TITLE PAGE

Division: Worldwide Development
Information Type: Worldwide Epidemiology Study Protocol

Title:	Drug Utilization of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray for Allergic Rhinitis Symptoms in Adults
Compound:	Fluticasone propionate
Development Phase	Post Authorization Study
Effective Date:	15-02-2016
Subject:	Seasonal Allergies
Author(s):	PPD

PASS information

Title	Drug Utilization of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray for Allergic Rhinitis Symptoms in Adults
Protocol version identifier	3.0
Date of last version of protocol	08 March 2016
EU PAS (ENCEPP) register number	EUPAS12436
Active substance	Fluticasone propionate Pharmacotherapeutic group: Intranasal Corticosteroids ATC Code: R01AD08
Medicinal product	Pirinase Hayfever Relief for Adults 0.05% Nasal Spray
Product reference	PL 00079/0688
Procedure number	N/A
Marketing authorisation holder(s)	Beecham Group Plc 980 Great West Road Brentford Middlesex TW8 9GS Trading as GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.
Joint PASS	No

Research question and objectives	The primary objective of this study is to evaluate if consumers comply with key warnings and directions on the outer label for selection and use of the drug. Primary Objectives The five primary objectives are the following: 1. To assess if consumers of the correct age use the product: Ages 18 and older 2. To assess the correct frequency of use: No more than 2 sprays in each nostril per day 3. To assess reduction of dose: If symptoms improve, 1 spray in each nostril per day 4. To assess if a physician is consulted before use: if a woman is pregnant or breastfeeding 5. To assess if a physician is consulted: If symptoms have not improved after using for 7 days, a doctor is consulted Secondary Objectives The two secondary objectives are the following: 1. To assess if consumers do not use if they are taking medications for Human Immunodeficiency Virus (HIV) 2. To assess if a physician is consulted: Not used more than 1 month continuously without consulting a doctor
Country of study	United Kingdom
Author	PPD Concentrics Research 9335 Delegates Row Indianapolis, IN 46240 PPD

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Beecham Group Plc 980 Great West Road Brentford Middlesex TW8 9GS Trading as GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.
MAH contact person	PPD PPD

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
CRO	Contract Research Organization
EU-PAS	European Union - Post-Authorisation Study
GCP	Good Clinical Practice
GSKCH	GlaxoSmithKline Consumer Healthcare
GSL	General Sale List
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MFC	Product Formulation Code
MHRA	Medicines and Healthcare Products Regulatory Agency
PII	Personally Identifiable Information
QR	Quick Response
SD	Standard Deviation
SPC	Summary of Product Characteristics
UK	United Kingdom

SPONSOR INFORMATION PAGE

WWEpi Project Identifier:

Sponsor Legal Registered and Contact Address:

GlaxoSmithKline Consumer Healthcare
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK
In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

2. ABSTRACT

Title

Drug Utilization Study for Pirinase Hayfever Relief for Adults 0.05% Nasal Spray

Rationale and background

The Medicines and Healthcare products Regulatory Agency (MHRA) has required this study to evaluate consumer compliance with the product labelling of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray over at least 2 allergy seasons for the treatment of seasonal allergic rhinitis including hayfever. The purpose is to obtain real-world information on how consumers are complying with the product labelling. This study will coincide with the launch of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray in the United Kingdom (UK).

Research question and Objectives

The primary objective of this study is to evaluate if consumers comply with key warnings and directions on the outer label for selection and use of the drug.

Study Objective

To evaluate if consumers comply with key warnings and directions on the outer label for selection and use of the drug

Primary Objectives

The five primary objectives are the following:

1. To assess if consumers of the correct age use the product: Ages 18 and older
2. To assess the correct frequency of use: No more than 2 sprays in each nostril per day
3. To assess reduction of dose: If symptoms improve, 1 spray in each nostril per day
4. To assess if a physician is consulted before use: if a woman is pregnant or breastfeeding
5. To assess if a physician is consulted: If symptoms have not improved after using for 7 days, a doctor is consulted

Secondary Objectives

The two secondary objectives are the following:

1. To assess if consumers do not use if they are taking medications for Human Immunodeficiency Virus (HIV)
2. To assess if a physician is consulted: Not used more than 1 month continuously without consulting a doctor

Study Design

This will be an online survey. Consumers who have purchased and used the product will opt into an online survey by scanning a QR code on the product package labelling or through an e-mailed invitation to those who have purchased the product at a Boots Pharmacy, which will also include a link to the survey. The anticipated study timeframe is approximately 2 calendar years so that data from at least 2 allergy seasons for the treatment of seasonal allergic rhinitis including hayfever are included. The intention will be to recruit approximately half the subjects in each year.

Population

An all comers population (consumers who opt in at their own discretion) of 1,537 consumers, will be included in this study. No targeting or enrichment for age, gender, and social backgrounds will be conducted. The demographics will be reported for those who choose to enter the online survey

Variables

Primary endpoints are comprised of the proportion of consumers who comply with each of the 5 endpoints listed below:

1. Consumer is 18 years of age or older
2. Consumer does not exceed 2 sprays/nostril per day
3. Dose is reduced to 1 spray/nostril per day if symptoms improve
4. Doctor is consulted before use if a woman is pregnant or breastfeeding
5. Doctor is consulted if symptoms do not improve after 7 days of use

Secondary endpoints are comprised of the proportion of consumers who comply with each of the specified endpoints below:

1. Those taking HIV medications do not use the drug
2. Doctor is consulted is medication is used more than 1 month *continuously*

<u>Demographics and Profiling Information</u>

Descriptive statistics will be used to report consumer demographics and additional profiling information. Demographic information is comprised of age, race, education and household purchase information (primary purchaser or other). The additional profiling information is comprised of the following:

- How long they have had allergies
- What type of allergies they have
- Typical allergy symptoms
- How often they see their doctor

Data Sources

Endpoints will be assessed based on data from self-reported consumer responses to the online survey.

