

Public Assessment Report
Mutual Recognition Procedure

Flunase Aqueous 50 Microgram Nasal Spray

MRP no: UK/H/0920/001
UK licence no: PL 00530/0761

Applicant: Norton Healthcare Limited

Flunase Aqueous 50 Microgram Nasal Spray
UK/H/0920/001
PL 00530/0761

LAY SUMMARY

Spain today approved Norton Healthcare Limited's Marketing Authorisation (licence) for the medicinal product Flunase Aqueous 50 microgram Nasal Spray (PL 00530/0761) following acceptance of the UK marketing authorisation. This is a prescription-only medicines (POM) used in the prophylaxis and treatment of seasonal allergic rhinitis (e.g. hay fever) and perennial rhinitis (blocked/runny nose and sneezing/itching caused by house dust mites or animals such as cats and dogs).

Flunase Aqueous 50 microgram Nasal Spray contains the active ingredient fluticasone propionate, which is one of a group of medicines called corticosteroids. These have anti-inflammatory properties, which reduce swelling and irritation when sprayed into the nose.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Flunase Aqueous 50 microgram Nasal Spray outweigh the risks; hence a marketing authorisation has been approved.

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Module 1

Product Name	Flunase Aqueous 50 microgram Nasal Spray
Type of Application	Abridged Initial application Generic, Article 10.1 [formerly 10.1(a)(iii)] Chemical substance Prescription only
Active Substance	Fluticasone propionate
Form	Nasal Spray
Strength	50 micrograms per 100microlitre metered dose
MA Holder	Norton Healthcare Limited (trading as IVAX Pharmaceuticals)
RMS	United Kingdom
CMS	Spain
Procedure Number	UK/H/0920/001/MR
Timetable	Day 90 16/10/2006

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flunase Aqueous 50 microgram Nasal Spray.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 microlitre metered spray contains 50 microgram of fluticasone propionate.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Nasal spray.

The medical product consists of a white, opaque aqueous suspension contained within an amber glass multidose bottle fitted with a metering pump.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Flunase Aqueous 50 microgram Nasal Spray is indicated for the prophylaxis and treatment of seasonal allergic rhinitis (including hay fever) and perennial rhinitis.

4.2 Posology and Method of Administration

Flunase Aqueous 50 microgram Nasal Spray is for administration by the intranasal route only.

Prior to first use Flunase Aqueous 50 microgram Nasal Spray must be primed by pressing down and releasing the pump six times. If Flunase Aqueous 50 microgram Nasal Spray has not been used for 7 days it must be reprimed by pressing down and releasing the pump a sufficient number of times until a fine mist is produced.

Discard three months after first using the spray.

Adults and children of 12 years of age and over:

Two sprays into each nostril once a day (200 mcg) preferably in the morning is recommended. In some cases two sprays into each nostril twice a day (400 mcg) may be required. Once symptoms are under control a maintenance dose of one spray per nostril once a day (100 mcg) may be used. If symptoms recur the dosage may be increased accordingly. The maximum daily dose should not exceed four sprays into each nostril (400 mcg). The minimum dose at which the effective control of symptoms is maintained should be used.

Elderly patients:

The normal adult dosage is applicable.

Children between ages of 4 and 11:

One spray into each nostril once a day (100 mcg), preferably in the morning, is recommended. In some cases one spray into each nostril twice a day (200 mcg) may be required. The maximum daily dose should not exceed two sprays into each nostril (200 mcg). The minimum dose at which the effective control of symptoms is maintained should be used.

Children less than 4 years old:

Flunase Aqueous 50 microgram Nasal Spray is not indicated for children under 4 years old.

For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient since maximum relief may not be obtained for 3 to 4 days after commencement of treatment.

4.3 Contraindications

Hypersensitivity to fluticasone propionate or to any of the excipients.

4.4 Special Warning and Precautions for Use

Local infections: infections of the nasal airways should be appropriately treated but do not constitute a specific contraindication to treatment with Flunase Aqueous 50 microgram Nasal Spray.

Administration of treatment may be necessary for several days for the full benefit of Flunase Aqueous 50 microgram Nasal Spray to be achieved.

Upon transferring patients from systemic steroid treatment to Flunase Aqueous 50 microgram Nasal Spray care must be taken if there is any reason to suppose that their adrenal function is impaired.

In most cases Flunase Aqueous 50 microgram Nasal Spray will control seasonal allergic rhinitis, however in the event of an abnormally heavy challenge of summer allergens appropriate additional therapy may be necessitated in certain instances. Such an instance may particularly be to control eye symptoms.

Systemic effects of nasal corticosteroids, particularly when prescribed at high doses for prolonged periods, may occur. Such systemic effects vary between patients and different corticosteroids (please refer to pharmacokinetic and pharmacodynamic information).

Some nasal corticosteroids have been reported to produce growth retardation in children when prescribed at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. If slowed growth is observed, a review of the therapy should be performed with a resultant reduction of the dose of nasal corticosteroid, if possible, to the lowest dose at which effective control of symptoms is maintained. Furthermore a referral of the patient to a paediatric specialist should be considered.

Adrenal suppression may occur to clinically significant levels as a result of treatment with higher than recommended doses of nasal corticosteroids. If there is evidence for higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Incidences of significant interactions between fluticasone propionate and potent inhibitors of the cytochrome P450 3A4 system (e.g. ketoconazole and protease inhibitors such as ritonavir) may occur. Increased systemic exposure to fluticasone propionate may be resultant.

4.5 Interaction with other Medicinal Products and other Forms of Interaction

Effects of fluticasone propionate on other drugs

No significant effect of fluticasone propionate on the pharmacokinetics of terfenadine and erythromycin has been shown during drug interaction studies.

Effects of other drugs on fluticasone propionate

No significant effect of terfenadine and erythromycin on the pharmacokinetics of fluticasone propionate has been shown during drug interaction studies.

