GlaxoSmithKline AG

Swiss Summary of the Risk Management Plan (RMP) for

BEXSERO (Meningococcal group B Vaccine (rDNA, component, adsorbed))

RMP Summary: Version 1, September 2020
EU RMP: Version 7.2, 22 November 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 Bexsero 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 Bexsero 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 Bexsero.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for *Bexsero* (Meningococcal group B vaccine, (rDNA, component, adsorbed)

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

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

This summary of the RMP for *Bexsero* 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 *Bexsero*'s RMP.

I. The medicine and what it is used for

Bexsero is authorised for invasive disease caused by *N. meningitidis* group B (see SmPC for the full indication). It contains three *N. meningitidis* recombinant proteins: NHBA (rp287-953), NadA (rp961c) and fHbp (rp936-741), formulated with OMV from *N. meningitidis* serogroup B strain NZ98/254, containing PorA P1.4 as the active substances and it is given by deep intramuscular injection.
Further information about the evaluation of *Bexsero*'s benefits can be found in *Bexsero*'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: 'Internet site'ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002333/human_med_001614.jsp&mid=WC0b01ac058001d124'.

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

Important risks of *Bexsero*, together with measures to minimise such risks and the proposed studies for learning more about Bexsero'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 *Bexsero* is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Bexsero* 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 *Bexsero*. 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	Guillain-Barré Syndrome (GBS) Acute Disseminated Encephalomyelitis (ADEM) Anaphylaxis including Anaphylactic shock Vasculitis/Kawasaki syndrome Seizures including Febrile Seizures Arthritis
Missing information	Vaccine Effectiveness Vaccination Failure (lack of efficacy) Strain/Serotype replacement data Elderly subjects Immuno-compromised subjects Safety during pregnancy or lactation

II.B Summary of important risks

Important potential risk: Guillain-Barré Syndrome (GBS)	
Evidence for linking the risk to the medicine	Patients vaccinated with *Bexsero* are not known to be at increased risk of this event as a result of vaccination. Rather, this event is considered a potential risk with *Bexsero* because it has been observed with other vaccines, such as rabies vaccines and a quadrivalent meningococcal vaccine.
Risk factors and risk groups	Children and adults of all ages and both sexes. There is some evidence to suggest an increased occurrence with advancing age, though this is not established.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Post-authorization safety study in the UK (V72_36OB)

Important Potential Risk: Acute Disseminated Encephalomyelitis (ADEM)	
Evidence for linking the risk to the medicine	Patients vaccinated with *Bexsero* are not known to be at increased risk of this event as a result of vaccination. Rather, this event is considered a potential risk with *Bexsero* because it has been observed with other vaccines, such as smallpox or rabies vaccine.
Risk factors and risk groups	• Children younger than 10 years of age. The occurrence in adulthood is unclear but less frequent than in childhood. • Past viral or bacterial infection.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Post-authorization safety study in the UK (V72_36OB)

Important Potential Risk: Anaphylaxis including Anaphylactic shock	
Evidence for linking the risk to the medicine	Anaphylaxis following vaccination is a serious, but rare event.
Risk factors and risk groups	1. Previous anaphylaxis 2. History of allergies or asthma
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.3 (PL section 2) • SmPC section 4.8 (PL section 4); • SmPC section 4.4 where recommendation is given to healthcare professionals to have appropriate medical treatment readily available Additional risk minimisation measures: None

Additional pharmacovigilance activities	Post-authorization safety study in the UK (V72_36OB)

Important Potential Risk: Vasculitis/Kawasaki syndrome	
Evidence for linking the risk to the medicine	Patients vaccinated with *Bexsero* are not known to be at increased risk of this event as a result of vaccination. This event is considered a potential risk with *Bexsero* because a few subjects participating to the clinical trials reported this event after *Bexsero*. The few cases that occurred in the *Bexsero* studies do not allow a definitive conclusion whether *Bexsero* could eventually cause Kawasaki syndrome.
Risk factors and risk groups	The cause of this event is unknown and there is no diagnostic test. Infections may trigger this event in genetically susceptible individuals.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 (PL section 4) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-authorization safety study in the UK (V72_36OB)