Study Size

1,537 consumers will complete the survey. No targeting or enrichment for age, gender, and social backgrounds will be conducted. The demographics will be reported for those who choose to enter the online survey. For the threshold of 80% for success, this sample size of 1537 achieves at least 91% power with an assumed compliance rate of 83.3% for each of these five primary endpoints, and the significance level of 0.05 using a two-sided exact binomial test.

Data Analysis

Primary endpoints will be analyzed individually and no adjustment for multiple comparisons will be performed. The compliance rate for each of the five primary endpoints will be reported and its two-sided 95% confidence limit will be computed using the exact method. The endpoint will have met the threshold for success if the lower bound of the 2-sided 95% exact confidence interval (CI) is at least 80%.

Secondary endpoints will be analyzed individually and no adjustment for multiple comparisons will be performed. The compliance rate for each of the secondary endpoints will be reported and its two-sided 95% confidence limit will be computed using the exact method. There are no success thresholds set for secondary endpoints.

Milestones

Milestones for this study include the following:

1. Start of data collection February 2016
2. Study progress report February 2017
3. End of data collection March 2018
4. Final report of study results June 2018

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	02MAR2016	8.8	Added in limitations of the research methods	MHRA request

2	08MAR2016	8.8	Added in additional limitation of the research methods	MHRA request

4. MILESTONES

Milestone	Planned date
Start of data collection	February 2016
End of data collection	March 2018
Study progress report 1*	February 2017
Final report of study results	June 2018

* An enrolment update will be submitted to MHRA after approximately 1 year of enrolment. No interim data analysis is planned.

5. RATIONAL AND BACKGROUND

5.1. Background

The Medicines and Healthcare products Regulatory Agency (MHRA) has required a post-approval commitment from GlaxoSmithKline Consumer Healthcare (GSKCH) for Pirinase Hayfever Relief for Adults 0.05% Nasal Spray. This spray will be marketed for General Sale (GSL) in the United Kingdom (UK).

5.2. Rationale

The post-approval commitment to MHRA is to provide observational data regarding the real-world use of Pirinase Hayfever Relief for Adults 0.05% Nasal Spray by consumers. Specifically, data about the consumer's compliance with key warnings and directions will be collected.

6. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective of this study is to evaluate if consumers comply with key warnings and directions on the outer label for selection and use of the drug.

The primary and secondary objectives and endpoints are listed below:

Primary Objectives	Primary Endpoints

• To assess if consumers of the correct age use the product: Ages 18 and older	• Consumer is 18 years of age or older
• To assess the correct frequency of use: No more than 2 sprays in each nostril per day	• Consumer does not exceed 2 sprays/nostril per day
• To assess reduction of dose: If symptoms improve, 1 spray in each nostril per day	• Dose is reduced to 1 spray/nostril per day if symptoms improve
• To assess if a physician is consulted before use: if a woman is pregnant or breastfeeding	• Doctor is consulted before use if a woman is pregnant or breastfeeding
• To assess if a physician is consulted: If symptoms have not improved after using for 7 days, a doctor is consulted.	• Doctor is consulted if symptoms do not improve after 7 days of use

Secondary Objectives	**Secondary Endpoints**
• To assess if consumers do not use if they are taking medications for Human Immunodeficiency Virus (HIV)]	• Those taking HIV medications do not use the drug
• To assess if a physician is consulted: Not used more than 1 month continuously without consulting a doctor	• Doctor is consulted if medication is used more than 1 month *continuously*

Demographic information that will be collected are listed below:

1. Age
2. Race
3. Education
4. Primary purchaser of medicines

Additional profiling information that will be collected are listed below:

1. How long they have had allergies
2. What type of allergies they have
3. Typical allergy symptoms
4. How often they see their doctor

6.1. Study Design

This is an online survey to evaluate consumer compliance with the product labelling for consumers who purchase Pirinase Hayfever Relief for Adults 0.05% Nasal Spray. Consumers will respond to screening criteria and if they qualify for the study, they will complete the online survey related to their use of the drug. After completing the survey consumer participation will be considered complete. Data collection will continue through at least 2 allergy seasons and until 1,537 surveys are completed.

Consumers will access an online survey by scanning a QR code on the product package labelling or through an e-mailed invitation to those who have purchased the product at a Boots Pharmacy, which will also include a link to the survey. The entire study will be conducted online; there will be no study visits.

The specific tasks include the following:

1) Consumers who have purchased the product will scan the QR code found on the product package labelling or by accessing the link in the e-mailed invitation.
2) A Participation Agreement will be displayed. The consumer will read and sign this Agreement electronically. Anyone who does not sign the Participation Agreement will not be admitted to the survey.
3) The online survey will begin with a set of brief screening questions related to the inclusion/exclusion criteria.
4) If the consumer qualifies and is interested, he or she will then be invited to complete the online survey. This process is voluntary for all participants.
5) The online survey will consist of closed-ended questions related to the consumer's use of the product.
6) Demographics and profiling information will be collected.
7) If a consumer has not used the product for at least a month when they initially complete the survey, a reminder message will be sent to them at a later time so that they can complete the question related to use after 1month.
8) After completing the survey, consumer participation in the study will be considered complete.