Care should be taken when administering fluticasone propionate in patients taking concurrent drugs that are highly potent inhibitors of the cytochrome P450 3A4 system (e.g. protease inhibitors such as ritonavir). In an interaction study in healthy subjects with intranasal fluticasone propionate, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) 100 mg b.i.d. increased the fluticasone propionate plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol concentrations. Cases of Cushing's syndrome and adrenal suppression have been reported. The combination should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects. Other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations (see section 4.4).

4.6 Pregnancy and Lactation

There is inadequate evidence of safety in human pregnancy. Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development, including cleft palate and intra-uterine growth retardation. There may therefore be a very small risk of such effects in the human foetus. It should be noted, however, that the foetal changes in animals occur after relatively high systemic exposure; direct intranasal application ensures minimal systemic exposure.

As with other drugs the use of Flunase Aqueous 50 microgram Nasal Spray during human pregnancy requires that the possible benefits of the drug be weighed against the possible hazards.

The secretion of fluticasone propionate in human breast milk has not been investigated. Subcutaneous administration of fluticasone propionate to lactating laboratory rats produced measurable plasma levels and evidence of fluticasone propionate in the milk. However, following intranasal administration to primates, no drug was detected in the plasma, and it is therefore unlikely that the drug would be detectable in milk. When Flunase Aqueous 50 microgram Nasal Spray is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

4.7 Effects on Ability to Drive and Use Machines

The medicinal product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $<1/10$), uncommon ($\geq 1/1000$ and $<1/100$), rare ($\geq 1/10,000$ and $<1/1000$) and very rare ($<1/10,000$) including isolated reports.

System Organ Class	Adverse Event	Frequency
Immune system disorders	Hypersensitivity reactions with the following manifestations:	
	Bronchospasm	Rare
	Anaphylactic reactions	Rare
	Anaphylactoid reactions	Rare
	Cutaneous hypersensitivity	Very rare
	Angioedema (mainly facial and oropharyngeal oedema)	Very rare
Nervous system disorders	Headache, unpleasant taste, unpleasant smell.	Common
System Organ Class	Adverse Event	Frequency
Eye disorders	Glaucoma, raised intraocular pressure, cataract These events have been identified from spontaneous reports following prolonged treatment.	Very rare
	Respiratory, Thoracic & Mediastinal disorders	Epistaxis
Respiratory, Thoracic & Mediastinal disorders	Nasal dryness, nasal irritation, throat dryness, throat irritation.	Common
	Nasal septal perforation, mucocutaneous ulceration Usually in patients who have had previous nasal surgery.	Very rare

Systemic effects of some nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods.

4.9 Overdose

There are no data available on the effects of acute or chronic overdosage with Flunase Aqueous 50 microgram Nasal Spray. Intranasal administration of 2 micrograms fluticasone propionate twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

Inhalation or oral administration of high doses of corticosteroids over a long period may lead to suppression of HPA axis function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: R01A D08

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14).

5.2 Pharmacokinetic Properties

Absorption: Following intranasal dosing of fluticasone propionate, (200mcg/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest C_{max} observed was 0.017ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Distribution: Fluticasone propionate has a large volume of distribution at steady-state (approximately 318L). Plasma protein binding is moderately high (91%).

Metabolism: Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Care should be taken when co-administering potent CYP3A4 inhibitors such as ketoconazole and ritonavir as there is potential for increased systemic exposure to fluticasone propionate.

Elimination: The elimination rate of intravenous administered fluticasone propionate is linear over the 250—1000mcg dose range and are characterised by a high plasma clearance (CL=1.1L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

5.3 Preclinical Safety Data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Glucose (Anhydrous)
Microcrystalline Cellulose
Carmellose Sodium
Phenylethyl Alcohol
Benzalkonium Chloride
Polysorbate 80
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

After first opening: 3 months

6.4 Special Precautions for Storage

Do not store above 25°C

6.5 Nature and Contents of Container

6ml or 15ml amber glass bottle [Type 1] fitted with an atomising metering pump.
Pack sizes: 60, 120 and 150 metered sprays.
Not all pack sizes may be marketed.

6.6 Instructions for Use and Handling

No special requirements

- 7. MARKETING AUTHORISATION HOLDER**
Norton Healthcare Limited T/A IVAX Pharmaceuticals UK,
Albert Basin,
Royal Docks,
London,
E16 2QJ,
UK
- 8. MARKETING AUTHORISATION NUMBER**
PL 00530/0761
- 9. DATE OF FIRST AUTHORISATION /RENEWAL OF THE AUTHORISATION**
12th May 2005
- 10 DATE OF REVISION OF THE TEXT**
24/03/2006

Module 3

Product Information Leaflet & Technical Leaflet

Please read this leaflet carefully before you start to use your medicine.

It contains important information.

If you are not sure about anything, or you want to know more, ask your doctor or a pharmacist.

Keep this leaflet safe, as you may want to read it again.

About your medicine

Your medicine is called Flunase Aqueous 50 microgram Nasal Spray (described as "Flunase Nasal Spray" throughout this leaflet) and contains 50 micrograms of the active ingredient, fluticasone propionate, in each spray. Fluticasone propionate is one of a group of medicines known as corticosteroids.

What is in your medicine

Each spray of Flunase Nasal Spray contains:
50 micrograms of fluticasone propionate (active ingredient), and Glucose (anhydrous), microcrystalline cellulose, carmellose sodium, phenylethyl alcohol, benzalkonium chloride, polysorbate 80, and purified water (inactive ingredients).
Each bottle of Flunase Nasal Spray contains 60, 120 or 150 sprays.

Who makes your medicine

Your medicine is made by IVAX Pharmaceuticals s.r.o., Opava, Czech Republic.
The marketing authorisation holder is IVAX Pharmaceuticals UK, Albert Basin, Royal Docks, London E16 2QJ, UK.

