Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Avamys (Fluticasone furoate nasal spray)

RMP version to be assessed as part of this application	
RMP Version number	12.0
Data lock point for this RMP	18 October 2023
Date of final sign off	17 January 2024

Rationale for submitting an updated RMP

1. Proposal to remove all safety concerns in line with the GVP Module V Revision 2:
    - Important Identified Risks: Headache; Nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events); Hypersensitivity; Cataract and glaucoma
    - Important Potential Risks: Taste and smell disorders; Pyrexia; Systemic corticosteroids effect: adrenal suppression; Systemic corticosteroid effect: growth retardation; Psychiatric effects
    - Missing Information: Use in pregnancy and lactation; Off-label use (sinusitis and children < 6 years of age)
2. Proposal to remove targeted follow up questionnaires.

    The routine use of targeted follow-up questionnaires developed for fluticasone furoate nasal spray for the events of: adrenal suppression/acute adrenal insufficiency, Cushing's syndrome/cushingoid features, cataract and glaucoma/increased ocular pressure are considered no longer required and are proposed to be removed from the fluticasone furoate nasal spray EU RMP.
3. Template update to align with GVP Module V Revision 2.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in the present EU-RMP
Whole document		Alignment with Revision 2 of GVP Module V template. Drug name updated for consistency with other regulatory documents.

PART	MODULE	Changes made in the present EU-RMP
PART I: Product(s) Overview		Update of Invented name(s) in the EEA. Alignment to the EU SmPC wording.
PART II: Safety Specification	Module SI Epidemiology of the indications and target populations	Update with more recent data covering the same related information.
	Module SII Nonclinical part of the Safety Specification	Update related to established pharma products: removal of key safety findings from non-clinical studies and relevance to human usage.
	Module SIII Clinical trial exposure	Replacement of detailed clinical exposure data with a concise summary of current data due to established nature of product.
	Module SIV Populations not studied in clinical trials	Changes to include up to date information.
	Module V Post authorization experience	Changes to reflect up to date post authorization exposure data.
	Module SVI Additional EU requirements for the safety specification	Update of content to align with Revision 2 of GVP Module V template.
	Module SVII Identified and Potential Risks	SVII.2: Proposed removal of: Important Identified Risks: Headache; Nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events); Hypersensitivity; Cataract and glaucoma Important Potential Risks: Taste and smell disorders; Pyrexia; Systemic corticosteroids effect: adrenal suppression; Systemic corticosteroid effect: growth retardation; Psychiatric effects Missing Information: Use in pregnancy and lactation; Off-label use (sinusitis and children < 6 years of age) SVII.3: Removal of the presentation of important identified risks and important potential risks.

PART	MODULE	Changes made in the present EU-RMP
	Module SVIII Summary of Safety Concerns	Changes of content to reflect removal of safety concerns proposed in SVII.2.
PART III Pharmacovigilance Plan (including post authorization safety studies)		Changes of content to reflect removal of safety concerns proposed in SVII.2. Proposed removal of routine use of targeted follow-up questionnaires.
PART IV Plans for post-authorization efficacy studies		Changes to align with the template.
PART V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)		Changes of content to reflect removal of safety concerns proposed in SVII.2.
PART VI: Summary of RMP		Changes of content to reflect removal of safety concerns proposed in SVII.2. Update of content: Summary of risk management plan for Avamys (fluticasone furoate nasal spray) to align with the template.
PART VII Annexes	Annex 1	Not applicable.
	Annex 2	Minor update of list of completed studies.
	Annex 3	Adjustment to the new EU RMP template.
	Annex 4	Changes of content to reflect removal of targeted follow-up questionnaires.
	Annex 5, 6	Adjustment to the new EU RMP template.
	Annex 7	Update of list of references.
	Annex 8	Update to reflect the summary of changes over time.

Other RMP versions under evaluation Not applicable		
RMP Version number	**Submitted on**	**Procedure number**
N/A	N/A	N/A
Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
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QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety and Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

ABBREVIATIONS

AE	Adverse Event
AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
ARS	Acute Rhinosinusitis
aRMM	Additional Risk Minimization Measure
CTD	Common Technical Document
EEA	European Economic Area
EPAR	European Public Assessment Report
FUM	Follow-up Measure
GVP	Good Pharmacovigilance Practices
HPA	Hypothalamic-Pituitary-Adrenal
IOP	Intraocular Pressure
MAA	Marketing Authorization Application
mcg	Microgram
mg	Milligram
ml	Milliliter
OD	Once Daily
PAR	Perennial Allergic Rhinitis
PhVWP	Pharmacovigilance Working Party
PI	Product Information
PL	Package Leaflet
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
PV	Pharmacovigilance
RMM	Risk Minimization Measure
SAR	Seasonal Allergic Rhinitis
SmPC	Summary of Product Characteristics
UK	United Kingdom
US	United States

Trademark Information

Trademarks of the GSK group of companies
Avamys

Trademarks not owned by the GSK group of companies
Flonase Sensimist Allergy Relief

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Fluticasone furoate
Pharmacotherapeutic group(s) (ATC Code)	R01AD12
Marketing Authorization Holder/ Applicant	GlaxoSmithKline (Ireland) Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Avamys
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Fluticasone furoate is a synthetic trifluorinated corticosteroid.
	Summary of mode of action: Fluticasone furoate possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action.
	Important information about its composition: Not applicable
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).
Indication(s) in the EEA	Current: Avamys is indicated in adults, adolescents and children (6 years and over) Avamys is indicated for the treatment of the symptoms of allergic rhinitis.
	Proposed: Not applicable

Dosage in the EEA	Current: Adults and Adolescents (12 years and over) The recommended starting dose is 2 spray actuations (27.5 mcg of fluticasone furoate per spray actuation) in each nostril once daily (total daily dose, 110 mcg) Once adequate control of symptoms is achieved, dose reduction to 1 spray in each nostril (total daily dose, 55 mcg) may be effective for maintenance. Children (6 to 11 years of age) The recommended starting dose is 1 spray actuation (27.5 mcg of fluticasone furoate per spray actuation) in each nostril once daily (total daily dose, 55 mcg). Patients not adequately responding to 1 spray actuation in each nostril once daily (total daily dose, 55 mcg) may use 2 spray actuations in each nostril once daily (total daily dose, 110 mcg). Once adequate control of symptoms is achieved, dose reduction to 1 spray actuation in each nostril once daily (total daily dose, 55 mcg) is recommended.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Nasal spray, suspension. White suspension. Each spray actuation delivers 27.5 micrograms of fluticasone furoate.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Allergic rhinitis