7. SCHEDULE OF EVENTS

Procedure / Assessment	Initial Survey Response Day	Subsequent Survey Response Day[2]
Inclusion / Exclusion Criteria	X	
Participation Agreement	X	
Online compliance survey completion	X	
Self-reported demographics	X	
Self-reported allergy profiling information	X	
Reminder message sent to consumers who have not used the product for at least 1 month at the initial response day[1]		X
Self-reported compliance with 1 month warning[1]	X	X
Study conclusion	X	

[1] Label Warning: To assess the correct frequency of use (not used more than 1 month continuously without consulting a doctor).

[2] Subsequent Survey Response Day: This is for consumers who had not used the product for at least 1 month when they initially completed the survey. This allows subject to complete the 1 month question on the survey.

7.1. Study Population and Setting

1,537 consumers in the UK who have purchased and used Pirinase Hayfever Relief for Adults 0.05% Nasal Spray for at least 7 days will be included in this study. No targeting or enrichment for age, gender, and social backgrounds will be conducted. The demographics will be reported for those who choose to enter the online survey.

The anticipated timeframe is approximately 2 calendar years so that data from at least 2 allergy seasons for the treatment of seasonal allergic rhinitis including hayfever are included. The allergy season in the UK can range from April through September with June often having the highest pollen counts and allergy sales; however, allergy seasons vary. If the sample size is not met within the 2-year period the study may be extended.

This is an all comers study which means that consumers will opt into the survey themselves. Consumers will access the online survey by scanning a QR code on the product package labelling or through an e-mailed invitation to those who have purchased the product at a Boots Pharmacy, which will also include a link to the survey. The population is expected to reflect a real-world population of consumers who will purchase and use the drug.

Inclusion:

A consumer will be eligible for inclusion in this study only if all of the following criteria apply:

1. Consumers will be required to review, and electronically sign a Participation Agreement prior to completing the online survey.
2. Consumers of any age may participate.
3. Consumers who have purchased and used Pirinase Hayfever Relief for Adults 0.05% Nasal Spray for at least 7 days and are willing to participate in the online survey.
4. Consumers of either gender may participate

Exclusion:

A consumer will not be eligible for inclusion in this study if any of the following criteria apply:

1. Anyone who is directly involved with medicines such as doctors, nurses, and pharmacists.
2. Consumers who decline participation in the online survey

7.2. Variables

7.2.1. Outcome definitions

Primary Endpoints

Primary endpoints are comprised of the proportion of consumers who comply with each of the 5 endpoints listed below:

- Consumer is 18 years of age or older
- Consumer does not exceed 2 sprays/nostril per day
- Dose is reduced to 1 spray/nostril per day if symptoms improve
- Doctor is consulted before use if a woman is pregnant or breastfeeding
- Doctor is consulted if symptoms do not improve after 7 days of use

Secondary Endpoints

Secondary endpoints are comprised of the proportion of consumers who comply with each of the specified endpoints listed below:

- Those taking HIV medications do not use the drug
- Doctor is consulted if medication is used more than 1 month *continuously*

Demographics and Profiling Information

Descriptive statistics will be used to report consumer demographics and additional profiling information. Demographic information is comprised of age, race, education and household purchase information (primary purchaser or other). The additional profiling information is comprised of the following:

- How long they have had allergies
- What type of allergies they have
- Typical allergy symptoms
- How often they see their doctor

7.3. Data sources

Endpoints will be assessed based on data from self-reported consumer responses to the online survey.

7.4. *Study size

1,537 consumers will complete the survey. No targeting or enrichment for age, gender, and social backgrounds will be conducted. The demographics will be reported for those who choose to enter the online survey. For the threshold of 80% for success, this sample size of 1537 achieves at least 91% power with an assumed compliance rate of 83.3% for each of these five primary endpoints, and the significance level of 0.05 using a two-sided exact binomial test.

7.5. Data management

7.5.1. Data handling conventions

The online survey will provide an audit trail so that data entry can be further reviewed or investigated, if needed. Programmed edit checks will be generated automatically, as the data is being entered into the system (e.g. the consumer will be restricted from proceeding in the survey until the previous question is answered). The CRO will monitor the survey status on a monthly basis by reviewing percent completed, percent of primary endpoints answered and demographics of the study population.

The online survey will be programmed and tested using DatStat Illume 2016 v.6.0 and DatStat Discovery v 6.0. There will be no formal query resolution for any missing data. Data will be locked after the planned sample size has been achieved or at such time as the sponsor concludes the data collection. Data is stored in the DatStat co-location TierPoint data center. TierPoint is a SSAE16 SOC1 & SOC2, Type II certified data center. TierPoint provides the physical security, power, backups, and DatStat IT has full control over the servers housed in the DatStat racks.

7.5.2. Resourcing needs

This study is being managed by Concentrics Research. FMD K&L will be involved in the data and analysis for this study

7.6. Data analysis

Detailed methodology for summary and statistical analyses of the data collected in this study, including the handling of missing data, will be documented in a Statistical Analysis Plan. This document, which will be dated and maintained by the Sponsor or designee, may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

7.6.1. Essential analysis

Primary endpoints will be analyzed individually and no adjustment for multiple comparisons will be performed. The compliance rate for each of the five primary endpoints will be reported and its two-sided 95% confidence limit will be computed using the exact method. The endpoint will have met the threshold for success if the lower bound of the 2-sided 95% exact confidence interval (CI) is at least 80%.