Important Potential Risk: Seizures including Febrile Seizures	
Evidence for linking the risk to the medicine	Fever is a common occurrence after vaccination. Febrile seizures are associated with any condition that results in fever, including vaccination, but most commonly occur with the fevers caused by typical childhood illnesses (e.g., acute otitis media, viral upper respiratory tract infections and roseola).
Risk factors and risk groups	The condition of a child being less developed mentally or physically than is normal for its age; discharge from a neonatal unit after 28 days; day care attendance; viral infections; a family history of febrile seizures; certain vaccinations; and possibly iron and zinc deficiencies.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 (PL section 4) Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-authorization safety study in the UK (V72_36OB)

Important Potential Risk: Arthritis	
Evidence for linking the risk to the medicine	Patients vaccinated with *Bexsero* are not known to be at increased risk of this event as a result of vaccination. Rather, this event is

	considered a potential risk with *Bexsero* because it has been observed after *Bexsero* but it is unknown if *Bexsero* is the cause.
Risk factors and risk groups	Advancing age; gender (more common in women); genetic (specific genes are associated with a higher risk of certain types of arthritis, such as rheumatoid arthritis, systemic lupus erythematous, and ankylosing spondylitis); family history or past history of arthritis; overweight and obesity; joint injuries and joint prosthesis; infections; smoking, intravenous drug abuse, alcoholism, diabetes; exposure to silica dust; dietary intake of vitamin D, antioxidants, fish, protein, and iron.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	None

Missing information: Vaccine Effectiveness	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Post-authorization effectiveness study in the UK (V72_38OB)

Missing information: Vaccination Failure (lack of efficacy)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 (PL section 2) warning that there are no data on the use of *Bexsero* in adults above 50 years of age; that the effectiveness of *Bexsero* is reduced in subjects with weakened immunity and that *Bexsero* may not fully protect all vaccines Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-authorization effectiveness study in the UK (V72_38OB)

Missing information: Strain/Serotype replacement data	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Post-authorization effectiveness study in the UK (V72_38OB)

Missing information: Elderly subjects	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 (PL section 2) with the warning that there are no data on the use of *Bexsero* in adults above 50 years of age

	Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Immuno-compromised subjects	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 (PL section 2) warning that it is possible that the effectiveness of *Bexsero* is reduced in subjects with weakened immunity Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Missing information: Safety during pregnancy or lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 warning that insufficient or no data are available on the use of *Bexsero* in pregnant or breast feeding women respectively Additional risk minimisation measures: None
Additional pharmacovigilance activities	Pregnancy registry (V72_82OB)

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 Bexsero.

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

Study/Activity (including study number)	**Objectives**	**Safety concerns/efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final study results**
V72_36OB – Post-licensure observational safety study after	To assess the safety of the *Bexsero* vaccine within the UK	Guillain-Barré Syndrome (GBS)	Ongoing	Progress reports are submitted to EMA every 6 months with the first

meningococcal B vaccine 4CMenB (*Bexsero*) vaccination in routine UK care (descriptive and a self-controlled-case-series analysis)	National Immunisation Programme (NIP).	Acute Disseminated Encephalomyelitis (ADEM) Anaphylaxis including Anaphylactic shock Vasculitis/Kawasaki syndrome Seizures including Febrile Seizures		being submitted by 31 May 2016. The final report will be submitted by 31 December 2020.
V72_38OB – Post-licensure observational effectiveness study of meningococcal B vaccine 4CMenB (*Bexsero*) vaccination in the UK NIP (descriptive and screening method)	To assess the impact on invasive meningococcal disease (all capsular groups) and effectiveness of *Bexsero* vaccination against MenB and vaccine-type disease, after introduction of *Bexsero* in the UK NIP.	Vaccine Effectiveness Vaccination Failure (lack of efficacy) Strain/Serotype replacement data	Ongoing	Interim reports are submitted to EMA every 6 months with the first being submitted by 31 May 2016. The final report will be submitted by 30 June 2020.
V72_82OB – *Bexsero* pregnancy registry: an observational study of the safety of *Bexsero* exposure in pregnant women and their offspring in the US	To evaluate the pregnancy outcomes among women immunised with the *Bexsero* vaccine.	Safety during pregnancy or lactation	Ongoing	Annual interim reports in line with periodic safety update regulatory reports. The final report will be submitted by 31 May 2020.