INCIDENCE

Estimates of incidence for rhinitis are scarce in the literature. The age-sex standardized incidence of AR was 5.57 per 1000 person-years in 2001 and increased by 33.0% to 7.41 per 1000 person-years in 2005. Lifetime age-sex standardized prevalence of a recorded diagnosis of AR increased by 43.2% from 46.35 per 1000 in 2001 to 66.37 per 1000 in 2005 [Ghouri, 2008].

The incidence rate of AR in children over the first 5 years of life was reported to be 17.2%, with a peak age at diagnosis between 24 and 29 months (2.5%) [Hill, 2016].

Nasal and ocular symptoms of AR have been shown to affect up to 30% of the population in the US and Europe annually [Izquierdo-Domínguez, 2013; Katelaris, 2012].

PREVALENCE

The prevalence of AR has increased the past three decades in developed and industrialized countries [Bergmann, 2020].

A recent literature review [Savoure, 2022] showed that prevalence of AR ranged from 3.6% to 22.8% for Africa, from 3.5% to 54.5% for America, from 1.0% to 47.9% for Asia, from 1.0% to 43.9% for Europe, and from 19.2% to 47.5% for Oceania.

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease

Meta-analysis studies have shown the sex-specific differences in the prevalence of AR with male predominance in childhood and a female predominance in adolescents [Frohlich, 2017; Pinart, 2017].

Allergic rhinitis has a multifactorial origin including both genetic and environmental components. Sensitization to allergens can occur at any age, including early in life. Allergens include both indoor and outdoor inhaled allergens, along with some occupational allergens and pollution. Major indoor allergens include mites, animal dander, insects and moulds, while major outdoor allergens include pollens and moulds [Bousquet, 2008].

Allergic rhinitis also has a genetic component characterized by a family history of atopy. People with family histories of allergy in both parents tend to develop symptoms before puberty, whereas persons with a history of allergy in one parent tend to have symptoms later in life, or not at all [Skoner, 2001].

Prevalence of AR has increased with years due to several risk factors including global urbanization as shown by several studies comparing AR prevalence in urban settings with rural areas [Elholm, 2016; Li, 2014].

It has been reported that AR is more prevalent in urban areas compared with rural areas [Li, 2014]. Climate changes also prolong pollen season as reported in Europe over the last three decades along with more frequent seasonal allergies [Bergmann, 2020].

Smoking however, did not show a significant association with the severity of nasal symptoms in AR but usually impacted patients with chronic rhinitis [Bousquet, 2009; Hisinger-Molkanen, 2018]. Conversely, maternal smoking conferred the greater risk in pediatric AR [Singh, 2018].

SI.1.2 The main existing treatment options

The goal of allergic rhinitis therapy is to manage both the acute and chronic manifestations of the disease by minimizing the associated symptoms and improving quality of life. To achieve this, current treatment recommendations include allergen avoidance, pharmacotherapy, and/or immunotherapy. Avoidance is difficult to achieve for the most common allergens (e.g., pollen, dust mites). Allergen specific immunotherapy is an additional option. Immunotherapy is effective in some patients as chronic therapy but it is time-consuming, inconvenient, and has potential for rare and serious adverse effects (such as large local reactions and anaphylaxis).

Clinical guidelines, such as Allergic Rhinitis and its Impact on Asthma (ARIA), recommend intranasal glucocorticoids for treatment of patients with AR [Bousquet, 2020]. Other authorized treatments include H1 antihistamines (oral, intranasal, intra-ocular), oral leukotriene receptor antagonists, systemic glucocorticoids, chromones (intranasal, oral, intra-ocular), intranasal ipratropium bromide and decongestants (oral, intranasal). Pharmaceutical management of AR rests on symptomatic treatments with antihistamines, nasal or oral glucocorticoids, nasal decongestants and leukotriene receptor antagonists that act as symptoms reliever in AR.

Antihistamines are the most utilized first line medication to treat mild AR, however, first generation of antihistamines (e.g., diphenhydramine and hydroxyzine) are no longer recommended due to various adverse side effects impacting the central nervous system, anticholinergic side effects and cardiac toxicity [Bousquet, 2008; McKay, 2016]. Newer generation of antihistamines (e.g., cetirizine, loratadine, desloratadine, fexofenadine, rupatadine, and bilastine) should be chosen.

Intranasal corticosteroids that act as first-line pharmacotherapy by suppressing immune cells infiltration in AR, are effective for mild and moderately severe AR in both children and adults [Zhang, 2022].

Leukotriene receptor antagonists (e.g., montelukast, zafirlukast, and pranlukast) block the activity of cysteinyl leukotrienes, an important potent allergic mediator that causes allergic inflammation and various allergic symptoms such as nasal congestion and mucus production [Hossenbaccus, 2020].

Nasal decongestants reduce nasal congestion symptoms through their agonistic action at Alpha1 and Alpha2-adrenergic receptors on endothelial cells of nasal mucosa, leading to reduced mucosa swelling [Mandhane, 2011]. Overuse of nasal decongestants can cause rhinitis medicamentosa (i.e., a condition of rebound congestion upon withdrawal of nasal decongestants).

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Allergic rhinitis is not a life-threatening condition [Izquierdo-Domínguez, 2013]. Although AR itself is not life-threatening (unless accompanied by severe asthma or anaphylaxis), morbidity from the condition can be significant.

