Public Assessment Report

Decentralised Procedure

Fluticasone propionate 50 micrograms/actuation nasal spray, suspension

(fluticasone propionate)

Procedure No: UK/H/5780/001/DC

UK Licence No: PL 44673/0102

GlaxoSmithKline Consumer Healthcare (UK) Trading Limited
LAY SUMMARY

Fluticasone propionate 50 micrograms/actuation nasal spray, suspension (fluticasone propionate)

This is a summary of the Public Assessment Report (PAR) for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension (PL 44673/0102, formerly PL 00079/0726; UK/H/5780/001/DC). It explains how the application for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Fluticasone propionate 50 micrograms/actuation nasal spray, suspension.

For practical information about using Fluticasone propionate 50 micrograms/actuation nasal spray, suspension patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Fluticasone propionate nasal spray’ in this report.

What is Fluticasone propionate nasal spray and what is it used for?

Fluticasone propionate nasal spray is a hybrid medicine. This means that Fluticasone propionate nasal spray is similar to a ‘reference medicine’ already authorised in the UK called Pirinase Hayfever 0.05% Nasal Spray (PL 00079/0616; Beecham Group plc), which was authorised in the UK on 08 March 1990.

Fluticasone propionate nasal spray is used in adults aged 18 and over to treat the allergic symptoms of hayfever and other airborne allergies such as allergy to pets, dust mites and mould spores. It relieves symptoms including sneezing, itchy and watery eyes and a runny, itchy or blocked-up nose, for up to 24 hours.

It may take 3 or 4 days to build up to the maximum level of protection. Therefore, it is important to continue regular use to achieve full therapeutic benefit.

The patient should consult the doctor if he/she does not feel better or if you feel worse after 7 days.

How does Fluticasone propionate nasal spray work?

Fluticasone propionate nasal spray contains the active ingredient fluticasone propionate, a corticosteroid which, when used every day, has an anti-inflammatory action. This spray helps to control the body’s reactions to allergens (‘triggers’) in the environment.

How is Fluticasone propionate nasal spray used?

This medicine should always be taken exactly as described in the package leaflet or as instructed by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if he/she is not sure.

Fluticasone propionate nasal spray is available as a nasal spray, suspension and is administered by inhalation through the nose. This medicine should not be swallowed.

Dose for adults aged 18 years and over:

The recommended dose is two sprays into each nostril once a day (200 micrograms fluticasone propionate), ideally in the morning.
Once the symptoms have improved, the patient may be able to reduce the dose to one spray into each nostril once daily.

If the symptoms are especially bad, the patient may need to increase the dose to two sprays into each nostril twice daily until the symptoms improve but this is for short term use only.

- No more than 8 sprays (4 per nostril) should be used in a day.

- The lowest dose possible to control symptoms should be used.

- If the patient’s symptoms do not improve, or are not well controlled, after 7 days, the patient should consult the doctor or pharmacist.

- More than the recommended dose should not be used.

**Use in children and adolescents**
Fluticasone propionate nasal spray should not be used in children or adolescents under 18 years of age.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Fluticasone propionate nasal spray can be obtained without a prescription.

**What benefits of Fluticasone propionate nasal spray have been shown in studies?**
Studies in patients have been limited to tests to determine that the applicant’s Fluticasone propionate nasal spray is similar to the reference medicine, Pirinase Hayfever 0.05% Nasal Spray (PL 00079/0616; Beecham Group plc). Two medicines are considered to be bioequivalent when they produce the same levels of the active substance in the body.

In addition, the company (Beecham Group plc) provided data from the published literature on fluticasone propionate.

**What are possible side effects of Fluticasone propionate nasal spray?**
Like all medicines, Fluticasone propionate nasal spray can cause side effects, although not everybody gets them.

**Common side effects**
These may affect up to 1 in 10 people:
- Sneezing after using the spray but this soon stops.
- Unpleasant taste or smell.
- Dryness or irritation in the nose or throat.
- Headache.

**Very common side effects**
These may affect more than 1 in 10 people:
- Occasional nose bleeds.

For the full list of all side effects reported with Fluticasone propionate nasal spray, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Fluticasone propionate nasal spray.
Why is Fluticasone propionate nasal spray approved?
The MHRA concluded that, in accordance with EU requirements, the benefits outweigh the identified risks and recommended that Fluticasone propionate nasal spray be approved for use.