Secondary endpoints will be analyzed individually and no adjustment for multiple comparisons will be performed. The compliance rate for each of the secondary endpoints will be reported and its two-sided 95% confidence limit will be computed using the exact method. There are no success thresholds set for secondary endpoints.

7.6.2. Exploratory analysis

Demographic and baseline characteristics will be summarized for the analysis population using descriptive statistics. Continuous demographic and baseline variables such as age will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables including sex, age group, and race will be summarized as number (percent) of consumers.

7.7. Quality control and Quality Assurance

This is an observational study with data being collected from consumers using an online survey. There is no plan for monitoring.

To ensure compliance with GCP and all applicable regulatory requirements, GSKCH may conduct a quality assurance assessment and/or audit of the records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The sponsor will be available to help prepare for an inspection.

Following closure of the study, the CRO will maintain all study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The CRO is required to keep study data on file for at least 15 years after completion or discontinuation of the study. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSKCH. The CRO must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records.

7.8. Limitations of the research methods

7.8.1. Limitations

This study will be conducted as an online survey and will be limited to only those who have access to the internet. Since internet usage is correlated to various demographics,

the age and gender of those who enrol could be slightly different from the general population. Also due to only being an online survey, baseline characteristic of those who are able to enrol could potential be different from those who do not have internet access and cannot enrol. This might limit the external validity of the study.

Consumers who have not used the product for greater than 1 month will be able to complete all of the survey except the questions around the 1 month usage. They will be invited back after they have had the opportunity to use the product for one month to complete the 1 month usage questions. There is a possibility that some of these consumers will not re-enter the survey after 1 month to complete those questions. Data for the secondary objective of *doctor is consulted if medication is used more than 1 month continuously* may be limited.

Given that there are approximately 100,000 HIV+ patients in the UK[1] and the proposed sample size for this study of 1,537, it is unlikely that consumers on HIV medications will complete the survey. Data for the secondary objective of *those taking HIV medications do not use the drug* may be limited.

7.8.2. Study closure/uninterpretability of results

GSKCH reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with applicable International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and all applicable consumer privacy requirements.

Prior to starting the online survey, each consumer will review and electronically sign a Participation Agreement.

8.2. Subject confidentiality

An online survey include all data collected for this study. Each consumer will be assigned and identified by a subject number. Any reference made to an individual consumer within the study will be done by using the unique subject number. In order to protect the privacy of consumers, limited Personally Identifiable Information (PII) will be collected in the survey. In the event that a consumer needs to be contacted for verification or follow-up purposes, limited contact information consisting of the consumer's name, e-mail address, and phone number will be collected in the survey.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

While there is no intent to elicit Adverse Events (AEs) in this post-marketing survey, consumers taking part in the survey might spontaneously report an AE. If an AE is spontaneously reported during the survey, it will be reported as per any post marketed medicinal product. Reference to the Yellow Card Scheme for reporting of side effects will be included at the end of the survey.

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10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Target Audience

The target audience for this study is the Medicines and Healthcare products Regulatory Agency (MHRA) as well as GlaxoSmithKline stakeholders (Medical, Regulatory and Global Clinical Safety and Pharmacovigilance).

10.2. Study reporting and publications

Progress reports and clinical study results will be posted into the EU-PAS Register within 2 weeks of their finalization. Final study report will be reported within 12 months of the end of data collection. Final study results may be reported in a manuscript and submitted to a peer reviewed scientific or medical journal within 18 months of last participant surveyed if required. The final manuscript may be also transmitted to the Agency within 2 weeks after acceptance of the publication.

11. REFERENCES

1. Yin, Z., Brown, A., Hughes, G., Nardone, A., & Gill Noel O. and Delpech, V. (2014, November). *Gov.UK*. Retrieved from www.gov.uk: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document Title	Date
1.	Summary of Product Characteristic (SmPC)	17/12/2015
2.	Product Artwork & Labelling	17/12/2015

ANNEX 2. Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pirinase Hayfever Relief for Adults 0.05% Nasal Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aqueous suspension of 0.05% micronised fluticasone propionate. Each actuation contains 50 micrograms of fluticasone propionate.

Excipient with known effect:
Benzalkonium Chloride

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal spray, suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of seasonal allergic rhinitis including hay fever.

This medicine also provides symptomatic relief of sneezing, itchy and runny nose, itchy and watery eyes, nasal congestion and associated sinus discomfort.

4.2 Posology and method of administration

For administration by the intranasal route only.

Adults aged 18 years and over: For the treatment of seasonal allergic rhinitis: -

Two sprays into each nostril once a day, preferably in the morning. Once symptoms are under control a maintenance dose of one spray may be used accordingly. The minimum dose at which effective control of symptoms is maintained should be used.

The maximum daily dose should not exceed two sprays into each nostril.

Elderly:- The normal adult dosage is applicable.

Children under 18 years of age: Should not be used by children and adolescents under 18 years of age.

For full therapeutic benefit regular usage is recommended.

Maximum benefit may require 3-4 days of continuous treatment in some people (see section 5.1, Pharmacodynamic Properties).

Shake gently before use.

Before use the bottle needs to be primed by pumping until a fine spray is produced.

4.3 Contraindications

Hypersensitivity to fluticasone propionate or any of the other ingredients.