AR typically appears in childhood or adolescence but lasts through much of adulthood [Torres-Borrego, 2008]. AR is a chronic disease with symptoms including rhinorrhoea, sneezing, nasal obstruction, nasal itching, ocular itching, and watery eyes that may be extremely troublesome and have a profound negative impact on the allergy sufferer's quality of life and their family [Torres-Borrego, 2008; Katelaris, 2012]. The symptoms of AR often disrupt sleep, leading to fatigue, memory deficits, irritability, daytime sleepiness and depression [Izquierdo-Domínguez, 2013; Katelaris, 2012]. AR impairs work among adults and school performance among children [WHO, 2012; Izquierdo-Domínguez, 2013].

SI.1.4 Important co-morbidities

AR may be associated with secondary complications and co-morbidities. Among children, asthma, atopic dermatitis/eczema, allergic conjunctivitis, chronic rhinosinusitis, and otitis media are associated with AR [Izquierdo-Domínguez, 2013; Bousquet, 2008]. The most frequent comorbidities among children with AR were conjunctivitis (54%), asthma (50%), and atopic dermatitis (40%) [Jáuregui, 2011]. Among adults, co-morbid conditions include conjunctivitis, chronic rhinosinusitis, nasal polyps, chronic cough, laryngitis, and gastro-esophageal reflux [Izquierdo-Domínguez, 2013; Bousquet, 2008].

The ARIA program examined the impact of AR on asthma and concluded that AR is a major chronic respiratory disease owing to its prevalence, impact on quality of life, impact on school and work performance and productivity, economic burden and links to asthma. According to the ARIA study and previous observations, allergic and nonallergic rhinitis should be considered risk factors for asthma, along with other known risk factors [Brozek, 2017].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Fluticasone furoate nasal spray is a mature product with 16 years of post-marketing clinical exposure. There are no outstanding nonclinical safety concerns. The pharmacological, pharmacokinetic, and toxicological effects of fluticasone furoate nasal spray have been well characterized in animals, and no new nonclinical information has come to light that would affect the safety of fluticasone furoate nasal spray for clinical use.

There are no nonclinical findings which warrant inclusion in the list of safety concerns.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Fluticasone furoate nasal spray was first approved on 27 April 2007. Accounting for an extensive post-marketing history, a brief summary of clinical trial experience is presented below up to 21 June 2023.

Extensive pharmacological and clinical investigations have been performed with fluticasone furoate nasal spray involving over 7110 participants. The duration of treatment ranged from 2 weeks to 104 weeks in adults and adolescents and 2 weeks to 76 weeks in pediatrics.

The cumulative number of participants from ongoing and completed GSK-sponsored interventional clinical trials investigating fluticasone furoate nasal spray for the treatment of allergic rhinitis is presented in Table 2.

Table 2 Cumulative number of participants from ongoing and completed GSK-sponsored interventional studies [1]

	Number of participants		
Study Designs / Treatment	**Ongoing**	**Completed (Exposure Years)**	**Total**
RHINITIS (Cross-Over Studies)[2]			
Fluticasone furoate nasal spray	0	972 (13.1 yrs)	972
Placebo	0	467 (17.4 yrs)	467
Other treatment arms	0	989 (14.2 yrs)	989
RHINITIS (Parallel-Group Studies)			
Fluticasone furoate nasal spray	0	6138 (1628.9 yrs)	6138
Placebo	0	4159 (855.5 yrs)	4159
Other treatment arms	0	759 (82.5 yrs)	759

1. Data as of 21 June 2023 Studies included in this table are:
   Completed RHINITIS (Cross-Over Studies) 200284, 200286, 201474, FFR10005, FFR10006, FFR10010, FFR10013, FFR101747, FFR105693, FFU105924, FFU105927, FFU108556
   RHINITIS (Parallel-Group Studies) 201492, FFR100010, FFR100012, FFR100650, FFR100652, FFR100688, FFR101782, FFR101816, FFR102123, FFR103184, FFR104503, FFR104861, FFR106080, FFR110537, FFR111158, FFR113342, FFR116364, FFR116365, FFR20001, FFR20002, FFR30002, FFR30003, FFR30006, FFR30007, FFR30008, FFS113203, FFU109045, FFU109047, FFU111439
2. Participants are included for each planned treatment period in which they took treatment.

Note: Calculation of the number of exposure years has only been made for completed studies

An estimate of cumulative number of participants exposed to fluticasone furoate nasal spray by age, sex and racial group for completed GSK-sponsored interventional studies with an approved clinical study report is presented in Table 3.

Table 3 Cumulative participant exposure to fluticasone furoate nasal spray in completed GSK sponsored interventional studies by age, sex and racial group [1]

	Number of participants
Total	7110
Age (years)	
<5 years	170
>=5 years to <12 years	1290
>=12 years to <18 years	468
>=18 years to <65 years	4996
>=65 years	186
Sex	
Male	3145
Female	3965
Racial Group	
White	4893
Black	512
Asian	1216
Other	486
Unknown	3

1. Data as of 21 June 2023

Studies included in this tableare:

Completed	RHINITIS (Cross-Over Studies)	200284, 200286, 201474, FFR10005, FFR10006, FFR10010, FFR10013, FFR101747, FFR105693, FFU105924, FFU105927, FFU108556
	RHINITIS (Parallel-Group Studies)	201492, FFR100010, FFR100012, FFR100650, FFR100652, FFR100688, FFR101782, FFR101816, FFR102123, FFR103184, FFR104503, FFR104861, FFR106080, FFR110537, FFR111158, FFR113342, FFR116364, FFR116365, FFR20001, FFR20002, FFR30002, FFR30003, FFR30006, FFR30007, FFR30008, FFS113203, FFU109045, FFU109047, FFU11143

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Fluticasone furoate nasal spray has been extensively studied in clinical studies and has a well-defined safety profile that is supported by over 16 years of post-marketing safety information.

There were no studies conducted specifically in special patient populations (i.e., pregnant or lactating women, patient with renal, hepatic or cardiac disorders) as part of the development program for fluticasone furoate nasal spray.

Exclusion from clinical trials have not resulted in a safety concern for the product. There is no missing information that is relevant for the approved indication.