What measures are being taken to ensure the safe and effective use of Fluticasone propionate nasal spray?
A risk management plan has been developed to ensure that Fluticasone propionate nasal spray is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Fluticasone propionate nasal spray, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Fluticasone propionate nasal spray.
Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, the Slovak Republic and the UK agreed to grant a Marketing Authorisation for Fluticasone propionate nasal spray on 21 April 2015. A Marketing Authorisation was granted in the UK to Beecham Group plc, trading as GlaxoSmithKline Consumer Healthcare on 20 May 2015.

Following the grant of a Change of Authorisation holder (CoA) procedure, the Marketing Authorisation were transferred to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0102) on 27 June 2016.

The full PAR for Fluticasone propionate nasal spray follows this summary.

For more information about treatment with Fluticasone propionate nasal spray, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2018.
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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension (PL 44673/0102, formerly PL 00079/0726; UK/H/5780/001/DC) could be approved. The product is a pharmacy (P) medicine indicated in adults aged 18 years and over for the symptomatic treatment of allergic rhinitis due to hay fever or other airborne allergens (such as dust mites, mould spores, or animal dander).

The product may be referred to as ‘Fluticasone propionate nasal spray in this report.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and the Slovak Republic as Concerned Member States (CMS). The application for Fluticasone propionate nasal spray was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application cross-referring to Pirinase Hayfever 0.05% Nasal Spray (PL 00079/0616; Beecham Group plc), which has been authorised in the UK since 08 March 1990.

Fluticasone propionate is a glucocorticosteroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. Fluticasone propionate has been shown to reduce inflammatory mediators in both the early and late phase reactions of allergic rhinitis. Once daily dosing with 200 micrograms fluticasone propionate is sufficient to help relieve symptoms (particularly nasal congestion) for up to 24 hours.

No new non-clinical or clinical data have been submitted, which is acceptable given that the application was based on being a hybrid application of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application as the applicant has confirmed that the product is identical in composition to the reference product, held by the same company.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

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

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 21 April 2015. After a subsequent national phase, a licence was granted in the UK to Beecham Group plc, trading as GlaxoSmithKline Consumer Healthcare on 20 May 2015.

Following the grant of a Change of Authorisation holder (CoA) procedure, the Marketing Authorisation were transferred to GlaxoSmithKline Consumer Healthcare (UK) Trading Limited (PL 44673/0102) on 27 June 2016.
II QUALITY ASPECTS

II.1 Introduction
The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as a white opaque, aqueous suspension of 0.5 mg (500 micrograms)/ml fluticasone propionate.

Each actuation delivers 100 mg suspension containing 50 micrograms of fluticasone propionate as a delivered dose.

The other ingredients consist of the pharmaceutical excipients anhydrous glucose, microcrystalline cellulose, carmellose sodium, phenylethyl alcohol, benzalkonium chloride, polysorbate 80 and purified water. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in amber glass bottles each fitted with a metering pump comprised of plastic, rubber and metal components, polypropylene nasal applicators and polypropylene dust covers.

Each bottle provides 60 metered sprays, with total content not less than 7.0 g.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance
Fluticasone Propionate
International Non-proprietary Name (INN): Fluticasone propionate
Chemical name: 6α,9-Difluoro-17-[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl propanoate
Molecular formula: C$_{25}$H$_{31}$F$_3$O$_5$S
Molecular mass: 500.6
Structural formula:

![Structural formula of fluticasone propionate](image)

Description: A white or almost white powder
Solubility: It is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol (96%) but freely soluble in dimethyl sulfoxide and dimethylformamide.
Polymorphism and solvates: Two crystal habits have been observed by microscopy. However, solid state infrared spectra and x-ray analysis show no evidence for the existence of more than one polymorphic form. Recrystallisation of fluticasone propionate from acetone and water has shown no evidence
for the formation of solvates or hydrates. No change in polymorphism on micronisation of fluticasone propionate has been detected through examination by solid state infrared spectroscopy.

Fluticasone propionate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable, nasal spray suspension containing fluticasone propionate 0.5 mg (50 micrograms)/actuation that was comparable in performance to the reference product Pirinase Hayfever 0.05% Nasal Spray (PL 00079/0616; Beecham Group plc). Suitable pharmaceutical development data have been provided for this application.

All excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeia monographs, with the exception of phenylethyl alcohol which is controlled to its United States Pharmacopeia (USP) monograph. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been approved for the product, with the special storage conditions ‘Do not store above 30°C.’

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this application as the applicant has confirmed that the product is identical in composition to the reference product, held by the same company.

II.4  Conclusion
It is recommended that a Marketing Authorisation is granted for this application for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension.

III  NON-CLINICAL ASPECTS
III.1  Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of fluticasone propionate are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
The pharmacology of fluticasone propionate is well known and is adequately described in the applicant’s non-clinical overview.

III.3  Pharmacokinetics
The pharmacokinetic properties of fluticasone propionate are well known and are adequately described in the applicant’s non-clinical overview.

III.4  Toxicology
The toxicological properties of fluticasone propionate are well known and are adequately described in the applicant’s non-clinical overview.

III.5  Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation Holder has provided an environmental risk assessment in accordance with EMEA/CHMP/SWP/4447/00 corr 2. A Phase I calculation has been performed for fluticasone propionate that is below the action limit of 0.01 µg/L. Therefore, no further examination in Phase II is required. In addition, there are no indications that fluticasone propionate will act as a PBT substance.

The applicant has indicated that they are currently exploring the endocrine modulating effects of fluticasone furoate, a structurally similar substance to fluticasone propionate. They have committed to complete studies for fluticasone furoate and should any concern be raised in terms of environmental safety then they will undertake steps to modify warnings and labelling for all their products containing either fluticasone propionate or fluticasone furoate. This is acceptable and at present adverse environmental effects are not expected to result from approval of Fluticasone Propionate nasal spray.
III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
This is a hybrid application as defined by article 10(3) of Directive 2001/83/EC, as amended, with the reference product Pirinase Hayfever 0.05% Nasal Spray (Beecham Group plc), which was originally granted in March 1990. No new bioequivalence, efficacy or safety study data are required to support this application as Fluticasone propionate 50 micrograms/actuation nasal spray, suspension satisfies the criteria of having the same quantitative and qualitative composition with the same pharmaceutical form when compared with the reference product. The product is identical in composition to the reference product, authorised to the same company.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The pharmacokinetic properties of fluticasone propionate are well known and are adequately described in the applicant’s non-clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.

IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of fluticasone propionate are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of fluticasone propionate is well-known. No new efficacy data were submitted and none are required for this application.

IV.5 Clinical Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fluticasone propionate nasal spray. The MAH identified the following as safety concerns:
### Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Local Effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local nasal effects including epistaxis and nasal septum perforation</td>
</tr>
<tr>
<td></td>
<td><strong>Systemic Effects:</strong></td>
</tr>
<tr>
<td></td>
<td>Ocular Events – cataract, glaucoma, raised intraocular pressure</td>
</tr>
<tr>
<td></td>
<td><strong>Interactions:</strong></td>
</tr>
<tr>
<td></td>
<td>Potent CYP3A4 inhibitors (ritonavir)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th><strong>Systemic Effects:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effects on the HPA axis</td>
</tr>
<tr>
<td></td>
<td>Effects on growth</td>
</tr>
<tr>
<td></td>
<td>Psychiatric or Behavioural Effects (psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression)</td>
</tr>
<tr>
<td></td>
<td>Effects on glucose metabolism</td>
</tr>
<tr>
<td></td>
<td>Effects on bone density</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>Effects Associated with the Switch to Non-Rx</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse Effects from Self-Diagnosis (i.e. use of FPANS for medical conditions with similar symptoms to allergic rhinitis)</td>
</tr>
<tr>
<td></td>
<td>Misuse/Maladministration (including overdose and off-label use in paediatric patients)</td>
</tr>
<tr>
<td></td>
<td>Use in pregnancy</td>
</tr>
</tbody>
</table>

| Missing information | None |

Routine Pharmacovigilance and routine risk minimisation are proposed for all safety concerns.
Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION
A user consultation with target patient groups on the package information leaflet has been performed on the basis of a bridging report making reference to the Patient Information Leaflet for the product Pirinase Hayfever 0.05% Nasal Spray (PL 00079/0616, Beecham Group plc). The bridging report submitted by the applicant has been found to be acceptable.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The important quality characteristics of Fluticasone propionate 50 micrograms/actuation nasal spray, suspension 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of fluticasone propionate are well-known, no additional data were required.