What your medicine does

Flunase Nasal Spray contains fluticasone propionate, which is one of a group of medicines called corticosteroids. Your medicine has anti-inflammatory properties. When sprayed into your nose it will reduce swelling and irritation. It is used to prevent and treat seasonal allergic

rhinitis (e.g. hayfever) and perennial rhinitis (e.g. blocked or runny nose and sneezing and itching caused by house dust mites or animals such as cats and dogs). It can be used by adults and children of 4 years of age and over.

Before you use your medicine

Do not use this medicine if you are allergic to fluticasone propionate or any other ingredients in this product (see section "What is in your medicine").
Please tell your doctor before you start to use your medicine if:

- You are pregnant, planning to become pregnant or breast-feeding
- You have ever had an operation to your nose
- You have recently been treated with injected steroids, or you have been taking oral steroids for a long time.

Please inform your doctor or your pharmacist if you are taking:

- Any medicines used in the treatment of fungal infections (e.g. ketoconazole)
 - Any antiviral medicine such as those used to treat HIV infection (e.g. ritonavir)
 - Any other regular treatment or using any other medicines - including those that you bought for yourself without a prescription
- Always ask your doctor if in any doubt.

How to use your medicine

You must use your medicine as your doctor has told you to. Do not stop using your medicine unless your doctor tells you, even if you feel better.

Adults and children of 12 years of age and over:

When you first start using Flunase Nasal Spray you normally take two sprays in each nostril once a day, preferably in the morning. Your doctor may increase this to a maximum of two sprays into each nostril twice a day.

Once your symptoms are under control your doctor may reduce your dose to one spray into each nostril once a day. If the use of such a reduced dose signals a worsening in your symptoms, your dose may be increased back to the starting dose.

Children between the ages of 4 and 11:

For children aged between 4-11 years old the dose is normally one spray in each nostril once a day, preferably in the morning. Your doctor may increase this to a maximum of one spray into each nostril twice a day.

This product is not suitable for children under 4 years old

Your doctor will prescribe the lowest dose of Flunase Nasal Spray capable of effectively controlling your symptoms. You must not take a larger dose, or use your Flunase Nasal Spray more often, than is prescribed by your doctor.

Your nose symptoms may only start to improve after you have been using your medicine for a few days - therefore it is very important that you use your medicine regularly as prescribed, and that you keep using your medicine unless your doctor tells you to stop, even if you feel better.

If your eyes remain itchy or watery as a result of hayfever despite using this medicine tell your doctor.

He/she may be able to give you another medicine to treat your eye symptoms.

If you forget to take a dose at the right time, take it as soon as you remember. Do not take two doses together. If it is almost time to take the next dose, wait until then and then carry on as before.

Before you use your nasal spray

Your Flunase Nasal Spray has a dust cap that protects the nozzle and keeps it clean - this must be taken off prior to using the spray and then replaced after use.

When your Flunase Nasal Spray is new, or you have not used it for a few days, it may not work at first. In such an instance the bottle must be primed as follows:-

1. Shake the bottle gently and then remove the dust cap.
2. Hold the bottle upright with your thumb under the bottle and your index finger and middle finger on either side of the nozzle. Ensure that the nozzle is pointing away from you when you do this.
3. Press down with fingers in order to pump the spray
4. Repeat steps 2 and 3 a further five times - the bottle is now primed.

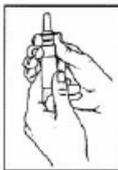


If you have not used your Flunase Nasal Spray for 7 days, prime until a fine mist is produced.

If after attempting to prime the bottle the spray still does not work and you think it may be blocked you may clean the spray using the following procedure:-

Cleaning your nasal spray

1. Remove the dust cap.
 2. Pull the white collar upwards to remove the nozzle.
 3. Place the nozzle and dust cap in warm water and soak for a few minutes, and then rinse by placing under a running tap.
 4. Shake off the excess water and allow the nozzle and dust cap to dry in a warm (not hot) place.
 5. Re-fit the nozzle.
 6. 'Prime' the bottle as necessary by pumping the spray a few times until a fine mist is produced.
- You should clean your nasal spray at least once a week to stop it from getting blocked up. Additional cleaning is required when your spray becomes blocked.
- You must NEVER attempt to unblock or enlarge the spray hole with a pin or other sharp object because this will destroy the spray mechanism.



Using your nasal spray

1. Shake the bottle and remove the dust cap.
2. Gently blow your nose.
3. Close one nostril by pressing your finger against it and place the nozzle of the spray in your other nostril. Tilt your head forward slightly so that the bottle is kept upright.



4. Breathe in slowly through your open nostril and, at the same time, press the collar of the nozzle down firmly with your fingers to squirt a spray of fine mist into your nostril.
5. Breathe out through your mouth. Repeat step 4 to take a second spray into the same nostril.
6. Remove the nozzle from this nostril and breathe out through your mouth.
7. Repeat steps 3 to 6 with your other nostril.



After using your nasal spray
Wipe the nozzle carefully with a clean tissue and put the dust cap back on.

What to do if you use too much medicine

It is important not to use more of your medicine than your doctor has told you to.
If you accidentally use more Flunase Nasal Spray than you were told to use please inform your doctor.
Take this leaflet, and your Flunase Nasal Spray, to show the doctor.

After using your medicine

You may sometimes sneeze a little - however this soon stops. Very occasionally you may experience an unpleasant taste or smell.

If you are using high doses of Flunase Nasal Spray you may require extra steroids in times of extreme stress, or during admission to hospital after a serious accident or injury, or before a surgical operation. Your doctor may decide to give you extra steroid medication during this period in the form of tablets or injection if you are in hospital.

Although most people do not have any problems using this medicine some people may experience the following:

Rare occurrences of a severe allergic reaction to this medicine have been reported. In the event of the sudden onset of a rash, swelling (usually of the tongue, face or lips) or difficulty in breathing discontinue using your nasal spray immediately and contact your doctor without delay.

