GlaxoSmithKline AG

Swiss Summary of the Risk Management Plan (RMP) for PRIORIX-TETRA (live attenuated measles virus (Schwarz strain), live attenuated mumps virus (RIT 4385 strain), live attenuated rubella virus (Wistar RA 27/3 strain) and live attenuated varicella virus (OKA strain))

RMP Summary:	Version 1, December 2019
EU RMP:	Version 7.0, 9 Jan 2019

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 Priorix-Tetra 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 Priorix-Tetra 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 published summary RMP of Priorix-Tetra.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Priorix-Tetra

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

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

I. The medicine and what it is used for

Priorix-Tetra is authorised for active immunisation of individuals from the age of 11 months against measles, mumps, rubella and varicella. (see SmPC for the full indication). It contains live attenuated of measles, mumps, rubella and varicella viruses as the active substance and it is given by subcutaneous route in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

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

Important risks of Priorix-Tetra, together with measures to minimise such risks and the proposed studies for learning more about Priorix-Tetra '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, 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 Priorix-Tetra are risks that need special risk management activities to further investigate or minimise 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 Priorix-Tetra. 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	Higher incidence of febrile convulsions following vaccination with Priorix-Tetra as a first dose as compared to vaccination with separate injection of MMR and V vaccine
Important potential risks	- Higher incidence of thrombocytopenia following vaccination with Priorix-Tetra as compared to vaccination with MMR or MMR+V - Shift in the age at varicella infection towards older age groups (unvaccinated cohorts) and as a result, a potential increase in the incidence of varicella in adolescents and adults (as compared to pre- vaccination levels) - Temporary increase in herpes zoster incidence in the population. - Disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.
Missing information	-Long-term effectiveness -Use in pregnant women -Use in lactating mothers

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

The risk of having seizure when fever occurs is higher following vaccination with Priorix-Tetra than after separate administration of Priorix and Varilrix

Evidence for linking the risk to the medicine	The higher risk of febrile convulsion post MMRV vaccine compared with separate administration of MMR and varicella vaccines has been demonstrated in the below studies: • Study EPI-MMRV-001 VS DE SUPP (e-track number -113729): Post-authorisation safety study to measure the risk of febrile convulsions after vaccination with MMRV vaccine when compared to vaccination with MMR alone or MMR given separately with varicella vaccine during the same visit. • Study EPI-MMRV-006 VS DE SUPP (e-track number 200335): Risk of febrile convulsions after a second immunisation against measles, mumps and rubella with MMRV as compared to MMR or MMR+V.
Risk factors and risk groups	Most febrile seizures occur between 3 months and 6 years of age [Bonhoeffer, 2004] with a peak incidence at 18 months of age [Waruiru, 2004]. Approximately 6-15% of the febrile seizures occur after 4 years of age, with occurrence after the age of 6 years being unusual [Waruiru, 2004]. Personal and/or family history of convulsion in siblings and parents are known risk factors. The risk period after MMRV vaccination ranges from 5 to 12 days post vaccination with dose 1.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 with cross-reference to section 4.8 and 5.1.

Higher incidence of thrombocytopenia following vaccination with Priorix-Tetra as compared to vaccination with MMR or MMR+V	
Evidence for linking the risk to the medicine	The benefit-risk analysis performed in 2012 considered two aspects: the additional number of hospitalisation for febrile convulsion vs the number of hospitalisation for varicella complications when moving from MMR + V scheme to MMRV scheme and parents' perception on severity and importance for each benefit and risk. Indeed, following a preliminary analysis done at the same time, the impact of possible increase of ITP on benefit risk was suggested to be neutral. The results of that analysis suggested that the potential increase of the number of ITP cases due to MMRV vaccination could be similar to the number of ITP cases averted due to the expected increase in the rate of vaccination for varicella. However, if the number of hospitalisation for ITP post MMRV vaccine is higher than the number of ITP cases averted due to the expected increase in the rate of vaccination for varicella, this parameter will have to be considered for the estimation of the quantitative benefit risk.
Risk factors and risk groups	Patient with history of thrombocytopenia after the first dose may develop worsening or recurrence of thrombocytopenia after a second dose. In such cases, the risk-benefit of immunising with Priorix-Tetra should be carefully evaluated.

Risk minimisation measures	No risk minimisation measures
Shift in the age at varicella infection towards older age groups (unvaccinated cohorts) and as a result, a potential increase in the incidence of varicella in adolescents and adults (as compared to pre-vaccinationlevels)	
Evidence for linking the risk to the medicine	Chickenpox is usually a relatively mild disease in healthy children, but the disease may be life threatening in some children, and in immunosuppressed patients, neonates, and healthy adults (e.g. due to multi-organ failure), and in smokers for whom the risk of varicella pneumonia is high. So, if the mathematical model is confirmed, the average age of infection will increase and the risk of complications from varicella disease will also increase.
Risk factors and risk groups	None
Risk minimisation measures	No risk minimisation measures
Temporary increase in herpes zoster incidence in the population.	
Evidence for linking the risk to the medicine	This is a theoretical assumption based on a mathematical model.
Risk factors and risk groups	None
Risk minimisation measures	No risk minimisation measures
Disseminated varicella with internal organ involvement following vaccination with Oka varicella vaccine strain mainly in immunocompromised subjects.	
Evidence for linking the risk to the medicine	It has been observed in rare occasions that the live attenuated varicella vaccine can disseminate into the body and cause severe complications in healthy individuals [Iwasaki, 2016] or in immunocompromised individuals [Costa, 2016]. People with undiagnosed immunosuppressive conditions (e.g. HIV infection) are at potential risk of severe complications [Maves etal, 2014 , Navalkele et al, 2017] caused by vaccine-strain-induced disseminated varicella
Risk factors and risk groups	The population at risk is individuals with impaired immune function and unrecognized immunosuppression (e.g. undiagnosed HIV infection).
Risk minimisation measures	Routine risk communication: SmPC section 4.4.

Long term effectiveness	
Risk minimisation measures	No risk minimisation measures

Use in pregnant women	
Risk minimisation measures	SmPC Section 4.3 and section 4.6
Use in lactating mothers	
Risk minimisation measures	SmPC Section 4.6

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Priorix-Tetra.

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

There are no studies required for Priorix-Tetra.