Efficacy
The clinical efficacy of fluticasone propionate is well-known.

SAFETY
The safety profile of fluticasone propionate is well-known. No new or unexpected safety issues or concerns arose from this application.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with fluticasone propionate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up livery to the regulatory authorities for approval before packs are marketed.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:
### PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

### BOTTLE LABEL

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate 50 micrograms/actuation nasal spray, suspension</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>For use in adults only.</td>
</tr>
<tr>
<td>Adults aged 18 and over:</td>
</tr>
<tr>
<td>Usual dosage 2 sprays in each nostril, once a day.</td>
</tr>
<tr>
<td>Shake gently and prime before use.</td>
</tr>
<tr>
<td>For nasal use.</td>
</tr>
<tr>
<td>Do not use more than 4 sprays in each nostril in a day.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 sprays</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Fluticasone propionate 50 micrograms/actuation nasal spray, suspension
Fluticasone propionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each actuation delivers 100 mg suspension containing 50 micrograms of fluticasone propionate.

3. LIST OF EXCIPIENTS

Excipients: Microcrystalline cellulose, carmellose sodium, glucose, polysorbate 80, purified water. Preservatives: benzalkonium chloride, phenylethyl alcohol.

Contains benzalkonium chloride. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Nasal spray, suspension
60 sprays per bottle.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For nasal use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For use in adults only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS
Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare (UK) Trading Limited
Brentford
TW8 9GS
U.K.

12. MARKETING AUTHORISATION NUMBER(S)

PL 44673/0102

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

For use in adults only.

Once a day dose.

Prevents and relieves symptoms of airborne allergens including:
Pollen (hayfever); pet hair; dust mite; mould spores.

Fluticasone propionate works to:
• Help relieve allergy symptoms for up to 24 hours.
• Help prevent the return of symptoms during the day.

Fluticasone propionate has a direct action to relieve allergy symptoms where they start.

How to use:
• Shake gently and prime before use.
• Use only in the nose.

Adults aged 18 years and over:
Usual dose: 2 sprays in each nostril, once a day. If your symptoms improve use 1 spray in each nostril once a day. If symptoms are especially bad: 2 sprays in each nostril may be used twice a day. Once symptoms improve, go back to the usual dose.
Children:
- Not for use in children under 18 years.

Do not use:
- More than 4 sprays in each nostril in a day.
- For more than 3 months continuously without consulting your doctor.

Consult your doctor:
- Before use, if you are pregnant or breast-feeding.
- If your symptoms have not improved after using the spray for 7 days.

16. INFORMATION IN BRAILLE

Fluticasone propionate nasal spray
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

The following table lists a non-safety update to the Marketing Authorisations for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension ((PL 44673/0102, formerly PL 00079/0726; UK/H/5780/001/DC) that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>To introduce changes to the environmental risk assessment as requested by the MHRA. The environmental risk assessment is partially complete and a further update is required.</td>
<td>UK/H/5780/001/II/010</td>
<td>None</td>
<td>09/12/2016</td>
<td>20/04/2018</td>
<td>Approval</td>
<td>Y (Annex 1.1)</td>
</tr>
</tbody>
</table>
Annex 1.1

Our Reference: PL 44673/0102, Application 0008
Product: Fluticasone propionate 50 micrograms/actuation nasal spray, suspension
Marketing Authorisation Holder: GlaxoSmithKline Consumer Healthcare (UK) Trading Limited
Active Ingredient(s): Fluticasone propionate.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5780/001/II/010

REASON:
To introduce changes to the environmental risk assessment as requested by the MHRA. The environmental risk assessment is partially complete and a further update is required.

SUPPORTING EVIDENCE
- The results of an Extended Fish Early Life Stage Test in which fluticasone furoate (OECD 210 and OECD 234)
- Updated ERA

RECOMMENDATION
Based on the review of the data on non-clinical (environmental risk assessment), the RMS considers that the variation for Fluticasone Propionate 50 micrograms/actuation nasal spray suspension, indicated for the prophylaxis and treatment of allergic rhinitis, for the following proposed changes regarding environmental risk assessment is approvable.

EXECUTIVE SUMMARY
Scope of the variation
In accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.