On very rare occasions treatment with nasal corticosteroids may affect the production of steroids in the body. The likelihood of such an incidence is increased by use of a high dose over a long period of time. Such an effect is that children may grow more slowly than others, and therefore children receiving treatment with nasal corticosteroids over a long period of time will have their height checked regularly by their doctor. Your doctor will help prevent this happening by prescribing the lowest dose of steroid capable of adequately controlling your symptoms.

Very rarely glaucoma (raised pressure in the eye) and cataracts (clouding of the lens in the eye) have been reported following prolonged treatment.

Some people may occasionally suffer from a headache after using this medicine.

Upon the occurrence of your nose or throat becoming sore, or if you have a bad nose bleed after having used this medicine, inform your doctor as soon as possible.

Extremely rarely the nose septum (the dividing partition in the nose) may become perforated.

If you feel unwell in any other way, tell your doctor or pharmacist as soon as you can.

Looking after your medicine

Keep your Flunase Nasal Spray in a safe place where children cannot see or reach it.

Do not store above 25°C.

Do not take Flunase Nasal Spray after the expiry date.

You should take any Flunase Nasal Spray that is out of date, or which you no longer need, back to your pharmacist to be destroyed.

This medicine is only for you. Only a doctor can prescribe it for you. Never give your medicine to anyone else, even if they seem to have the same symptoms.

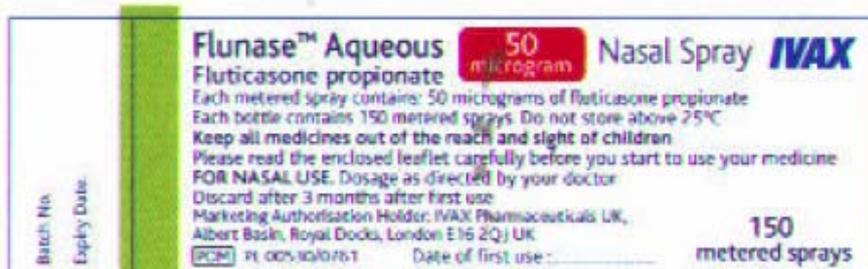
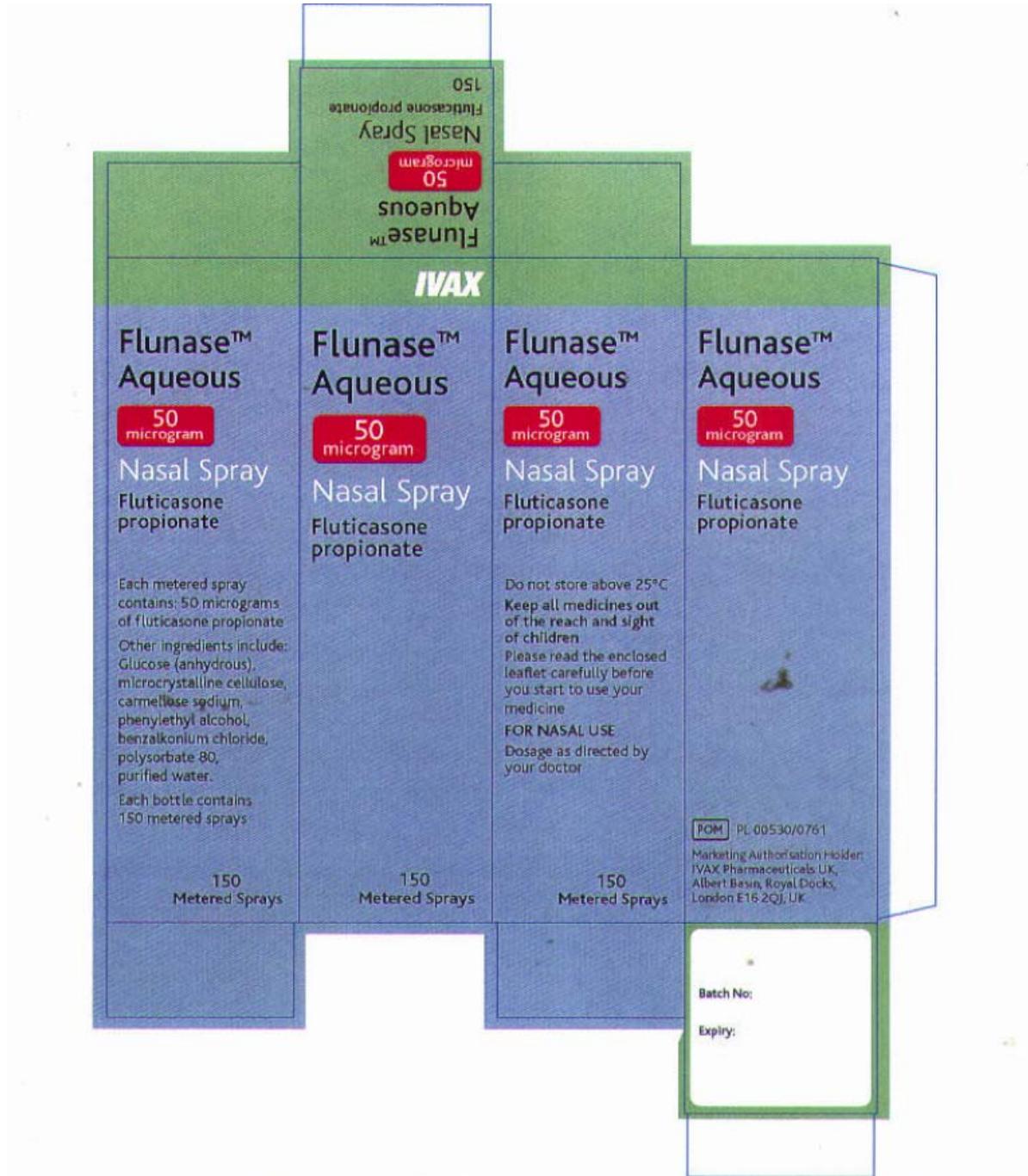
This information applies only to IVAX Pharmaceutical's Flunase Nasal Spray

PL 00530/076 1

This leaflet was written in April 2005.