Concomitant use with HIV medicines (see section 4.5).

4.4 Special warnings and precautions for use

Treatment should be stopped or the advice of a doctor sought if an improvement is not seen within 7 days. The advice of a doctor or pharmacist should also be sought if symptoms have improved but are not adequately controlled.

This medicine should not be used for more than 1 month continuously without consulting a doctor.

Medical advice should be sought before using this medicine in the case of;

- concomitant use of other corticosteroid products, such as tablets, creams, ointments, asthma medications, similar nasal sprays or eye/nose drops
- an infection in the nasal passages or sinuses.
- recent injury or surgery to the nose, or problems with ulceration in the nose.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence of higher than recommended doses being used then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

Significant interactions between fluticasone propionate and potent inhibitors of the cytochrome P450 3A4 system, e.g. protease inhibitors, such as ritonavir, and cobicstat may occur. This may result in increased systemic exposure to fluticasone propionate.

Systemic effects of nasal corticosteroids may occur, particularly at high doses prescribed for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Contains Benzalkonium Chloride which may cause bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

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. Although not studied, concomitant use of intranasal fluticasone and cobicistat-containing regimens for the treatment of HIV may increase plasma concentrations of fluticasone and result in reduced serum cortisol concentrations.The combination of fluticasone and potent P450 3A4 inhibitors should be avoided unless the benefit outweighs the increased risk of systemic glucocorticoid side-effects.

Other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Care is advised when co-administering cytochrome P450 3A4 inhibitors, especially in long-term use and in case of potent inhibitors, as there is potential for increased systemic exposure to fluticasone propionate.

4.6 Fertility, pregnancy and lactation

There is inadequate evidence of the safety of fluticasone propionate 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 this medicine 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 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 this medicine is used in breast feeding mothers the therapeutic benefits must be weighed against the potential hazards to mother and baby.

The label will include a warning that medical opinion should be sought, before using this medicine, in the case of pregnancy or breast feeding.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. Rare and very rare events were generally determined from spontaneous data. In assigning adverse event frequencies, the background rates in placebo groups were not taken into account.

System Organ Class	Adverse Event	Frequency
Immune system disorders	Hypersensitivity reactions, anaphylaxis/anaphylactic reactions, bronchospasm, skin rash, oedema of the face or tongue	Very rare
Nervous system, disorders	Headache, unpleasant taste, unpleasant smell	Common
Eye disorders	Glaucoma, raised intraocular pressure, cataract	Very rare

Respiratory, thoracic and mediastinal disorders	Epistaxis	Very common
	Nasal dryness, nasal irritation, throat dryness, throat irritation	Common
	Nasal septal perforation	Very rare

As with other nasal sprays, dryness and irritation of the nose and throat, unpleasant taste and smell, headache and epistaxis have been reported.

Nasal ulceration and nasal septal perforation have been reported following the use of intranasal corticosteroids, usually when there has been previous nasal surgery.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at:www.mhra.gov.uk/yellowcard.

4.9 Overdose

There are no data available on the effects of acute or chronic overdosage with this medicine. Intranasal administration of fluticasone propionate at 20 times the recommended starting dose in adults (2mg twice daily) for seven days to healthy human volunteers had no effect on hypothalamic-pituitary-adrenal axis function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids

ATC Code: R01AD08

Fluticasone propionate is a glucocorticosteroid which has potent anti-inflammatory activity by acting via the glucocorticoid receptor. However, when used at up to four times the recommended daily dose on the nasal mucosa, has no detectable systemic activity and causes little or no hypothalamic pituitary adrenal (HPA) axis suppression. Following intranasal dosing of fluticasone propionate, (200 micrograms/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio 1.01, 90%CI 0.9-1.14).

Fluticasone propionate has been shown to reduce inflammatory mediators in both the early and late phase reactions of allergic rhinitis.

Once daily dosing with 200µg fluticasone propionate is sufficient to help relieve symptoms (particularly nasal congestion) for up to 24 hours.

5.2 Pharmacokinetic properties

Absorption: Following intranasal dosing of fluticasone propionate, (200 micrograms/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest Cmax 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 250-1000 micrograms dose range and are characterized 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 the other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrose (anhydrous)

Microcrystalline cellulose

Carboxymethylcellulose sodium

Phenylethyl alcohol

Benzalkonium chloride

Polysorbate 80

Purified water

Dilute hydrochloric acid

6.2 Incompatibilities

None reported

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

An amber glass bottle fitted with a metering pump and a nasal applicator.

Each bottle provides approximately 60 metered sprays.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Beecham Group Plc
980 Great West Road
Brentford
Middlesex
TW8 9GS

Trading as
GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00079/0688

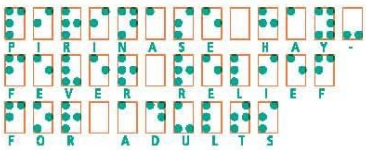
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2015

10 DATE OF REVISION OF THE TEXT

17/12/2015

* ANNEX 3. Product Artwork & Labelling



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PIRINASE HAY-
FEVER RELIEF
FOR ADULTS