SIV.1 Exclusion criteria in pivotal clinical studies withinthe development program

Table 4 Exclusion criteria

Criteria	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Participants with known hypersensitivity to corticosteroids or any excipients in the product	It is standard practice to exclude participants with a known hypersensitivity. Other treatment options (e.g., antihistamines) are available for patients that are hypersensitive to any ingredients.	NO	Contraindication in patients with hypersensitivity to the active substance or to any of the excipients is included in the Contraindications section of the EU SmPC. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria are listed in the EU SmPC with frequency 'rare' under the Undesirable effects section.
Historical or current evidence of clinically significant uncontrolled disease of any body system	Potentially confounding significant pre-existing diseases.	NO	Exclusion criteria which prevented participants with significant co-morbidities from being enrolled into the studies were not considered to present a safety concern. Extensive experience has shown that for other intranasal corticosteroids these

Criteria	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
			patient groups do not have any additional risk factors that may predispose them to a more severe and/or differing adverse event profile. Therefore, further study in these patient groups was not considered warranted.
A severe physical obstruction of the nose (e.g., deviated septum or nasal polyp) or nasal septal perforation that could affect the deposition of study drug	Potentially confounding significant pre-existing diseases	NO	Previous experience with intranasal corticosteroids has not contraindicated use in this population.
Recent (in the last 6 months) nasal septal or facial cosmetic surgery	Potentially confounding significant pre-existing diseases	NO	Previous experience with intranasal corticosteroids has not contraindicated use in this population.
Asthma, with the exception of mild intermittent asthma	Potentially confounding significant pre-existing diseases	NO	Only participants with mild intermittent asthma were enrolled into the studies. Participants with asthma of greater severity requiring concomitant inhaled corticosteroid therapy were not studied. Epidemiology data show that asthma is a significant co-morbid condition in patients with rhinitis. Over 80% of asthmatics have AR, while 10-40% of individuals with AR have asthma [Egan, 2015]. Although asthmatic patients were not specifically studied, given the low dose of fluticasone furoate nasal spray and its low systemic bio-availability, the addition of this therapy to these patients' inhaled corticosteroid regimen is

Criteria	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
			considered unlikely to present an additional safety concern as reported with other intranasal corticosteroids with low systemic bio-availability [**Error! Reference source not found.**, 2005; **Error! Reference source not found.**, 2004].
Documented evidence of acute or significant chronic sinusitis Current or history of herpes simplex Clinical evidence of a Candida infection of the nose or oropharynx	Potentially confounding significant pre-existing diseases	NO	Exclusion criteria which prevented participants with significant co-morbidities from being enrolled into the studies were not considered to present a safety concern. Extensive experience has shown that for other intranasal corticosteroids these patient groups do not have any additional risk factors that may predispose them to a more severe and/or differing adverse event profile. Therefore, further study in these patient groups is not considered warranted.
Current history of glaucoma and/or cataracts	Potentially confounding significant pre-existing diseases	NO	Warning and precaution included in relation to potential systemic effects.
History of adrenal insufficiency	Potentially confounding significant pre-existing diseases	NO	Warning and precaution included in relation to potential systemic effects.
History of psychiatric disease, intellectual deficiency, poor motivation or substance abuse	Potentially poor study participation and compliance	NO	Extensive experience has shown that for other intranasal corticosteroids these patient groups do not have any additional risk factors that may predispose them to a more severe and/or differing adverse event profile.

Criteria	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
			Therefore, further study in these patient groups was not considered warranted.
Corticosteroids (oral, intranasal, inhaled, intravenous and dermatological corticosteroid) with the exception of hydrocortisone 1% or less	Potential for confounding of safety and efficacy data	NO	Use of other corticosteroids during the study, would confound the efficacy results. Intranasal corticosteroids have a low systemic exposure. A warning is included in the EU SmPC in relation to potential systemic effects and that this risk is greater with oral steroids.
Any medications that significantly inhibit the cytochrome P450 subfamily enzyme CYP3A4, including ritonavir and ketoconazole	Potential for interaction with study medication	NO	A warning in relation to potential interaction with ritonavir is included in the EU SmPC.
Pregnant or lactating women or women of child bearing potential not using a reliable method of contraception	Excluded from trials as safety not established in pregnancy and lactating females	NO	EU SmPC indicates that fluticasone furoate nasal spray can only be used when benefit outweighs any potential risk. The excretion of fluticasone furoate into human breast milk has not been investigated.

SIV.2 Limitations to detect adverse reactions in clinicaltrial development program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 5 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	Over 5650 adults and adolescents and 1460 participants aged 2 to 11 treated with intranasal fluticasone furoate during the clinical development program (including studies completed post-authorisation).	The overall safety profile of fluticasone furoate is consistent with that reported for licensed intranasal corticosteroids for allergic rhinitis. Although rare events may not have been observed during clinical studies, there is a large amount of experience with intranasal corticosteroids. In addition, there are over 30 million patient years exposure from post-marketing experience.
Due to prolonged exposure	The initial clinical trials program included 1564 adults and adolescents and 425 children exposed to 110 mcg fluticasone furoate, 1989 in total, of these at least 500 adults and adolescents were exposed to fluticasone furoate for 1 year and over 100 children were exposed for a period of 3 months. Post-marketing clinical studies included a 1 year growth study and a 2 year ocular safety study.	Potential risks of chronic use are likely to be similar to those observed with other intranasal corticosteroids.
Due to cumulative effects	The initial clinical trials program included 1564 adults and adolescents and 425 children exposed to 110 mcg fluticasone furoate, 1989 in total, of these at least 500 adults and adolescents were exposed to fluticasone furoate for 1 year and over 100 children were exposed for a period of 3 months. Post-marketing clinical studies included a 1 year growth study	There was no evidence to suggest cumulative effect for AEs with fluticasone furoate.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	and a 2 year ocular safety study.	
Which have a long latency	The initial clinical trials program included 1564 adults and adolescents and 425 children exposed to 110 mcg fluticasone furoate, 1989 in total, of these at least 500 adults and adolescents were exposed to fluticasone furoate for 1 year and over 100 children were exposed for a period of 3 months. Post-marketing studies including a 1 year growth study and a 2 year ocular study have been completed.	Potential for growth retardation demonstrated in 1 year growth study is likely to be similar to the risk with other intranasal corticosteroids [Murphy, 2006; Allen, 2002]. No further additional risks have been identified from over 16 years of post-marketing experience.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 6 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Pregnant women were excluded from participating in the clinical development program. Females of child-bearing potential who were enrolled in clinical studies were required to use contraceptive measures with a failure rate of<1%. There were 12 pregnancies reported during clinical development. The following event PTs were reported: exposure during pregnancy (n=7), delivery (n=4), abortion spontaneous (n=3), live birth (n=2), abortion induced (n=1), with the following pregnancy outcomes: normal infant (n=3), unknown (n=2), live infant no apparent congenital anomaly (n=2), spontaneous abortion no apparent congenital anomaly (<22wk) (n=2), lost to follow up (n=1), spontaneous abortion (n=1), elective termination no apparent congenital anomaly (n=1).
Breastfeeding women	The excretion of fluticasone furoate into human breast milk has not been investigated. Therefore, breast-feeding women were excluded from participating in the clinical development program.