Module 4

Labelling



Module 5

Scientific discussion during initial procedure

1. INTRODUCTION

Background

This application was submitted by Norton Healthcare Limited for a generic version of Flunase Aqueous 50 Microgram Nasal Spray, via the Mutual Recognition Procedure. The originator product is Flixonase Nasal Spray, which was licensed to GlaxoWellcome UK Limited on 15th September 1995 (PL 10949/0036), following a change of ownership from Allen and Hanbury Limited (PL 00045/0153), who were granted the licence on 8th March 1990.

Fluticasone propionate is a glucocorticosteroid, which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. Fluticasone propionate has been licensed in the UK for nasal use since 1990. There are two nasal preparations containing fluticasone propionate currently licensed in the UK; Flixonase Aqueous Nasal Spray (PL 10949/0036) for the prophylaxis and treatment of seasonal allergic and perennial rhinitis, and Flixonase Nasal Drops (PL 10949/0323) for the treatment of nasal polyps.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Flunase Aqueous 50 Microgram Nasal Spray could be approved for the prophylaxis and treatment of seasonal allergic rhinitis (including hay fever) and perennial rhinitis.

A Marketing Authorisation was approved in Spain, where the product name is Nastricin. A Marketing Authorisation had previously been granted in the reference member state (RMS, i.e. the UK) on 12th May 2005.

Overall Benefit/Risk Assessment

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

Clinical studies on Flunase Aqueous 50 microgram Nasal Spray were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that for the generic product, therapeutic efficacy and bioavailability was comparable to that of the innovator product.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The SPC is satisfactory from the clinical, preclinical and pharmaceutical point of view for a product of this nature.

2. QUALITY ASPECTS

3.2.S DRUG SUBSTANCE

Fluticasone propionate is a white to almost white powder. It is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol.

Chemical Name: S-fluoromethyl 6 α , 9 α -difluoro-11 β 17-dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carbothioate, 17propionate.
Molecular formula: C₂₅H₃₁ F₃O₅S
Molecular weight: 500.6
Chirality: There are nine chiral centres.

A DMF has been provided from the manufacturer of active fluticasone propionate. A declaration has been provided stating that none of the ingredients used in the manufacture of active fluticasone propionate is of animal origin.

3.2.S.4 Control of Drug Substance

The drug substance is tested according to the *Ph Eur* monograph for fluticasone propionate. Additional tests are also performed for residual solvents, these are in line with current guidelines.

3.2.S.4.4.2 Batch Analyses – Drug Product Manufacturer

The drug product manufacturer's tests and limits are in line with those of the active ingredient manufacturer. There is also an additional test for particle size. The appropriate validation data has been provided. Certificates of analysis (CoA) for one batch of fluticasone propionate tested by the Finished Product Manufacturer (FPM) has been provided. The data show compliance with the proposed specification.

3.2.S.7 Stability

Stability data are provided in the DMF for three pilot scale batches packed in scaled down version of the marketed pack and stored at 40°C/75%RH for 6 months and at 25°C/60%RH for 48 months.

Based on the stability data, the appropriate storage conditions to apply are not to store above 25°C. The product will be stored by at the European manufacturing facility of the finished product manufacturer under ambient conditions with a re-test period of 2 years.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The product is presented as one strength, 50 micrograms per 100microlitre dose. Pack sizes are 60, 120 and 150 doses.

Component	Reference
Active ingredient	
Fluticasone propionate	Ph Eur
Excipients	
Glucose anhydrous	Ph Eur
Polysorbate 80	Ph Eur
Cellulose dispersible	BP
Phenylethyl alcohol	USP
Benzalkonium chloride 50%	Ph Eur
Water purified	Ph Eur

The same composition is already on the UK market for over a decade and marketed as Flixonase.

3.2.P.2 Pharmaceutical Development

Formulation Development

The active substance is practically insoluble in water and is, therefore, formulated as an aqueous suspension. The efficacy of the product relies on the local action of the Fluticasone in the nasal mucosa. To provide an even and wide distribution in the mucosa, a small particle size distribution is desirable.

As the chosen formulation is an aqueous suspension it is important to ensure a homogeneous suspension to provide consistent dose content uniformity during use. A small particle size distribution of the active formulated with Avicel provides such a system.

There are no novel or unusual excipients in the formulation. The excipients have been chosen based on the reference product and are acceptable. The marketing authorisation holder has provided comparative data to show that the formulation is quantitatively and qualitatively the same as the marketed product.

Manufacturing Process Development

Satisfactory manufacturing process development data have been provided.

Container-Closure System Development

Satisfactory data have been provided to show that the packaging is appropriate for a product of this nature.

Essential Similarity

The applicant has provided the following information to support their claim of essential similarity:

- (i) Satisfactory comparative impurity profiles are provided for the test and reference products
- (ii) The active substance complies with the Ph. Eur. There are no new impurities.

- (iii) The Finished Product Specification complies with ICH and Ph Eur general requirements and impurities are generally in line with that approved for the reference product.

Essential similarity is considered proven.

3.2.P.3 Manufacture

Satisfactory manufacturing authorisations have been provided for the site of manufacture and the batch release site. A satisfactory batch formula and batch data have been provided.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

A description of the manufacturing process has been provided. In-process controls have been provided and are acceptable.

3.2.P.3.5 Process Validation

Process validation data have been provided for three production-scale batches. Proposed equipment and production systems intended for routine manufacture were used. All three bottles filled into standard bottles of 60, 120 or 150 actuations. The batch data provided for these were satisfactory.

