GlaxoSmithKline AG

Swiss Summary of the Risk Management Plan (RMP) for Relvar Ellipta (Fluticasone furoate/Vilanterol)

RMP Summary:	Version 1, April 2023
EU RMP:	Version 11.2, 1.12.2021

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Relvar Ellipta is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Relvar Ellipta in Switzerland is the „Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

GlaxoSmithKline AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP for Relvar Ellipta.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

VI.1 Summary of risk management plan for RELVAR ELLIPTA (fluticasone furoate/vilanterol)

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

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

This summary of the RMP for RELVAR ELLIPTA 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 RELVAR ELLIPTA's RMP.

I The medicine and what it is used for

RELVAR ELLIPTA is authorised for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinalproduct (long-acting beta-2-agonist and inhaled corticosteroid) is appropriate (i.e. patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta-2-agonist) and patients already adequately controlled on both inhaled corticosteroid and long-acting beta-2-agonist. RELVAR ELLIPTA is indicated for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy (see SmPC for the full indication). It contains fluticasone furoate/ vilanterol as the active substance and it is given by inhalation. For Asthma: FF/VI 100/25mcg (delivered dose 92/22mcg), FF/VI 200/25mcg (delivered dose 184/22mcg) once daily and for COPD: FF/VI 100/25mcg (delivered dose 92/22mcg) once daily.

Further information about the evaluation of RELVAR ELLIPTA’s benefits can be found in RELVAR ELLIPTA’s 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/relvar-ellipta.

II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of RELVAR ELLIPTA together with measures to minimise such risks and the proposed studies for learning more about RELVAR ELLIPTA's risks, are outlined below.

Measures to minimise 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 authorised 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 minimise its risks.

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

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

If important information that may affect the safe use of RELVAR ELLIPTA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of RELVAR ELLIPTA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 RELVAR ELLIPTA. 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	Pneumonia in patients with COPD and asthma
Important potential risks	Serious cardiovascular events
	Corticosteroid-associated eye disorders
Missing information	Safety in pregnancy and lactation

II.B Summary of important risks

Important Identified Risk: Pneumonia in patients with COPD and asthma	
Evidence for linking the risk to the medicine	In two replicate 12 month studies (HZC102871 and HZC102970) in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the fluticasone furoate (at strengths of 50, 100, and 200 micrograms)/vilanterol 25 micrograms combination than in those receiving vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving fluticasone furoate/vilanterol (all strengths) and in <1% of patients receiving vilanterol. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with fluticasone furoate/vilanterol 200/25 micrograms,

	one during treatment with fluticasone furoate/vilanterol 100/25 micrograms and one post-treatment with vilanterol monotherapy. Risk factors for pneumonia observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with an FEV_1<50% predicted. There was no significant evidence in SLS-COPD of any difference in pneumonia risk between FF/VI and usual care which included FP/salmeterol and other ICS/LABAs. The data in SLS-COPD are consistent with the PRAC review (EMA: EMA/H/A-31/1415, 2016), which did not find any conclusive evidence of differences in pneumonia risk for different inhaled corticosteroid medicines in the treatment of COPD. In SUMMIT, when FF/VI was compared with placebo, there was no meaningful difference in the incidence of pneumonia. Recent evidence suggests that asthma is an independent risk factor for pneumonia. In asthma, an integrated analysis of all FF/VI clinical studies regardless of duration and patient population showed that the incidence of pneumonia was low (<1%) in all treatment groups (ISS V2 Doc Ref 2013N187157). The calculated incidence of pneumonia (adjusted for exposure) for FF/VI 100/25 mcg of 8.5/1000 subject years was similar to placebo (9.3/1000 subject years). This is in line with literature evidence of the incidence of pneumonia reported in the general population. A slightly higher incidence in the FF/VI 200/25 mcg arm was observed (18.3/ 1000 subject years). For both pneumonia and serious pneumonia incidences calculated, confidence intervals were wide and overlapped across all treatment groups including placebo. In SLS-Asthma, when analysed by current treatment, the incidence of Pneumonia was similar between FF/VI and other asthma maintenance therapy (usual care).
Risk factors and risk groups	A detailed analysis of potential risk factors demonstrates increased hazard ratios with FF/VI compared with VI for BMI<25 kg/m^2, current smoker, history of pneumonia at screening and FEV_1<50% predicted). A BMI≤21 kg/m^2, also shows a strong relationship with event of pneumonia. Both lower BMI and low FEV_1 are known risks for pneumonia and worse outcomes with pneumonia.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8, PIL section 2, 4 (see Approved Product Information). Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important Potential Risk: Serious cardiovascular events

Evidence for linking the risk to the medicine	Cardiovascular events occurred at a similar incidence to placebo (in controlled studies). In SUMMIT (HZC113782), the risk of an on-treatment CV composite event was similar among all treatment groups. These data support the lack of a significant effect of FF/VI on all-cause mortality, which is primarily driven by CV mortality. In this population with history and/or risk of CV disease, subjects treated with VI (as VI alone or FF/VI) did not report a higher incidence or exposure-adjusted rate of cardiovascular events (assessed by all terms in MedDRA SMQs of hypertension, cardiac arrhythmia, cardiac failure, ischemic heart disease, and central nervous system haemorrhages and cerebrovascular conditions). In asthma, there were very few adverse events within the cardiac system disorder class.
Risk factors and risk groups	Older age, a history of previous cardiac disease and worse lung function were predictive of increased risk of cardiovascular events in the COPD population.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, PIL section 2, 3, 4 (see Approved Product Information). Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Important Potential Risk: Corticosteroid-associated eye disorders	
Evidence for linking the risk to the medicine	This is considered a class risk for ICS-containing products. There were few ocular associated adverse events reported during clinical studies. In the COPD placebo controlled lung function studies these were few events, and these were distributed across the treatment arms, including placebo. In the COPD one year exacerbation studies, the incidence of events was similar across treatment arms, and there was no clear difference between events on arms containing FF, than in the VI monotherapy treatment arm. These events are likely to represent the background rate in this population. In the SUMMIT study, the incidence of corticosteroid associated eye disorders was similar across treatment arms including placebo. The proportion of subjects experiencing at least one ADR/ one serious AE of special interest of corticosteroid associated eye disorders was similar between the two treatment arms. There were few ocular associated adverse events reported during the Asthma studies. In the one year safety study (HZA106839) Ophthalmic examinations, including Lens Opacities Classification System, Version III (LOCS III) lens grades, intraocular pressure (IOP), horizontal cup-to-disc ratio, and visual acuity using Logarithm of

	the Minimum Angle of Resolution (LogMAR), were performed at Screening, Week 28 and Week 52. Of these ophthalmic measures, the posterior subcapsular opacity (P) lens grade is considered to be the most relevant assessment of drug-related cataract formation. The results of this study showed that FF/VI 100/25 and FF/VI 200/25 had no apparent ophthalmic effects, including lens opacification and IOP.
Risk factors and risk groups	As a clear association with glaucoma and cataract has not been demonstrated with inhaled corticosteroids, it is not possible to determine any specific risk factors. It can be assumed that those patients with a predisposition for glaucoma or cataract may be more at risk from any additional influences.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, PIL section 2, 4 (see Approved Product Information). Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Safety in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and PIL section 2 (see Approved Product Information). Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.I Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of RELVAR ELLIPTA.

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

There are no studies required for RELVAR ELLIPTA.