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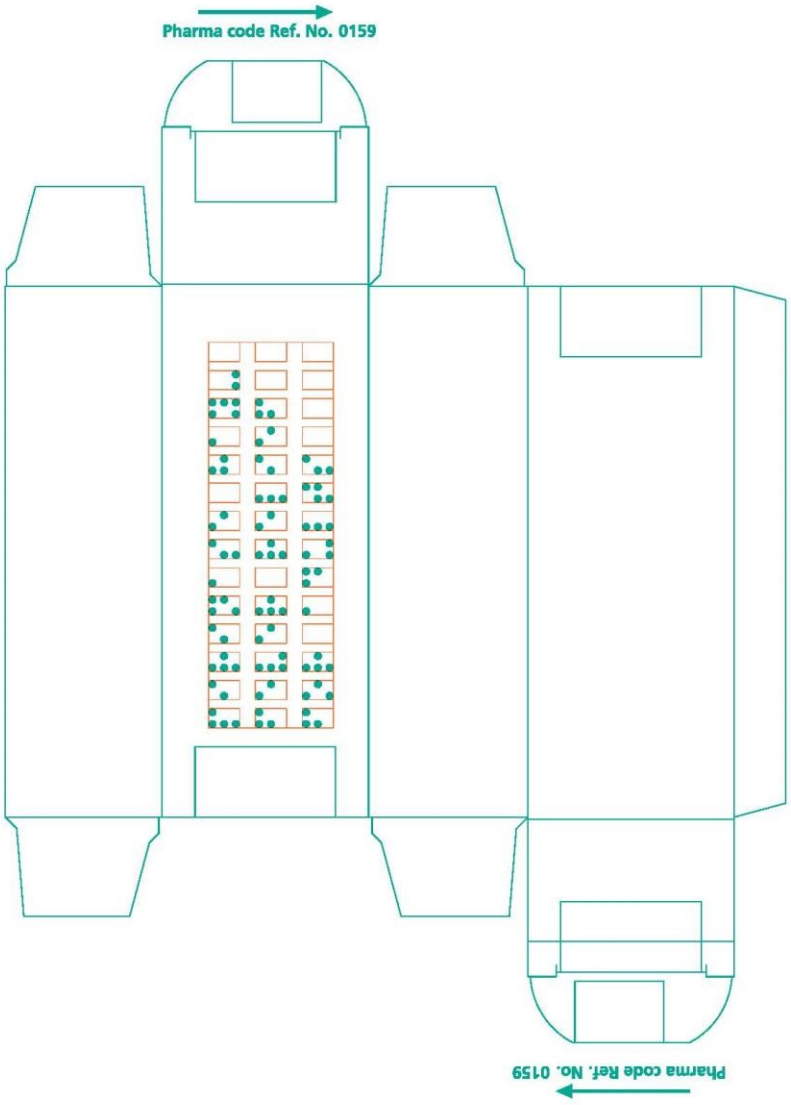

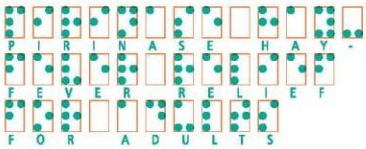

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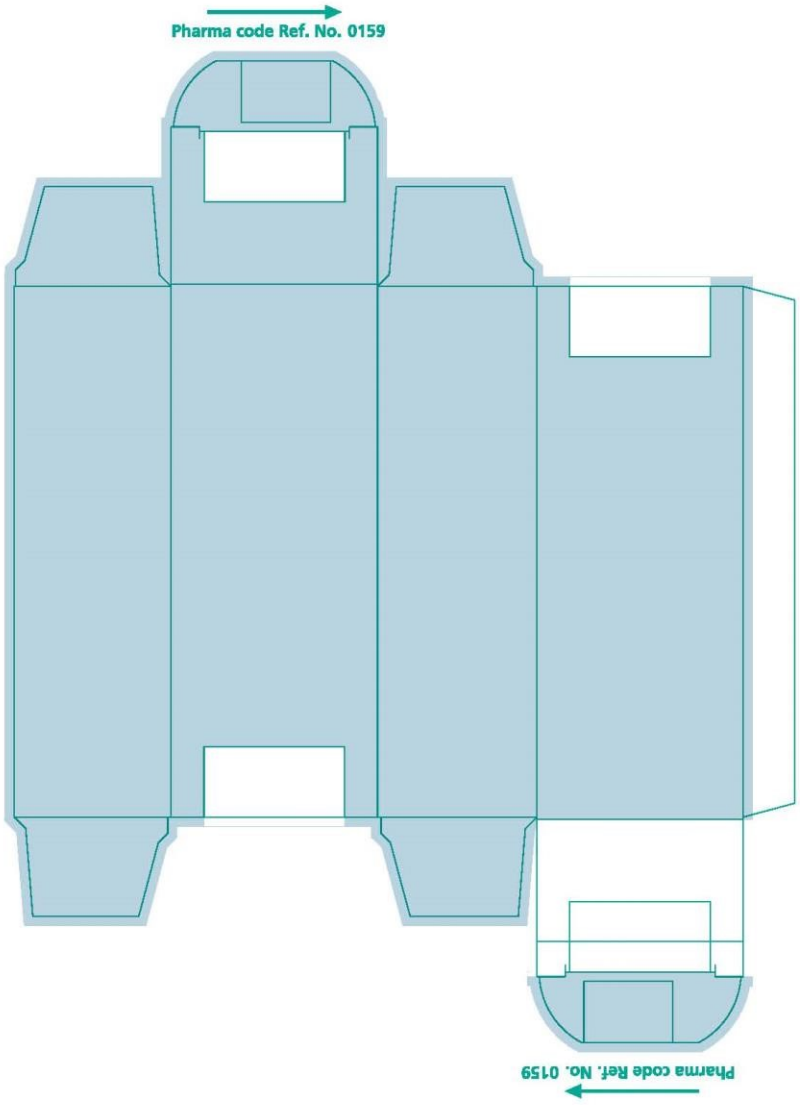

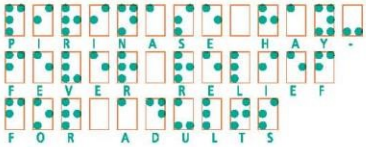

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Pharma code Ref. No. 0117

pirinase

Hayfever Relief for Adults

0.05% Nasal Spray

Fluticasone Propionate

Please read right through this leaflet before you start using this medicine. This medicine is available without prescription, but you still need to use Pirinase Hayfever Relief for Adults 0.05% Nasal Spray carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- If you have any questions, or if there is anything you do not understand, ask your pharmacist.