3.2.P.4 Control of Excipients

Glucose anhydrous, polysorbate 80, Benzalkonium Chloride 50% solution and purified water comply with Ph. Eur specification. Dispersible cellulose complies with BP and phenylethyl alcohol complies with the USP/NF. Certificates of analysis from the finished product manufacture and the supplier are provided and are acceptable.

No excipients of human or animal origin are used in this product.

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification

The product release and shelf-life specifications have been provided. These comply with ICH guidelines and Ph Eur requirements for nasal products.

3.2.P.5.2 Analytical Procedures

Details of all analytical methods have been provided and are satisfactory.

3.2.P.5.3 Validation of Analytical Procedures

Appropriate validation data have been provided.

3.2.P.5.4 Batch Analyses.

Certificates of analysis have been provided for four production-scale batches of finished product to show compliance with the finished product specification.

3.2.P.5.5 Characterisation of Impurities

All impurities present in the finished product have been suitably characterised.

Satisfactory limits for impurities have been included in the specification.

3.2.P.5.6 Justification of Specifications

The finished product specification complies with the ICH guidelines and Ph Eur requirements for nasal products. Satisfactory justifications have been provided for all test parameters and limits.

3.2.P.6 Reference Standards or Materials

Satisfactory certificates of analysis have been provided for all reference standards.

3.2.P.7 Container Closure System

Fluticasone Propionate 50mcg Nasal Spray is supplied in amber, type I glass bottles fitted with a white, metering, atomising pump, white nasal adapter and clear dust cap in a carton. Three pack sizes of 60, 120 and 150 sprays are proposed. There are two bottle sizes, 6 and 15ml. The 6ml bottle contains 60 sprays and the 15ml bottle either 120 or 150 sprays each delivering 50mcg of fluticasone propionate in 100mg of formulation through the nasal adapter.

Schematics of the packaging components have been provided. Satisfactory testing is carried out by the finished product manufacturer on receipt of each batch of packaging.

No certificates have been provided to show compliance of the bottle in relation to the European regulations concerning contact with foodstuff. However, certificates of quality from the suppliers have been provided showing compliance to Ph Eur requirements for Type I glass bottles.

Certificates of compliance for rubbers used in the nasal spray pump show conformity with European Directive 93/11/EEC. A comprehensive list of components in the pump, actuator and cap has been provided, which show compliance with EU and US requirements for packaging, food and pharmaceutical use.

3.2.P.8 Stability

Two stability studies have been provided. The first study was performed on three batches of product manufactured in the US. Batches were placed on stability for 24 months at 25°C/60%RH and 3 months at 40°C/75%RH. This study is considered as supportive data only as the manufacturing site differs from that proposed for the finished product.

The second study was performed on nine batches manufactured at the proposed manufacturing site. Batches were placed on stability for 12 months at 25°C/60%RH, 12 months at 30°C/60%RH and 6 months at 40°C/75%RH. All batches of finished product tested were in the packaging proposed for marketing and all pack sizes proposed for marketing were tested.

For both studies, all batches remained within specifications at all timepoints tested. No trends were observed in any parameters, except preservatives, which changed as expected and remained within specifications.

The applicant has committed to continue the second stability study up to a minimum of 24 months, with one batch a year being placed on stability annually.

No photostability testing has been provided, but since the product is contained in an amber glass bottle and the reference product has no special warnings regarding light exposure, this is acceptable.

An initial in-use shelf life of 3 months is claimed. This has been justified by the applicant with the following points:

- (i) The product is formulated and packaged with the same materials as the brand leader (GSK's Flixonase Aqueous Nasal Spray). This product has no in-use life stated and therefore the in-use life is the same as the unopened product.
- (ii) Although the product is "opened" before first use, the closure is not removed and the only exposure the contents receive is when the container equalises with atmospheric pressure after an actuation. A volume of air of equivalent volume to an actuation (approximately 0.1ml) will enter.
- (iii) A production batch made by the proposed finished product manufacturer has fully complied with the Ph. Eur. PET criteria A after 12 months storage of the closed product at 25°C.
- (iv) Product made by IVAX US at full strength, 90%, 75% and 50% preservatives has robustly complied with the USP PET equivalent to the Ph Eur criteria B.
- (v) Full term stability of the product in the US trial, 12 months real time and six months accelerated from the European trials demonstrate the robust stability of the closed product.
- (vi) Within the Scope of CPMP/QWP/2934/99, the product is not subjected to repeated opening and closing, it is robust with respect to physical or chemical degradation and resists the growth of micro-organisms.

This is accepted. The in-use shelf life of 3 months will be further confirmed and then possibly extended following satisfactory completion of the in-use stability programme agreed by the MHRA during national assessment.

The stability data provided support a shelf life of 2 years (with a shelf life of 3 months after opening) with the storage conditions "Do not store above 25 degrees".

SPC, LABELS AND PACKAGE LEAFLET

SPC, labels and leaflet were supplied and are satisfactory.

PHARMACEUTICAL CONCLUSIONS

A product licence can be granted for this product.

3. NON-CLINICAL ASPECTS

This application for a generic product claims essential similarity to Flixonase Aqueous Nasal Spray (Glaxo Wellcome UK trading as Allen & Hanburys, UK), which has been licensed within the EEA for over 10 years.

No new preclinical data has been supplied with these applications, however, a preclinical expert report summarising relevant non-clinical studies has been included in the MR dossier; this is satisfactory.

4. CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: R01A D08

Fluticasone has a high topical anti-inflammatory potency.

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24-hour serum cortisol AUC was found compared to placebo (ratio 1.01, 90% CI 0.9-1.14).

Pharmacokinetics

The applicant has undertaken a pharmacokinetic study comparing the bioavailability of their fluticasone aqueous nasal spray (FANS) formulation with that of the innovator product. The study was undertaken according to the principles of GCP.

