RISK MANAGEMENT PLAN - PART VI

PART VI - SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s) (INN or common name)	Diphtheria, Tetanus, Pertussis (acellular, component), Poliomyelitis (inactivated) vaccine (adsorbed) and *Haemophilus influenzae* type b conjugate (HIB (PRP/T) vaccine Referred to in this document as DTaP-IPV/Hib.
Product's concerned (Brand name(s))	PENTAXIM® / PENTAVAC®: Powder and suspension for injection.
Name of Marketing Authorization Holder or Applicant	Sanofi Pasteur 14 Espace Henry Vallée 69007 Lyon, France For EEA countries Sanofi Pasteur Europe 14 Espace Henry Vallée 69007 Lyon, France Phone: +33 4 3737 0100 Fax: +33 4 3737 7737
Data lock point (DLP) for this module	**13-NOV-2017**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 2.0**

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ABBREVIATIONS

DTaP-IPV/Hib	Diphtheria, Tetanus, acellular Pertussis, inactivated Poliomyeleitis vaccine -Hib (reconstituting Act-HIB)
DLP:	Data Lock Point
EPAR:	European Public Assessment Report
HHE	Hypotonic Hyporesponsive Episode
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
PBRER:	Periodic Benefit-Risk Evaluation Report

Summary of risk management plan for PENTAVAC®/ PENTAXIM® (DTaP-IPV/Hib)

DTaP-IPV/Hib vaccine summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how DTaP-IPV/Hib vaccine, should be used.

VI.1. THE MEDICINE AND WHAT IT IS USED FOR

DTaP-IPV/Hib vaccine contains Diphtheria, Tetanus, Pertussis (acellular, component), Poliomyelitis (Inactivated) and *Haemophilus influenzae* type b conjugate (HIB (PRP/T) vaccine (adsorbed).

DTaP-IPV/Hib vaccine, suspension for injection, is obtained by reconstitution (rehydration) of the powder of conjugate Hib vaccine (vial) with the suspension of combined diphtheria, tetanus, aP and IPV, adsorbed (prefilled syringe).

DTaP-IPV/Hib vaccine is authorized for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive infections caused by Hib (such as meningitis, septicemia, cellulitis, arthritis, epiglottitis, pneumopathy, and osteomyelitis) (see SmPC for the full indication).

DTaP-IPV/Hib vaccine is indicated in infants and children from 6 weeks of age through 24 months of age.

VI.2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of DTaP-IPV/Hib vaccine, together with measures to minimize such risks and the proposed studies for learning more about DTaP-IPV/Hib vaccine's risks, are outlined in the next sections.

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 medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

Information about adverse reactions is collected continuously and regularly analysed, including PBRER 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 DTaP-IPV/Hib vaccine is not yet available, it is listed under 'missing information' outlined in the next section.

VI.2.1. List of important risks and missing information

Any identified and potential risks of DTaP-IPV/Hib vaccine require investigation to assure product safety. Identified risks are concerns for which sufficient evidence of a link to the use of DTaP-IPV/Hib vaccine exists. Potential risks are concerns for which significant causal evidence has not been established. Missing information refers to topics for which there is no or limited data with which to determine causality.

Important identified risks*	Anaphylactic reactions/shock* Convulsions with or without fever* Hypotonic Hyporesponsive Episode (HHE)*
Important potential risks**	Guillain-Barré syndrome** Brachial neuritis** Encephalopathy/ Encephalitis**
Missing information	DTaP-IPV-Hib vaccine has not been studied in: • Age group: in infants < 6 weeks of age, and ≥ 24 months of age. • Special groups: Immunocompromised individuals, subjects with thrombocytopenia or bleeding disorders, chronic illness and history of severe prematurity. Populations with genetic polymorphism. Waning of protection with regard to the acellular pertussis component of the vaccine***

*Anaphylactic reaction (Sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing.); Convulsion (Fits / seizures sometimes associated with fever); HHE: Low responsiveness -low muscle tone episode;
** Guillain-Barré Syndrome (rapid-onset muscle weakness as a result of damage to the peripheral nervous system);); Brachial neuritis (decreased movement or sensation in the arm due to nerve problem); Encephalopathy/encephalitis: Diffuse disease of the brain that alters brain function or structure.
***The protection against disease induced by most vaccinations wanes over time.

