.001 vs placebo

Proven and consistent efficacy across all seven nasal and ocular symptoms

FFNS improves health-related QoL in adults with PAR

Change from baseline in RQLQ score

Overall Activities Sleep Non-nose symptoms Practical problems Nose symptoms Eye symptoms Emotional problems

FFNS 110 µg Placebo

*P<0.001

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Vasar M et al. *Allergy Asthma Proc* 2008;29:313–21
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FFNS 55mcg: 2-week SAR study and 6 week PAR study; FFNS 110mcg:2-week SAR study, 12-week and 6-week PAR study

FFNS has a favorable safety and tolerability profile in patients aged 6–11 years with PAR or SAR

Summary

• Allergic rhinitis is a common type of chronic rhinitis.
• Prevalence of the disorder is increasing in developing countries e.g. Kenya
• AR negatively impacts quality of life
• INS are the mainstay of treatment
• Fluticasone furoate is an ideal INS for the management of AR
GSK is committed to the effective collection and management of human safety information relating to our products and we encourage healthcare professionals to report adverse events to us on +254 20 693 3200 or email us on ke.safety@gsk.com

• Full Prescribing Information is available on request from GlaxoSmithKline Pharmaceutical Kenya Ltd, P.O. Box 78392-00507, Likoni Road, Nairobi Kenya.
Fluticasone Furoate

Contraindications

• Fluticasone furoate nasal spray is contraindicated in patients with hypersensitivity to any of the ingredients.

Warnings and Precautions

• Based on data with another glucocorticoid metabolised by CYP3A4 co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate (see Interactions and Pharmacokinetics).

• Systemic effects with nasal corticosteroids have been reported, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. A reduction in growth velocity has been observed in children treated with fluticasone furoate 110 micrograms daily for one year (see Adverse Reactions and Clinical Studies). Therefore, children should be maintained on the lowest dose which delivers adequate symptom control (see Dosage and Administration). As with other intranasal corticosteroids, physicians should be alert to potential systemic steroid effects including ocular changes (see Clinical Studies).