Study IXR-103-1 162

Protocol

This was a randomised, open-label, three-way crossover study comparing the pharmacokinetic and safety profile of the IVAX 0.05% formulation with that of the originator intranasal fluticasone products (Flonase, GSK Ltd (US product) and Flixonase, GSK Ltd (UK product)). A total of 80 subjects aged 18-54 years were screened and 60 were randomised, seven patients withdrew from the study for personal reasons. As only a minimal amount of fluticasone is absorbed by the nasal route a dose of 800 mcg was chosen in order to provide measurable plasma levels in the picogram/ml range.

Following screening subjects received a single 800 microg dose (8 sprays of 50 microg per nostril) of one of the three study treatment on three separate occasions 2-7 days apart. Plasma samples were taken pre-dose and at 10, 20, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 18 and 24 hours post dose on each occasion.

Analytical Methods

0.5ml plasma samples were analysed for fluticasone using liquid chromatography mass spectrometry (LC-MS/MS). The lower limit of quantification was 3 pg/ml.

Results

Please note that the results that are directly relevant to the assessment of the product in Europe, i.e. the comparison of the IVAX formulation versus the European comparator product (Flixonase, GSK Limited, UK), are presented.

	t_{max} (hours) (SD)	t_{1/2} (hours) (SD)	Ratio AUC_{0-t}(pg/ml.hr) (90% CI)	Ratio C_{max} (pg/ml) (90% CI)
FANS	0.96 (0.11)	15.97 (2.85)	-	-
Flixonase	0.94 (0.11)	20.40 (2.85)	0.95 (0.80-1.06)	0.95 (0.88-1.03)

Medical Assessor's Comment

The values for the ratio of AUC_{0-t} and Ratio of C_{max} for FANS to Flixonase (EU innovator product) fall between 80 to 125% confidence intervals and show that the systemic exposure to fluticasone is similar for both formulations.

EFFICACY

The applicant undertook a single therapeutic equivalence study.

Study IXL-301-16-162

Protocol

This was a multicentre, randomised, double-blind, double-dummy, parallel-group study undertaken in patients aged 12 years or older designed to investigate the safety and efficacy of FANS compared to Flonase and Flixonase and placebo administered for 13 to 15 days. The study was conducted at six study sites located in central Texas during the December 2001 to February 2002 mountain cedar (*Juniperus ashei*) pollen season. There were four study visits at Screening, Day 1, Day 8 and Day 15. There was a 3- to 21-day run in period between the Screening visit and Day 1. Patients were randomly assigned in a 2:1 ratio (active to placebo) and study drug was administered for 13 to 15 days.

The primary objective of the study was to establish bioequivalence of the investigational product, FANS, with Flixonase and Flonase. In addition, the efficacy of each active formulation versus placebo was to be demonstrated.

There was a 4-week placebo run-in period. The ITT population has 514 patients in it. 74 on placebo, 146 on FANS, 146 on Flonase and 148 on Flixonase.

Efficacy Measurement

Primary Endpoint:

The mean patient rated total nasal symptom score (TNSS) over the entire treatment period (using AM and PM individual nasal symptom scores averaged from diary cards). The TNSS (reflective score) was comprised of the four symptoms most prevalent in seasonal allergic rhinitis: rhinorrheas, nasal stuffiness/congestion, nasal itching, and sneezing.

Results

Primary Endpoint:

The primary endpoint was the difference in mean $\log_{10}(TNSS+1)$ between the FANS and both the Flonase and Flixonase groups. The primary analysis of this endpoint was an analysis of covariance with fixed effects for treatment group and investigator, and with baseline-combined AM and PM TNSS as a covariate.

Statistical Assessor's Comment

This analysis is appropriate. However, an analysis of the change from baseline in TNSS would also be useful in interpreting any differences between treatments.

“Bioequivalence” was concluded if the 90% confidence interval for the difference in mean $\log_{10}(TNSS+1)$ between the FANS, and both the Flonase and Flixonase groups difference in mean $\log_{10}(TNSS+1)$, lay within -0.0969 and 0.0969 (equivalent to limits of 0.80 to 1.25 on a ratio scale)

Medical Assessor's Comment

The applicant was asked to justify its choice of limits for bioequivalence as the study was essentially a therapeutic equivalence study. Also 95%, not 90%, confidence intervals for all analyses presented were requested and additional analyses of the change from baseline in mean TNSS between treatment groups were requested for comparison.

In the response, the applicant presented all the analyses requested and provided 95% confidence intervals for all these analyses. The applicant explained that the original 0.80 to 1.25 limits were specified by the FDA. The choice of limits is discussed further after summarising the results of the study.

The results on the original scale with 95% confidence intervals for the primary endpoint for the per-protocol population are summarised in the table below. Note the results for the ITT population are very similar.

Equivalence Assessment	Estimate ¹	95% Confidence Interval ²
(Log ₁₀ Scale) Mean difference between FANS and combined Flonase and Flixonase groups	0.0074	(-0.0324,0.0472)
(Absolute Scale) Mean Ratio of FANS to combined Flonase and Flixonase groups	1.02	(0.93,1.11)

¹ The Analysis is based on a linear two-way analysis of covariance with fixed effects for treatment group and investigator, and with baseline combined AM and PM TNSS as a covariate.

² Equivalence to FANS to a reference product was concluded if the 95% CI for the difference in mean log₁₀ (TNSS+1) was contained within the interval of (-0.0969,0.0969) (i.e. (0.8,1.25) on the ratio scale).

For comparison, the results for the original TNSS scale (average change over the treatment period and average percentage change from baseline on this scale) are shown in the tables below (per-protocol analysis). Note the results for the ITT analyses were very similar.