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment	In the EU SmPC it is stated that no dose adjustment is required in patients with hepatic impairment. There are no data on intranasal fluticasone furoate in participants with hepatic impairment. Data are available following inhaled administration of fluticasone furoate (as fluticasone furoate or fluticasone furoate/vilanterol) to participants with hepatic impairment that are also applicable for intranasal dosing. At the maximum clinical dose (110 mcg once-daily), systemic concentrations of intranasal fluticasone furoate are generally below the limit of quantitation (10 pg/mL). Therefore, to assess the likely bioavailability of the marketed formulation, an absolute bioavailability study was performed using multiple doses of a high strength suspension (Study FFR10010). The results from this study using 8-fold higher multiple dose (fluticasone furoate nasal spray at 880 mcg 3 times a day for a total of 10 doses) showed the absolute bioavailability of intranasal fluticasone furoate to be 0.50% (90% CI: 0.34% to 0.74%). In comparison, absolute bioavailability of inhaled fluticasone furoate was 13.9%, (90% CI: 12.7% to 15.3%; Study FFR115441). These results indicate that fluticasone furoate systemic exposure following intranasal administration is at least 27-fold lower (13.9/0.5) than that following inhaled administration without taking into account 8-fold higher dose or accumulation that resulted from 3-times a day administration used in the FFR10010 study. Due to this significantly lower systemic exposure with intranasal fluticasone furoate, evidence does not suggest that hepatic impairment would be correlated with increased risk. Study HZA111789 demonstrated an increase in fluticasone furoate systemic exposure in patients with moderate and severe hepatic impairment on repeat inhaled dosing but not after a single inhaled dose. Although single dose study FFA10013 did show higher fluticasone furoate systemic exposure in moderate hepatic impairment subjects compared to their healthy counterparts following inhaled fluticasone furoate, variability was high in that study with wide confidence intervals for parameters which indicates that estimates should be interpreted with caution. Increased systemic exposure after repeat dose but not after single dose in HZA111789 suggests reduced hepatic clearance of absorbed fluticasone furoate rather than just a reduction in the first-pass metabolism of the swallowed portion of the fluticasone furoate inhaled dose. Since intranasal fluticasone furoate shows very little/negligible absorption, increased (two-fold) fluticasone furoate systemic exposure that may occur as a result of moderate/severe hepatic impairment (reduced clearance) will also be very low (approximately 13-fold lower than inhaled fluticasone furoate administration) and clinically not relevant. Due to this significantly lower systemic exposure with intranasal fluticasone furoate, evidence does not suggest that hepatic impairment would be correlated with increased risk.

Type of special population	Exposure
• Patients with renal impairment	There are no dose adjustments required in patients with renal impairment. No clinical trial exposure to the intranasal formulation. Since the PK of fluticasone furoate is similar to that following fluticasone furoate /vilanterol (FFA114496), data from clinical pharmacology study HZA113970 with fluticasone furoate /vilanterol provided information on the effects of renal impairment on the PK of fluticasone furoate. A total of 0 (0%) and 9 (5%) participants with renal impairment were exposed to fluticasone furoate monotherapy and fluticasone furoate /vilanterol treatment in the Clinical Pharmacology program, respectively.
• Patients with cardiovascular impairment	Not included in the clinical development program. Participants with clinically significant uncontrolled disease were excluded
• Immunocompromised patients	Not included in the clinical development program. Participants with clinically significant uncontrolled disease were excluded
• Patients with a disease severity different from inclusion criteria in clinical trials	Studies recruited patients with different levels of disease severity. The efficacy measures for nasal (rhinorrhea, nasal congestion, nasal itching, and sneezing) and ocular (itching/burning eyes, tearing/watering eyes, and eye redness) symptoms were based on participant-rated, individual symptom assessments as evaluated on a 4-point (0 to 3) categorical scale, recorded on the diary card or electronic diary. The reflective rating represented how the participant had been feeling over the preceding 12 h. This assessment provided information on how effective the treatment was throughout a 12-h period of time and was performed twice daily (AM and PM). The AM assessment was performed in the morning prior to administering the dose of study drug and assessed how the participant felt during the night. The PM assessment was performed approximately 12 h after dosing and before bedtime and assessed how the participant felt during the day. The instantaneous rating represented how the participant felt at the time of the assessment. The instantaneous assessment was performed once daily, in the morning prior to administering the dose of study drug. This assessment provided information on the efficacy of the treatment at the end of the 24-h dosing interval.

