PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Boostrix

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

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

I. The medicine and what it is used for

Boostrix is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards. It is a diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) and it is given by deep intramuscular injection preferably in the deltoid region.

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

Important risks of *Boostrix*, together with measures to minimise such risks and the proposed studies for learning more about *Boostrix'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*.

If important information that may affect the safe use of *Boostrix* is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of *Boostrix* 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 *Boostrix*. 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	Blunting (Immune interference)
Missing information	Tdap use in pregnant women Tdap waning of immunity

II.B Summary of important risks

Important potential risk: Blunting (Immune interference)	
Evidence for linking the risk to the medicine	A potential concern raised was whether antibodies elicited by dTpa vaccination during pregnancy and transferred to the foetus could interfere with the immune response to the paediatric vaccines an outcome referred to as "blunting". This effect was previously described in infants from pregnant women with high antibody titers following whole cell pertussis vaccination. There is scientific evidence showing that high concentrations of maternally acquired antibodies (from pre-pregnancy vaccination or natural infection) interfere with the infant's immune response to vaccination. Nowadays, in the context of dTpa maternal recommendation, higher levels of diphtheria, tetanus and pertussis antibodies (and poliovirus antibodies in case of dTpa-IPV vaccine) were shown to be transferred to the new-born during pregnancy resulting potentially in higher impact on infant vaccination series, as compared with no dTpa /dTpa-IPV vaccination during pregnancy (Maertens K, 2016a; Maertens K, 2016b; Maertens K, 2017). However currently the clinical significance of blunting is unknown and more scientific evidence is still required from large clinical studies to assess the extent and clinical relevance of blunting on infant vaccination series. The mechanisms behind this phenomenon, as well as the factors that trigger it, are not yet fully understood.
Risk factors and risk groups	As pertussis has a higher mortality and morbidity among children less than one year that have not yet received all childhood vaccination series, this subpopulation would be considered at higher risk.

Risk minimisation measures	**Routine risk minimisation measures:** To inform the prescriber about the limited clinical information regarding the use of *Boostrix* in pregnancy and its potential consequence in the offspring, the approved section 4.6 of the EU SmPC "Fertility, pregnancy and lactation" reads as follows: *"Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix during pregnancy. The clinical relevance of this observation is unknown. "* **Additional risk minimisation measures:** Not required at this moment
Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Plan to monitor scientific evidence on the effectiveness of pertussis maternal immunization to prevent the disease in infants and on the impact of maternal immunization programs on pertussis epidemiology. • **Additional pharmacovigilance activities:** <u>Ongoing</u> • DTPA (BOOSTRIX)-048 PRI (201330) • DTPA (BOOSTRIX)-049 BST: 048 (201334)

Missing information: Tdap use in pregnant women	
Evidence for linking the risk to the medicine	Limited data on the safety or immunogenicity of *Boostrix* during pregnancy or lactation are available. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating women and their child. In response to pertussis outbreaks, the US was the first country (in 2011) to recommend the use of Tdap in pregnant women who had not been previously vaccinated with Tdap in adulthood. This recommendation updated in 2013 states that women should receive a Tdap vaccination during each pregnancy, irrespective of the woman's prior history of vaccination with Tdap [CDC, 2013] as anti-pertussis antibody levels wane substantially during the first year after vaccination. Following the initial recommendation in the US by the Advisory Committee on Immunization Practices (ACIP) in 2011 [ACIP, 2012], Tdap immunization programs for pregnant women have been implemented in more than 34 countries worldwide. Until very recently, no published or unpublished clinical data on immunogenicity, efficacy, or effectiveness in pregnant women were available since pregnant women have been routinely excluded from clinical trials. However, there are no specific safety concerns or expectations of harm, and use in pregnancy is not contraindicated. But the use of Tdap in pregnancy is considered as missing information regarding the safety profile of Tdap in pregnant women and the effect of it on the foetus.
Risk factors and risk groups	Pregnant and lactating women and their offspring

Risk minimisation measures	**Routine risk minimisation measures:** To inform the prescriber about the current safety information regarding the use of Boostrix in pregnancy, the approved section 4.6 of the EU SmPC "Fertility, pregnancy and lactation" reads as follows: Pregnancy: *Safety data from a prospective observational study where Boostrix was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from passive surveillance where pregnant women were exposed to Boostrix or to Boostrix Polio (dTpa-IPV vaccine) in the 3rd and 2nd trimester have shown no vaccine related adverse effect on pregnancy or on the health of the foetus/newborn child.* *The use of Boostrix may be considered during the third trimester of pregnancy.* *Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available. However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix harms the foetus at any trimester of pregnancy. The benefits versus the risks of administering Boostrix during pregnancy should be carefully evaluated.* *Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development.* *Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix during pregnancy. The clinical relevance of this observation is unknown.* *Breastfeeding:* *The effect of administration of Boostrix during lactation has not been assessed. Nevertheless, as Boostrix contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering Boostrix to breastfeeding women should carefully be evaluated by the health-care providers.* Fertility: *No human data from prospective clinical studies are available. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility (see section 5.3 of SmPC).* **Additional risk minimisation measures:** Not required at this moment

Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Ongoing • DTPA (BOOSTRIX)-047 (116945) • DTPA (BOOSTRIX)-048 PRI (201330) • DTPA (BOOSTRIX)-049 BST: 048 (201334) • EPI-PERTUSSIS-028 VS US PR (201327) Completed: • EPI-PERTUSSIS-037 VS BR (203153) • EPI-PERTUSSIS-025 VS NZ SUPP (201024)

Missing information: Tdap waning of immunity	
Evidence for linking the risk to the medicine	Recently a resurgence of pertussis has been observed in various countries, including those considered to achieve a high coverage of Tdap and full antigen content-DTPa. This has included children less than one year of age, who are at highest risk of mortality and sequelae from pertussis. Whilst previously adolescents and adults rarely presented with pertussis, cases in this age group are also now increasingly being detected suggesting an epidemiological shift towards these older ages, especially in United States, Europe and Australia [ACIP, 2013; CDC, 2013]. Waning of immunity by acellular pertussis vaccines has been proposed as a potential explanatory factor for these outbreaks. Large observational studies have demonstrated that Tdap protection wanes within 2-4 years in adolescents [Acosta, 2015] and does not protect against outbreaks. Furthermore, conclusions from systematic reviews show that the short-term protective effect against WHO-defined pertussis in young children was lower for currently available acellular pertussis vaccines than whole cell pertussis vaccines [Fulton, 2016].
Risk factors and risk groups	The waning of immunity could lead to an increase of susceptible individuals and favor the occurrence of pertussis outbreaks, therefore increasing the burden of disease by both morbidity and mortality increase.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.4 'Special warnings and precautions for use' of the EU SmPC states: "As with any vaccine, a protective immune response may not be elicited in all vaccinees" Section 4.2 "posology" of the EU SmPC: "Repeat vaccination against diphtheria, tetanus and pertussis should be performed at intervals as per official recommendations (generally 10 years)". **Additional risk minimisation measures:** Not required at this moment

Additional pharmacovigilance activities	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow up questionnaire for vaccination failure / lack of efficacy in DTP vaccines **Additional pharmacovigilance activities:** None See section II.C of this summary for an overview of the post-authorisation development plan.