In this leaflet:

1. What Pirinase Hayfever Relief does

Pirinase Hayfever Relief is used to treat the allergic symptoms of hayfever including sneezing, itchy and watery eyes and a runny, itchy or blocked-up nose, for up to 24 hours.

The active ingredient is fluticasone propionate, a corticosteroid which, when used every day, has an anti-inflammatory action and works in a similar way to natural body chemicals to control inflammation. This helps to control your body's reactions to allergens (pollen) in the environment.

2. Check before you use Pirinase Hayfever Relief

Do not use Pirinase Hayfever Relief:

- If you are allergic to any other medicines for HIV.
- Do not use if you have ever had an allergic reaction to fluticasone propionate or to any of the other ingredients (listed in Section 6).
- Do not use if you are under 18 years.

Take special care with Pirinase Hayfever Relief

- Talk to your doctor or pharmacist before using Pirinase Hayfever Relief if you have an infection in your nose or sinuses, if you have a high temperature or you have recently had surgery, an injury or ulcers in your nose.
- If your symptoms do not improve after 7 days, or they are still not well controlled, talk to your doctor or pharmacist.
- Do not use continuously for more than 1 month unless your doctor tells you to.

If you are taking other medicines

Do not use this medicine if you are taking medicines for HIV.

Talk to your doctor or pharmacist before using this medicine if you are taking any prescribed medicines, particularly corticosteroid medicines (including some contraceptives), asthma inhalers, tablets, injections, nasal sprays, and eye or nose drops).

Pregnancy and breast-feeding

Talk to your doctor before using Pirinase Hayfever Relief if you are pregnant, trying to become pregnant or are breast-feeding.

3. How to use Pirinase Hayfever Relief

Always shake well before use. Only use in the nose. Do not swallow.

To get the best results from Pirinase Hayfever Relief, use the spray every day.

Pirinase Hayfever Relief quickly starts to reduce inflammation and swelling in your nose, although it may take 3 or 4 days to build up to its maximum protective effect. You should try to use the spray in the morning.

Adults aged 18 years and over:
Spray two puffs into each nostril once daily.
Once your symptoms have improved, you may be able to reduce the dose to one puff into each nostril once daily.

- Do not spray more than 4 sprays (200 micrograms) in a day.
- Use the lowest dose possible to control your symptoms.
- If your symptoms do not improve after 7 days, or they are still not well controlled, talk to your doctor or pharmacist.
- Do not use more than the recommended dose.

If you use too many sprays

Tell your doctor.

If you forget to use the spray

Take your next dose at the usual time. Never take two doses together.

Before using a new bottle of Pirinase Hayfever Relief

- Your Pirinase Hayfever Relief spray has a dust-cap which protects the nozzle and keeps it clean. Remember to take it off before you use the spray (Picture 1).
- Before you start to use a new bottle of Pirinase Hayfever Relief, or if you have not used the spray for a few days, press the pump down several times until a fine mist appears.
- Hold the bottle as shown with your forefinger and middle finger on the collar either side of the nozzle and your thumb underneath the bottle.
- Keeping your thumb still, press down with your fingers to pump the spray (Picture 2).
- When doing this make sure you do not point the nozzle at yourself or someone else.
- If the spray still doesn't work, try to clean it as described under the 'To clean the spray' section. Do not try to unblock or enlarge the fine spray hole with a pin or other sharp objects as this will destroy the spray mechanism.