Type of special population	Exposure
Population with relevant different ethnic origin	There are no dose adjustments required based on racial differences or ethnic origin. Across six integrated SAR and PAR clinical studies in adults and adolescents (FFR20001, FFR20002, FFR30002, FFR30003, FFR103184, FFR104861) the majority of participants were White (81%); Black participants made up 7% of the population and participants in the 'Other' race subgroup made up 13% of the population. The majority of participants (79%) were of Non-Hispanic/Non-Latino ethnicity. Across three integrated pediatric SAR/PAR studies (FFR100010, FFR30008, FFR100012) the majority of participants were White (76%); Black participants comprised 11% and participants in the 'Other' race subgroup comprised 13% of the population. The majority of participants (63%) were of Non-Hispanic/Non-Latino ethnicity.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program. No specific analysis of genetic polymorphisms were conducted in the clinical development program.
Patients with other relevant co-morbidity	There are no other relevant co-morbidities to discuss for this product and indication.
Children	Although allergic rhinitis signs and symptoms may be present in young children, the disease may not be present or may be difficult to diagnose in patients younger than age 2 years. Children aged 2 to 11 years were studied during development and 1460 children of this age were included. Fluticasone furoate nasal spray is approved for use in children aged 6 years and above in the EU, however in some other markets it is approved for use in children aged 2 years and older. Adolescents were studied with adults in the clinical development program, a total of 468 adolescents were studied during development. The results of the one year growth study FFR101782 identified an effect on growth in children (treatment difference to placebo -0.27cm/year [95% CI: -0.48 to -0.06]) treated for a year. The EU SmPC has been updated with appropriate information following the results of this study.
Older Adults	In the studies included in the initial clinical development program the ages ranged from 12 to 85 years. In the clinical development program, a total of 5182 adult participants were included, of which 4996 were in the 18 to <60-year age group. Only 186 (2.6%) participants were 65 years or older.

	As indicated by the epidemiology of SAR and PAR the majority of patients with allergic rhinitis are adults and fewer elderly patients (>=65 years old) seem to experience this disease. This probably accounts for the smaller numbers of this subset that were available for recruitment into the clinical trial program.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for fluticasone furoate nasal spray.

SV.1.1 Method used to calculate exposure

The algorithm used to derive post-approval exposure data from IQVIA is an average daily dose of four sprays. Note that the recommended starting dose is two sprays in each nostril, once daily (27.5 mcg of fluticasone furoate per spray; total daily dose of 110 mcg). An average dose per patient year is four sprays x 365 days.

SV.1.2 Exposure

Based on IQVIA data, cumulative post-marketing exposure up until 31 March 2023 to fluticasone furoate nasal spray is estimated to be 31 138 083 patient years.

A detailed breakdown of patient exposure data by indication, sex, age, dose, formulation and region for the cumulative period 01 January 2012 to 31 March 2023 is presented in Table 7.

The data in Table 7 is sourced from IQVIA's "MIDAS Diagnosis Insights (detailed medical data)". This covers office-based prescribing in over 11 key countries (including major markets in Europe, Asia and the Americas) and patient demographics as well as diagnosis specific prescribing information. Diagnosis Insights data is limited to data from the last 11 years, and it does not include hospital-based doctors, with the exception of Japan, where hospital data is also covered. Medical audits reflect country prescribing practices and care should be taken when comparing countries or analyzing on a regional or global basis. The data reflects prescriptions that are written. Information regarding prescriptions dispensed and refills is not included.

Table 7 Exposure table by indication, sex, age, dose and formulation for the cumulative period of 01 January 2012 to 31 March 2023.

01 JANUARY 2012 TO 31 MARCH 2023 (PRESCRIPTIONS SHOWN IN THOUSANDS)													
INDICATION	**SEX**			**AGE (YEARS)**							**DOSE**		**F***
	MALE	**FEMALE**	**U****	**Less Than 2**	**2 to 5**	**6 to 11**	**12 to 17**	**18 to 65**	**>65**	**U**	**27.5Y/DOSE**	**U**	**Topical**
Allergic rhinitis, unspecified	2168	2389	44	1	52	212	308	3338	675	15	4597	0	4601
Allergic rhinitis due to pollen	365	401	0	3	24	99	82	480	75	3	766	0	766
Other allergic rhinitis	561	678	2	0	64	144	124	823	86	0	1241	0	1241
Other seasonal allergic rhinitis	32 799	34 570	447	160	4164	8234	5423	38 610	11 028	197	67 759	3	67 816
Others	27 224	29 165	367	265	3799	5021	3380	33 385	10 814	92	53 158	40	56 756

*F-Formulation;
**U–Unknown;

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

GSK does not consider that there is a potential for misuse for illegal purposes with fluticasone furoate nasal spray. No instances of the abuse of study medications were reported in the clinical studies in the fluticasone furoate nasal spray development programme.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the listof safety concerns in the RMP

This section is not applicable.

SVII.1.2 Risks considered important for inclusion in the listof safety concerns in the RMP

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Proposed removal of safety concerns from fluticasone furoate nasal spray EU RMP in line with GVP Module V Revision 2

Important identified risks/ important potential risks

The safety concerns for fluticasone furoate nasal spray were reviewed in line with the definitions in GVP module V revision 2. Fluticasone furoate nasal spray has been on the market for more than 16 years with an estimated post-marketing patient exposure of 30 million patient-years.

As further described below, the risks initially listed in the EU RMP are no longer considered important and do not require any additional pharmacovigilance activities or additional risk minimization measures to characterize or mitigate them. Therefore, all the risks are proposed for removal from the summary of safety concerns.

Important identified risk: Headache

The risk of headache is considered sufficiently characterized, appropriately managed and adequately reflected in the fluticasone furoate nasal spray EU SmPC (Section 4.8). The risk has been considered an adverse reaction since 2011, following a signal assessment. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this identified risk different from the safety profile characterized thus far.

No additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are considered warranted. Thus, the risk of headache is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important identified risk: Nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events)

As part of two signal assessments (performed in 2010 and 2015) a review of data from multiple sources, including clinical trials, published literature and spontaneous adverse event reports led to the update of the EU PI to include the following nasal adverse events: rhinalgia, nasal discomfort (including nasal burning, nasal irritation, and nasal soreness), nasal dryness and nasal septum perforation as an adverse reactions. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this identified risk different from the safety profile characterized thus far.

The risk of nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events) is considered sufficiently characterized, appropriately managed and adequately reflected in the fluticasone furoate nasal spray EU SmPC (Section 4.8).