An environmental risk assessment (ERA) is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure. Fluticasone Propionate 50 micrograms/actuation nasal spray suspension was granted on 20 May 2015 via a decentralised procedure with the following commitment:
“The applicant has indicated that studies with fluticasone furoate are ongoing and will not be available until November 2015. The applicant has committed to provide an updated ERA once ongoing studies with fluticasone furoate are completed.”

The Applicant has provided the Extended Fish Early Life Stage report (OECD 210 and OECD 234) which was an ongoing study with fluticasone furoate, this study has been reviewed by the RMS. An updated ERA has been provided.
SCIENTIFIC DISCUSSION
Non clinical aspects
Environmental risk assessment (taken from RMS Day 70 Non-Clinical AR for UK/H/5780/01/DC):

Background:
An Environmental Risk Assessment (ERA) for Fluticasone propionate nasal spray (0.05% w/v, 50μg per spray) has been provided.

The applicant has focussed their ERA on the drug product component of the fluticasone product - fluticasone propionate.

The remaining components of fluticasone propionate nasal spray products, including packaging, are already introduced into the environment from a variety of sources in much greater quantity, and so their impact on the environment is not expected to result in any adverse environmental effects.

Phase I
Calculation of Predicted Environmental Concentration (PEC) in surface water
A Phase I calculation of the Predicted Environmental Concentration (PEC) for fluticasone propionate (conducted according to the guidance on the environmental risk assessment of medicinal products for human use CHMP/SWP/4447/00) gave a calculated PEC value of 0.002 µg/L, below the trigger value for Phase II assessment of 0.01 µg/L. Therefore, no further examination in Phase II is required.

Persistence, bioaccumulation and toxicity (PBT) assessment
Fluticasone propionate has a measured partition coefficient (Log Pow) below 3, indicating that fluticasone propionate will not have a tendency to sorb to lipid surfaces and therefore bioconcentration in the tissues of organisms is unlikely to be a concern. On that basis, fluticasone propionate will not be screened for persistence, bioaccumulation and toxicity (PBT).

The applicant has stated that it is investigating the environmental aspects of a similar active substance, fluticasone furoate (a substance developed by the applicant that is similar in structure and activity to fluticasone propionate). There are indications that fluticasone furoate (and potentially fluticasone propionate) act as an endocrine modulator at environmentally relevant concentrations.

The applicant committed to complete studies with fluticasone furoate and provide the results of these studies that give rise to any concerns regarding the potential for effects on the environment. The applicant has also committed to undertake steps to ensure that any warnings or recommendations for usage and disposal are applied to all its products containing either fluticasone propionate or fluticasone furoate.

Newly completed study (provided in support of variation UK/H/5780/001/II/010):
Extended Fish Early Life Stage Test (OECD 210 and OECD 234)
The objective of the study was to determine whether exposure of the freshwater fish species fathead minnow (Pimephales promelas) embryo-larvae to the test substance affected hatching, survival, growth, development, secondary sexual characteristics or spawning ability.

The study was conducted based on the requirements of the OECD Chemicals Testing Guideline No. 210 Fish, Early Life Stage Toxicity Test (July 2013) and OECD Chemical Testing Guideline No 234 Fish Sexual Development Test (July 2011). These tests were completed with fluticasone furoate, which is structurally similar to fluticasone propionate.

A range-finding test was conducted between at nominal concentrations of 0.010, 0.10, 1.0, 10 and 100 µg/L. Based on nominal concentrations, the results of the range-finding test suggested that effects on growth were observed at concentrations of 10 µg/L and above.
As a result, a definitive test was conducted at nominal concentrations of 0.032, 0.10, 0.32, 1.0 and 3.2 μg/L between 29 June 2015 (egg addition) and 29 October 2015. Control and solvent control groups were also included.

Hatching:
First egg hatch in the majority of test vessels occurred on Day 3 (pre-hatch). Hatching was complete by Day 3 (post-hatch). This indicated no difference in the time to first hatch or completion of hatching between treatments when compared to the control groups.

Mean hatching success in the treatments ranged between 73% - 88%. There were no statistically significant effects (p<0.05) on hatching success at any of the test concentrations employed in the test compared to the combined controls. The No Observed Effect Concentration (NOEC) and Lowest Observed Effective Concentration (LOEC) values for hatching success were therefore considered to be 3.2 and >3.2 μg/L, respectively.