VI.2.2. Summary of important risks

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

Table 1 –Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important identified risk: Anaphylactic reaction

Important identified risk – Anaphylactic reaction	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	Anaphylactic reaction following a previous immunization. Hereditary predisposition, history of atopy or allergy.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.3, 4.4 and 4.8 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 2 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important identified risk: Convulsion with or without fever

Important identified risk – Convulsion with or without fever	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	Previous history of convulsions or encephalopathy following administration of Pertussis-containing vaccine; uncontrolled epilepsy, progressive encephalopathy or any progressive, evolving, unstable neurologic condition. Typically benign and short-lived, especially when associated with fever. Febrile seizures form a particular subgroup of generalized convulsive seizures. Febrile convulsions occur in 2-4% of children between the ages 3 months and 5 years. Upper respiratory tract and otorhinolaryngologic viral infections were the most often implicated provoking factors, occurring in 69.5% of patients. Fever is a common adverse effect of vaccinations and a necessary cause of febrile seizures.
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.4 and 4.8 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 3 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important identified risk: Hypotonic-Hyporesponsive Episode (HHE)

Important identified risk – Hypotonic-Hyporesponsive Episode (HHE)*	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	HHE is characterized by sudden onset, in a child under 2 years of age, of reduced muscle tone, and hyporesponsiveness, and change of skin colour (pallor or cyanosis). Usually, with combination vaccine, HHE is more commonly observed after the primary immunization series and particularly after the first dose
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in sections 4.4 and 4.8 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 4 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important potential risk: Guillain-Barré Syndrome

Important identified risk – Guillain-Barré Syndrome	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	Preceding infection (especially respiratory or gastrointestinal) History of GBS within 6 weeks of a previous vaccine administration with the same antigens. Believed autoimmune disorder, with generation of autoimmune antibodies with cross-reactivity to epitopes on peripheral nerves and nerve roots. Possible association with tetanus-toxoid containing vaccines per USA IOM analysis; not confirmed in epidemiologic studies(1)
Risk minimization measures	**Routine risk minimization measures:** SmPC**:** Labelled in section 4.4 and 4.8 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 5 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important potential risk: Brachial neuritis

Important identified risk – Brachial neuritis	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	History of brachial neuritis within 6 weeks of a previous vaccine administration with the same antigens. Although brachial neuritis is mainly a disease of young adults, a few cases have been described in children. Most cases in children are sporadic, some are related to a hereditary disposition, and only a few cases have followed immunization for diphtheria, tetanus and pertussis (DTP). Brachial neuritis following tetanus toxoid immunization has been reported in adults. Other non-vaccine causes include infection and trauma.(1)(2)
Risk minimization measures	**Routine risk minimization measures:** SmPC**:** Labelled in section 4.4 and 4.8 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 6 - Important risks with corresponding risk minimization activities and additional pharmacovigilance activities if any: Important potential risk: Encephalopathy/ Encephalitis

Important identified risk –Encephalopathy/ Encephalitis	
Evidence for linking the risk to the medicine	DTaP-IPV/Hib vaccine postmarketing individual case safety reports and postmarketing surveillance (PBRER).
Risk factors and risk groups	Existing or potential neurological condition.
Risk minimization measures	**Routine risk minimization measures:** SmPC**:** Labelled in section 4.3 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 7 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Age groups: infants below 6 weeks of age and children above 2 years of age.

Missing information – Age groups: infants below 6 weeks of age and children above 2 years of age.	
Risk minimization measures	To date, infants below 6 weeks of age and children above 2 years of age ares event under close monitoring through routine Pharmacovigilance activities. **Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics.

Table 8 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Missing information: Special groups: subjects with immunodepression (immunodeficiency), thrombocytopenia or bleeding disorders, history of severe prematurity

Missing information – Special groups: subjects with immunodepression (immunodeficiency), thrombocytopenia or bleeding disorders, history of severe prematurity	
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labelled in section 4.4 **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics

Table 9 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Missing information: Special groups: subjects with chronic illness

Missing information – Special groups: subjects with chronic illnesses	
Risk minimization measures	To date, subjects with chronic illnesses are events under close monitoring through routine Pharmacovigilance activities. **Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics

Table 10 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Missing information: Special groups: Populations with genetic polymorphism

Missing information – Special groups: Populations with genetic polymorphism	
Risk minimization measures	To date, populations with genetic polymorphism are events under close monitoring through routine Pharmacovigilance activities. **Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics

Table 11 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any: Missing information: Waning of protection with regard to the acellular pertussis component of the vaccine.

Missing information – Waning of protection with regard to the acellular pertussis component of the vaccine.	
Risk minimization measures	To date, waning of protection is an event under monitoring through routine Pharmacovigilance activities. **Routine risk minimization measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

PBRER: Periodic Benefit-Risk Evaluation Report; SmPC: Summary of Product Characteristics

VI.2.3. Post-authorisation development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of DTaP-IPV/Hib vaccine.

VI.2.3.2. Other studies in post-authorisation development plan

There are no studies required for DTaP-IPV/Hib vaccine.

REFERENCES

1. Institute of Medicine. Adverse Effects of Vaccines: Evidence and Causality 2012 (available at https://www.nap.edu/download/13164 (accessed on 25 September 2018).

2. Hamati-Haddad A1, Fenichel GM.- Brachial neuritis following routine childhood immunization for diphtheria, tetanus, and pertussis (DTP): report of two cases and review of the literature- Pediatrics. 1997 Apr;99(4):602-3. Available at: http://pediatrics.aappublications.org/content/99/4/602.full.pdf+html (accesed on 25 September 2018)