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. Thus, the risk of nasal events (including: epistaxis, nasal ulceration, nasal septum perforation and other nasal events) is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important identified risk: Hypersensitivity

The risk of hypersensitivity is considered sufficiently characterized, appropriately managed and adequately reflected in the fluticasone furoate nasal spray EU SmPC (Section 4.3 and 4.8).

As part of the signal assessment performed in 2008 a review of data from multiple sources, including clinical trials, published literature and spontaneous adverse event reports led to the update of the EU PI to include hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria as an adverse reactions. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this identified risk different from the safety profile characterized thus far.

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. Thus, the risk of hypersensitivity is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important identified risk: Cataracts and glaucoma

Following the assessment of the EU PSUR (27 April 2012 to 26 April 2015) and the EU RMP v10 (PSUSA/00009154/201504) risk of cataracts and glaucoma was reclassified from important potential to important identified risk in the EU RMP v11 approved 23 June 2016.

Ocular effects were specifically evaluated with intranasal fluticasone furoate in a 2-year ocular safety study (201077) and there were no adverse event reports of cataract or glaucoma. Events of cataract, glaucoma/ raised IOP were reviewed through ongoing routine pharmacovigilance. Also, targeted follow-up questionnaires to obtain further information on relevant reports were introduced. No new information on cataract and glaucoma/ raised IOP was identified from targeted follow-up questionnaires.

The risk associated with cataract, glaucoma or raised IOP is adequately reflected in the EU SmPC (sections: 4.4, 4.8 and 5.1) for fluticasone furoate nasal spray.

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. Thus, the risk of ocular effects: cataract, glaucoma and raised IOP is proposed to be removed from EU RMP. Targeted follow-up questionnaires for cataract and glaucoma/ raised IOP are considered no longer required. GSK will continue to monitor these events via routine pharmacovigilance activities.

Important potential risk: Taste and smell disorders

Reviews of anosmia events were carried out in 2008 and 2009 upon the request of EMA in the PSURs. In October 2010, a signal assessment was performed of all the data on smell and taste disorders as a follow-up to the earlier reviews. All of those assessments concluded that there was no evidence of a causal relationship of taste and smell disorders and fluticasone furoate nasal spray. In May 2023, a re-evaluation of all data was conducted for fluticasone furoate nasal spray relative to its potential risk of taste and smell disorders. As a result of a cumulative review of clinical trials, published literature and spontaneous adverse event reports it was concluded that there is insufficient evidence to establish that events related to taste and smell disorders are reasonably causally associated with administration of fluticasone furoate nasal spray. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this potential risk different from the safety profile characterized thus far.

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. More than 16 years of post-marketing experience has not generated a change in the assessment to elevate the risk to an identified risk. Thus, the risk of taste and smell disorders is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important potential risk: Pyrexia

Pyrexia as an adverse event of special interest was first introduced to the EU RMP in 2007. A further evaluation of the pyrexia noted in children in the integrated pediatric data was requested during the MAA in the Day 120 List of Questions in 2009. However, that review did not highlight any serious safety concerns associated with the event of pyrexia and with the limited data available causality could not be assigned. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this potential risk different from the safety profile characterized thus far.

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. More than 16 years of post-marketing experience has not generated a change in the assessment to elevate the risk to an identified risk. Thus, the risk of pyrexia is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important potential risk: Systemic corticosteroid effect: adrenal suppression

The Phase 3 clinical program included 2 specific safety studies (adult/adolescent: FFR20002 and pediatric: FFR100012), as well as additional urine cortisol assessments in the long-term studies in both patient groups (FFR102123 and FFR30008). A pediatric safety study (FFR101782; Phase 3b), evaluated the effects of long term (1-year) course of fluticasone furoate nasal spray 110 mcg once daily on growth in pediatric participants with perennial allergic rhinitis and it also included 24-hour urine cortisol assessments. There were no events associated with HPA axis suppression from the clinical trial program. Events of adrenal suppression were reviewed through ongoing routine pharmacovigilance. Also, targeted follow-up questionnaires to obtain further information on relevant reports were introduced. No new information on adrenal suppression/acute adrenal insufficiency was identified from targeted follow-up questionnaires.

The risk of systemic corticosteroid effect: adrenal suppression is adequately reflected in the fluticasone furoate nasal spray EU SmPC (Sections: 4.4 and 5.1). The EU SmPC states that fluticasone furoate 110 mcg once daily was not associated with HPA axis suppression in adult, adolescent or pediatric subjects. However, the dose of fluticasone furoate nasal spray should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained.

There are no further additional pharmacovigilance activities to investigate or further characterize the risk and no additional risk minimization measures in place. More than 16 years of post-marketing experience has not generated a change in the assessment to elevate the risk to an identified risk. Thus, the risk of corticosteroid effect: adrenal suppression is proposed to be removed from EU RMP. Targeted follow-up questionnaires for adrenal suppression/acute adrenal insufficiency are considered no longer required. GSK will continue to monitor effects on HPA axis via routine pharmacovigilance activities.

Important potential risk: Systemic corticosteroid effect: growth retardation

The results of the 1-year growth study (FFR101782) identified an effect on growth in children (treatment difference to placebo -0.27cm/year [95% CI: -0.48 to -0.06]) treated with fluticasone furoate in dose of 110 mcg once daily.

The risk of systemic corticosteroid effect: growth retardation is adequately reflected in the EU SmPC (sections: 4.4, 4.8 and 5.1) for fluticasone furoate nasal spray. The treatment periods with fluticasone furoate nasal spray should be maintained on the lowest possible efficacious dose and is recommended that the growth of children receiving prolonged treatment with nasal corticosteroids is regularly monitored.

There are no additional pharmacovigilance activities to investigate or further characterize the risk and no additional risk minimization measures in place. Thus, the risk of corticosteroid effect: growth retardation is proposed to be removed from EU RMP. GSK will continue to monitor events of growth retardation via routine pharmacovigilance activities.