Patient rated combined AM and PM TNSS score average over the treatment period (Per protocol)

	Placebo N=69	FANS N=142	Flixonase N=143	FANS v Flixonase
Mean (SD)	6.5 (2.7)	4.9 (2.3)	4.9 (2.5)	-
LS Mean (SE)	6.4 (0.27)	4.9 (0.18)	4.9 (0.18)	-
95% CI	5.9-6.9	4.5-5.3	4.5-5.3	-
Median	7.0	4.7	4.7	-
Min, Max	1.2, 11.7	0.5, 10.6	0.4, 12.0	-
LSM Difference (SE)	-	-	-	0.0089 (0.261)
95% CI	-	-	-	-0.5.05 – 0.522
P value	-	-	-	0.9729

Average change over the treatment period in patient rated combined AM and PM TNSS (Per protocol)

	Placebo N=69	FANS N=142	Flixonase N=143	Difference FANS v Flixonase
Mean (SD)	-1.8 (2.46)	-3.1 (2.63)	-3.1 (2.48)	
95% CI	-2.4, -1.2	-3.5, -2.7	-3.5, -2.7	-0.58, 0.58 (p =0.999)
Median	-1.6	-2.9	-3.1	
Min, Max	-9.7, 3.2	-11.5, 3.0	-9.9, 2.7	

Average percentage change from baseline in patient rated combine AM and PM TNSS (Per protocol)

	Placebo N=69	FANS N=142	Flixonase N=143
Mean (SD)	-19.6 (29.55)	-35.7 (30.49)	-37.8 (28.93)
95% CI	-26.6, -12.7	-40.6, -30.9	-42.6, -32.9
Median	-20.5	-37.0	-39.8
Min, Max	-82.7, 60.4	-95.5, 70.1	-93.2, 55.4

Statistical Assessor's Comment

The original analysis provided with 90% confidence intervals was not sufficient; 95% confidence intervals are required and have now been presented. The use of the standard bioequivalence limits in a therapeutic equivalence trial is also not considered appropriate. However, in this case the observed limits of the 95% confidence interval are much tighter than these limits (0.93, 1.11).

In addition, this study provides clear evidence that all active treatment groups are superior to placebo. Hence all that remains is to establish that the difference in efficacy between FANS and Flixonase can be considered clinically insignificant. The results from this study show very similar efficacy for all three active products. The 95% confidence interval for the difference between FANS and Flixonase on the change from baseline of the TNSS scale has a lower limit of about -0.5 units.

As discussed above, the applicant was asked to justify the clinical insignificance of differences that would correspond to differences of 0.80 or 1.25 on the ratio scale. The applicant states that these limits correspond to a $\pm 20\%$ difference between treatments and that it corresponds to a minimal measurable clinical difference on the TNSS scale of 1 unit. The applicant also discusses other studies in this area that have used similar equivalence limits. The observed limits of the confidence interval are about ± 0.5 units.

As placebo-controlled data have been submitted, the superiority of FANS over placebo is not in question. The appropriate size of equivalence margin then becomes a clinical decision of what constitutes a clinically insignificant difference between treatments. Provided it is accepted that the minimum detectable difference on the TNSS scale is 1 unit, then these data provide good evidence of therapeutic equivalence, as the data suggest that the difference between FANS and Flixonase is unlikely to be more than 0.5 units on the TNSS scale.

Conclusions

- The difference between the average TNSS scores for FANS and Flixonase are both clinically and statistically insignificant.
- The difference between the average change from baseline TNSS scores for FANS and Flixonase are both clinically and statistically insignificant.
- FANS and Flixonase may be regarded to be therapeutically equivalent.

SAFETY**Introduction**

A total of 684 patients were randomised into the two clinical studies. Of these, 74 received placebo, 204 received FANS, 206 received Flonase and 207 received Flixonase.

Adverse Events

The incidence of adverse events was similar across the treatment groups. Those adverse events considered treatment-related included nasal burning, headache and epistaxis.

There was not judged to be any clinically significant difference between the active treatment groups.

There were no serious adverse events or deaths reported.

Laboratory Data

No clinically relevant differences were seen in routine laboratory parameters. There was a slight increase in mean serum cortisol values over the course of the study in all treatment groups. Four patients were found to have a low serum cortisol level at Day 15 (one on placebo, two on FANS and one on Flixonase), but these were not considered clinically significant.

The safety of intra nasal fluticasone preparations is reviewed in the clinical overview.

Medical Assessor's Comments

- The safety of FANS is similar to that of Flixonase.
- It is well-recognised that minor nose bleeds occur with steroid nasal sprays, likewise other adverse event seen in the clinical studies were consistent with the known adverse effects of nasal fluticasone preparations.

CLINICAL OVERVIEW

The clinical overview was written by an appropriately qualified Doctor who is currently a consultant to the pharmaceutical industry. The overview provides an adequate review of the efficacy and safety of fluticasone and concludes that FANS has been shown to be essentially similar to Flixonase and it would, therefore, be expected that it would deliver have the same benefit and risks as the innovator product when used at the same dose for the same indication.

SUMMARY OF PRODUCT CHARACTERISTICS

This is medically satisfactory and consistent with that for the reference product

PATIENT INFORMATION LEAFLET

This is medically satisfactory and consistent with that for the reference product

LABELS

These are medically satisfactory.

MAA Form

This is medically satisfactory.

DISCUSSION

The FANS medicinal product has been compared to the EU innovator product Flixonase in two clinical studies. The first study demonstrated that the absolute bioavailability of the products was essentially similar. The second study demonstrates that the two products are essentially similar in terms of efficacy and safety. The benefit/risk profile of the FANS preparation is acceptable and similar to that for Flixonase.

CONCLUSIONS

On the basis of materials provided in support of safety and efficacy, it is considered that a licence may be granted for this product.

5. OVERALL CONCLUSION QUALITY

The important quality characteristics of Flunase Aqueous 50microgram Nasal Spray are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

Fluticasone propionate is a well-known corticosteroid and has been used for many years as an anti-inflammatory in the prophylaxis and treatment of seasonal allergic and perennial rhinitis. The applicant has demonstrated that this is a generic product of the originator product, Flixonase Nasal Spray.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with fluticasone propionate is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.