Survival:
The results for survival of hatched fish at the end of the test are presented in the table below:

Mean post-hatch survival in the treatments ranged between 73% - 92%. There were no statistically significant effects (p<0.05) post-hatch survival at any of the test concentrations employed in the test compared to the combined controls. The NOEC and LOEC values for post-hatch survival were therefore considered to be 3.2 and >3.2 μg/L, respectively.

Reproduction:
The results of the reproduction phase are presented in the table below:
The number of spawns produced by the fish in the 1.0 μg/L test group was lower compared to the control and remaining test concentrations. This was considered to be due to poor selection of fish rather than an effect of the test substance given that no effects were observed at the highest test concentration of 3.2 μg/L compared to the control.

There were no statistically significant effects (p<0.05) on reproduction at any of the concentrations employed in the test compared to the combined controls. The NOEC and LOEC values for reproduction were therefore considered to be 3.2 and >3.2 μg/L, respectively.

Fish Total Lengths and Wet Weights:
The results for total length (cm) and wet weight (g) measurements are summarised in the table below:

<table>
<thead>
<tr>
<th>Nominal concentration (μg/L)</th>
<th>Male fish</th>
<th>Female fish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.3</td>
<td>2.3722</td>
</tr>
<tr>
<td>Solvent control</td>
<td>5.6</td>
<td>2.3724</td>
</tr>
<tr>
<td>0.03</td>
<td>5.4</td>
<td>2.2465</td>
</tr>
<tr>
<td>0.10</td>
<td>5.4</td>
<td>2.2315</td>
</tr>
<tr>
<td>0.30</td>
<td>5.6</td>
<td>3.7717</td>
</tr>
<tr>
<td>1.0</td>
<td>5.6</td>
<td>2.7383</td>
</tr>
<tr>
<td>3.2</td>
<td>5.6</td>
<td>2.4966</td>
</tr>
</tbody>
</table>

There were no statistically significant effects (p<0.05) on either fish length or fish wet weight at any of the concentrations employed in the test compared to the combined controls for either male or female fish. Taking into account length and wet weight, the NOEC and LOEC values for growth at the end of the test were therefore considered to be 3.2 and >3.2 μg/L, respectively.

Phenotypic Sex Determination:
The phenotypic sex based on visual observation was conducted for each fish. A summary of the observations conducted on the male fish are presented in the table below:

<table>
<thead>
<tr>
<th>Nominal concentration (μg/L)</th>
<th>Fish ID</th>
<th>Body shape (scale 1 to 3)</th>
<th>Size (scale 1 to 3)</th>
<th>Fat pad (scale 1 to 3)</th>
<th>Number of spermatozoa</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
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<td>7</td>
<td>3</td>
<td>2</td>
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<td>10</td>
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<td>2</td>
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<td>14</td>
</tr>
<tr>
<td>Mean</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Solvent control</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>20</td>
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<tr>
<td></td>
<td>15</td>
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</tr>
<tr>
<td></td>
<td>19</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Mean</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>0.03</td>
<td>25</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<td>2</td>
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<td>34</td>
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<td>1</td>
<td>6</td>
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<tr>
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<td>29</td>
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</tr>
<tr>
<td>0.10</td>
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<td>2</td>
<td>1</td>
<td>16</td>
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<td>46</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Mean</td>
<td>41</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>0.32</td>
<td>49</td>
<td>3</td>
<td>2</td>
<td>1</td>
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</tr>
<tr>
<td></td>
<td>57</td>
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<td>2</td>
<td>1</td>
<td>10</td>
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<td>55</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>24</td>
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<tr>
<td>Mean</td>
<td>52</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>1.0</td>
<td>61</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>64</td>
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<td>2</td>
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<td>16</td>
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<td>67</td>
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<td>70</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td>63</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>3.2</td>
<td>72</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>76</td>
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<td>2</td>
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<td>14</td>
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<td>82</td>
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<td>16</td>
</tr>
<tr>
<td>Mean</td>
<td>78</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>14</td>
</tr>
</tbody>
</table>

All but a single female fish at 0.32 μg/L showed the presence of urogenital papillae. No differences were observed between the controls and test concentrations in terms of phenotypic sex. Reproduction was observed at all concentrations and no statistically significant effects were observed during the test, histology of the fish was not conducted.
Evaluation
The objective of the study was to determine whether exposure of the fresh water fish species fathead minnow (Pimephales promelas) embryo-larvae to the test substance affected hatching, survival, growth, development, secondary sexual characteristics or spawning ability (OECD 210 and OECD 234).