Important potential risk: Psychiatric effects

In November 2010, the PhVWP published a review of the risk of systemic adverse reactions associated with inhaled and intranasal corticosteroids. The review concluded that given the reported cases, coupled with biological plausibility and the knowledge on adverse psychiatric and behavioural reactions to corticosteroids administered systemically (i.e. orally or by injection) – harmonised key elements should be added to the existing SmPC's and PLs across all corticosteroids for each formulation. GSK has performed a review of its worldwide safety database and published literature for the psychiatric and behavioural effects and has adopted the proposed wording to the EU SmPC for fluticasone furoate nasal spray. Since then, ongoing review of the risk via routine pharmacovigilance has not identified any new information on this potential risk different from the safety profile characterised thus far.

The risk of psychiatric effects is considered sufficiently characterized, appropriately managed and adequately reflected in the fluticasone furoate nasal spray EU SmPC (Section 4.4). The EU SmPC states that systemic effects of nasal corticosteroid may occur, particularly at high doses prescribed for prolonged periods. The risk of systemic corticosteroid effects at recommended doses of fluticasone furoate nasal spray is considered to be low.

There are no additional pharmacovigilance activities to investigate or further characterize this risk and no additional risk minimization measures are in place. More than 16 years of post-marketing experience has not generated a change in the assessment to elevate the risk to an identified risk. Thus, the risk of psychiatric effects is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Missing information

In accordance with GVP module V, revision 2, missing information refers to gaps in the knowledge about safety of fluticasone furoate nasal spray for use in a specific population in the approved indication where insufficient exposure to determine whether the safety profile differs from that characterized so far. However, the absence of data itself does not automatically constitute a safety concern. No additional pharmacovigilance activities nor additional minimization measures are planned to collect information on Use in pregnancy and lactation, and Off-label use (sinusitis and children < 6 years of age), hence this missing information is proposed for removal from the list of safety concerns. A change in benefit risk profile in this specific population is not expected.

Further justification for removal of each missing information is provided below.

Missing information: Use in pregnancy and lactation

The safety profile is not expected to be different in this patient population. Ongoing review of the missing information via routine pharmacovigilance has not identified any safety issues from the reported cases related to use in pregnancy and lactation. Absence of adequate data concerning the use in pregnant women or excretion of intranasal formulation of fluticasone furoate into human breast milk is addressed in the relevant section of the EU SmPC (section 4.6) of the fluticasone furoate nasal spray. The EU SmPC states that

fluticasone furoate should be used in pregnancy only if the benefits to the mother outweigh the potential risks to the foetus or child, while administration of fluticasone furoate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Use in pregnancy and lactation is proposed to be removed from the list of safety concerns as there are no additional pharmacovigilance activities planned to collect information on pregnant or lactating women. GSK will continue to monitor the use of fluticasone furoate nasal spray in aforementioned populations via routine pharmacovigilance activities.

Missing information: Off-label use (sinusitis and children < 6 years of age)

Off-label use in sinusitis

Possible off-label uses may include use in conditions with symptoms similar to those seen with allergic rhinitis, such as sinusitis. Off –label use has been analysed in each PSURs/PBRERs and the review of the AE's associated with the use of fluticasone furoate nasal spray for the indication of sinusitis did not highlight any significant safety issues.
Based on a 2-week treatment study evaluating the safety and efficacy of fluticasone furoate nasal spray 110 mcg, administered either once daily or twice daily, compared with placebo, as effective monotherapy in the treatment of uncomplicated ARS in adult and adolescent subjects 12 years of age and older (FFS113203) conducted in 2010, the safety profile of fluticasone furoate nasal spray in uncomplicated ARS was similar to that in allergic rhinitis.

Off-label use in children <6 years of age

Safety and efficacy studies were performed in a total of 271 patients from 2 to 5 years of age in both seasonal and perennial allergic rhinitis, of whom 176 were exposed to fluticasone furoate. As addressed in section 4.2 and 5.1 of the EU SmPC, safety and efficacy of fluticasone furoate nasal spray in children under the age of 6 years have not been well established. Fluticasone furoate nasal spray is approved in the EU for children six years and older, however in some other EU markets including the US (Flonase Sensimist Allergy Relief) and Japan, it is approved for use in children aged 2 years and older. Therefore, it is likely that under-age off-label use in the EU might be influenced by medical practice in other countries. Ongoing review of the off-label use via routine pharmacovigilance has not identified any safety issues from the reported cases related to use in children under the age of 6 years.

The off-label use (sinusitis and children < 6 years of age) is proposed to be removed from the list of safety concerns as there are no additional pharmacovigilance activities planned to collect information on off-label use. Off-label use only meets the criteria for inclusion as a missing information if there is a scientific rationale to suggest the expected usage in the off-label population may have a different safety profile. GSK will continue to monitor the off-label use via routine pharmacovigilance activities.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified/potential risks associated with fluticasone furoate nasal spray.

SVII.3.2 Presentation of the missing information

There is no missing information associated with fluticasone furoate nasal spray.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 8 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine PV activities beyond adverse reaction reporting and signal detection activities are required.

III.2 Additional pharmacovigilance activities

Not required.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going or planned additional pharmacovigilance activities for fluticasone furoate nasal spray.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES.

There is no post-authorization efficacy study required for this product.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimization Plan

No risk minimization measures beyond standard routine measures are needed.

V.1. Routine Risk Minimization Measures

Not applicable.

V.2. Additional Risk Minimization Measures

Not applicable.

V.3 Summary of risk minimization measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Avamys (fluticasone furoate nasal spray)

This is a summary of the risk management plan (RMP) for Avamys. The RMP details important risks of Avamys, how these risks can be minimized, and how more information will be obtained about Avamys' risks and uncertainties (missing information).

Avamys' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Avamys should be used.

This summary of the RMP for Avamys should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Avamys' RMP.

I. The medicine and what it is used for

Avamys is authorized for the treatment of the symptoms of allergic rhinitis in adults, adolescents and children (6 years and over). (see SmPC for the full indication). It contains fluticasone furoate as the active substance and it is given by nasal spray, suspension.

Further information about the evaluation of Avamys' benefits can be found in Avamys' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/avamys

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Avamys, together with measures to minimize such risks and the proposed studies for learning more about Avamys' risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Avamys are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Avamys. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not Applicable

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Avamys.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Avamys.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAM

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.