Please turn over ➡

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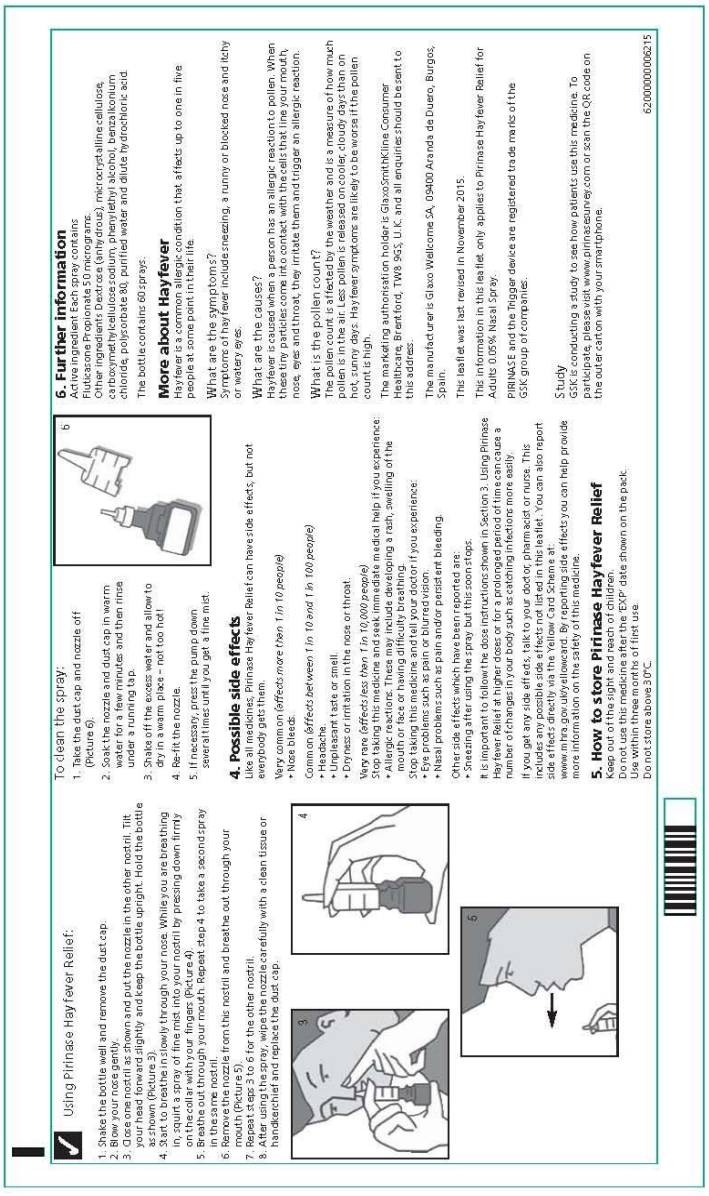

Using Pirinase Hayfever Relief:

1. Shake the bottle well and remove the dust cap.
2. Blow your nose gently.
3. Close one nostril as shown and put the nozzle in the other nostril. Tilt your head forward slightly and keep the bottle upright. Hold the bottle as shown (picture 3).
4. Start to breathe in slowly through your nose. While you are breathing in, squirt a spray of fine mist into your nostril by pressing down firmly on the collar with your fingers (picture 4).
5. Breathe out through your mouth. Repeat step 4 to take a second spray in the same nostril.
6. Remove the nozzle from this nostril and breathe out through your mouth (picture 5).
7. Repeat steps 3 to 6 for the other nostril.
8. After using the spray, wipe the nozzle carefully with a clean tissue or handkerchief and replace the dust cap.

To clean the spray:

1. Take the dust cap and nozzle off (picture 6).
2. Soak the nozzle and dust cap in warm water for a few minutes and then rinse under a running tap.
3. Shake off the excess water and allow to dry in a warm place – not too hot!
4. Re-fit the nozzle.
5. If necessary, press the pump down several times until you get a fine mist.

4. Possible side effects

Like all medicines, Pirinase Hayfever Relief can have side effects, but not everybody gets them.

Very common (affects more than 1 in 10 people)
- Nose bleeds.

Common (affects between 1 in 10 and 1 in 100 people)
- Headache.
- Unpleasant taste or smell.
- Dryness or irritation in the nose or throat.

Very rare (affects less than 1 in 10,000 people)
Stop taking this medicine and seek immediate medical help if you experience:
- Allergic reactions. These may include developing a rash, swelling of the mouth or face or having difficulty breathing.

Stop taking this medicine and tell your doctor if you experience:
- Eye problems such as pain or blurred vision.
- Nasal problems such as pain and/or persistent bleeding.

Other side effects which have been reported are:
- Sneezing after using the spray but this soon stops.

It is important to follow the dose instructions shown in Section 3. Using Pirinase Hayfever Relief at higher doses or for a prolonged period of time can cause a number of changes in your body such as catching infections more easily.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pirinase Hayfever Relief

Keep out of the sight and reach of children.
Do not use this medicine after the 'EXP' date shown on the pack.
Use within three months of first use.
Do not store above 30°C.

6. Further information

Active ingredient Each spray contains
fluticasone propionate 50 microgrammes.
Other ingredients Dextrose (as monohydrate), microcrystalline cellulose, carboxymethylcellulose sodium, phenylethyl alcohol, benzalkonium chloride, polysorbate 80, purified water and dilute hydrochloric acid.

The bottle contains 60 sprays.

More about Hayfever

Hayfever is a common allergic condition that affects up to one in five people at some point in their life.

What are the symptoms?
Symptoms of hayfever include sneezing, a runny or blocked nose and itchy or watery eyes.

What are the causes?
Hayfever is caused when a person has an allergic reaction to pollen. When these tiny particles come into contact with the cells that line your mouth, nose, eyes and throat, they irritate them and trigger an allergic reaction.

What is the pollen count?
The pollen count is affected by the weather and is a measure of how much pollen is in the air. Less pollen is released on cooler, cloudy days than on hot, sunny days. Hayfever symptoms are likely to be worse if the pollen count is high.

The marketing authorisation holder is GlaxoSmithKline Consumer Healthcare, Brentford, TW8 9GS, U.K. and all enquiries should be sent to this address.

The manufacturer is Glaxo Wellcome SA, 09400 Aranda de Duero, Burgos, Spain.

This leaflet was last revised in November 2015.

This information in this leaflet only applies to Pirinase Hayfever Relief for Adults 0.05% Nasal Spray.

PIRINASE and the Trigger device are registered trade marks of the GSK group of companies.

Study
GSK is conducting a study to see how patients use this medicine. To participate, please visit www.pirinasestudy.com or scan the QR code on the outer carton with your smartphone.

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