Fish were exposed to nominal concentrations of fluticasone furoate of 0.032, 0.10, 0.32, 1.0 and 3.2 μg/L. Overall no statistically significant effects were observed between the controls and any concentrations of fluticasone furoate on hatching success, post-hatch survival, growth or spawning ability. NOEC and LOEC values were considered to be the highest concentrations of fluticasone furoate exposed to fish; these values were therefore considered to be 3.2 and >3.2 μg/L, respectively.

The published literature indicates that fluticasone furoate and fluticasone propionate are different drugs with different properties. The main message of the paper is: “Fluticasone 17α esters are remarkably stable and remain attached to the fluticasone backbone even during metabolism. Their pharmacological activity is mediated by the entire molecule (backbone + ester) and they share no common metabolites – neither fluticasone furoate nor fluticasone propionate is metabolised to fluticasone. Fluticasone furoate and fluticasone propionate are therefore structurally distinct drug substances with distinct properties.” Therefore, it was not considered acceptable to bridge the results from the above study to fluticasone furoate to the active substance fluticasone propionate. The applicant was therefore asked to conduct a test with the active ingredient, fluticasone propionate, and not with a structural similar substance.

In response the applicant provided further discussion of their read-across approach between fluticasone furoate and fluticasone propionate.

The applicant has suggested that fluticasone furoate is roughly equipotent to fluticasone propionate with regard to the tested receptor proteins and submitted a battery of receptor binding in vitro tests from 2006. The glucocorticoid affinity of all of these molecules look similar in the FP binding assay format. However, this is mainly due to the tight-binding limit of the assay being reached at approximately 10nM, and all of the molecules being studied being over this artificial affinity limit. Independent of the above, results of receptor binding assays in general do not allow an extrapolation to ecological relevant apical endpoints, necessary for an Environmental Risk Assessment.

Data for ecotoxicity studies are sparse and not usable as a bridging approach. On the other hand, the repeated dose studies with rats display a significant difference between the two substances.

The NOEL for fluticasone furoate is 3 mcg/L/day in a 26 week study compared to a NOEL for fluticasone propionate of 0.2 mcg/L/day in a 28 day study. This means a much longer exposure to fluticasone furoate is 10-fold less sensitive than a considerable shorter exposure to fluticasone propionate.

Furthermore, there are concerns about the equalisation of both substances because in the submitted FSDT-study (OECD 234) with fluticasone furoate the NOEC is 0.29 μg/L; this is much higher than a NOEC value received in a Fish Full Life Cycle Test for fluticasone propionate in a different application. Here the NOEC was clearly in the lower ng/L range.

Both, the rat studies and even more the fish studies, clearly do not support the use of fluticasone furoate as a surrogate for fluticasone propionate.

Therefore, the requirement remains for a fish study with active ingredient fluticasone propionate.
It is noted that a Fish Full Life Cycle Test with fluticasone propionate was already submitted in an independent application and there might be a possibility for the results to be shared in the interests of 3R’s (Replacement, Reduction and Refinement of the use of animals) and for continuing animal welfare.

**Overall conclusion**

The benefit-risk-balance for Fluticasone propionate 50 micrograms/actuation nasal spray, suspension remains positive.

Based on the available data, a final conclusion on potential risk of Fluticasone Propionate 50 micrograms/actuation nasal spray, suspension to the environment cannot be drawn.

The provided updated ERA is partially complete; a further update is required. It is noted that a Fish Full Life Cycle Test with fluticasone propionate was submitted in an independent application and there might be a possibility for the results to be shared in the interests of the 3R’s and for continuing animal welfare. The applicant has committed to attempt to obtain these data in order to report NOEC values from a Fish Full Life Cycle Test for Fluticasone propionate.

**Decision**

The variation was approved on 20 April 2018. As the data were not complete, the conclusion stated in the FVAR was that the Applicant is to commit to obtaining data in order to report NOEC values from a Fish Full Life Cycle Test for Fluticasone Propionate.