VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

TdaP Vaccine SSI is a vaccine indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards.
Booster vaccines are vaccines that are administered to enhance the effect of primary vaccinations. Usually booster vaccines do not contain as much antigen as vaccines for primary use.

Tetanus

Tetanus is an acute disease characterised by muscular rigidity with agonising contractions. It is caused by the tetanus bacterium, *Clostridium tetani*. Onset of tetanus is gradual, occurring over 1-7 days, and progresses to severe generalised muscle spasms. In recent years, approximately 11% of reported tetanus cases have been fatal. Wherever immunization programs are in place, the largest proportion of cases occur in unimmunized individuals as protection against tetanus can only be obtained through vaccination (1).

Diphtheria

Diphtheria is a bacterial infection of the upper respiratory tract caused by *Corynebacterium diphtheriae*. Diphtheria is characterized by sore throat, low fever and an adherent membrane on the tonsils, pharynx, and/or nasal cavity. A milder form of diphtheria can be restricted to the skin. Less commonly diphtheria can affect the heart and result in neurological complications (3). Diphtheria is a contagious disease spread by direct physical contact or breathing the aerosolized secretions of infected individuals. Historically quite common, however, diphtheria has largely been eradicated in nations with widespread vaccination.

Pertussis

Whooping cough (pertussis) is an acute bacterial infection of the respiratory tract caused by *Bordetella pertussis*. It affects all age groups, but is most frequently recognised in children (5) and the disease is most severe in infants and young children, whereas infection in adolescents and adults is usually without symptoms, even though it can be serious (6). Pertussis infection among adolescents and adults is therefore primarily of concern because adolescents and adults with asymptomatic pertussis infection may spread the infection to infants at risk of severe complications of pertussis (5;10). The primary method of prevention against pertussis is vaccination, and the incidence of pertussis has decreased significantly since the introduction of pertussis vaccination. However, the protection conferred by vaccination is not life-long and revaccination is necessary.

VI.2.2 Summary of treatment benefits

A total of 3,600 subjects were included in the seven clinical trials included in the clinical development program for TdaP Vaccine SSI. Of these 2,918 received TdaP Vaccine SSI or a similar SSI vaccine. The main measure was the production of protective antibodies in the individuals. The studies showed that TdaP Vaccine SSI was as effective at producing protective levels of antibodies as separate vaccines containing the same active substances. Overall, between

99% and 100% of the individuals had protective antibodies against diphtheria and tetanus, and 92% to 97% had protective antibodies against pertussis one month after booster vaccination.

VI.2.3 Unknowns relating to treatment benefits

Persons > 55 years of age

There are no data for TdaP Vaccine SSI investigating booster vaccination of individuals > 55 years. Changes in the immune system occur with ageing whereby immunogenic effects of vaccination in these persons are can be influenced. It is generally accepted that administration of inactivated vaccines to these persons can be considered safe.

Pregnant or lactating women

There are no data for TdaP Vaccine SSI investigating booster vaccination of pregnant or breastfeeding women. It is generally accepted, that immunisation during pregnancy and lactation with vaccines containing inactivated toxins is not associated with any increased risks to the foetus or breastfed infants.

Immunocompromised individuals

There are no data for TdaP Vaccine SSI investigating booster vaccination of immunocompromised individuals. Vaccines may be less effective in immunocompromised persons. It is generally accepted that administration of inactivated vaccines to immunocompromised individuals can be considered safe.

Different ethnic origins

There is no reason to expect that TdaP Vaccine SSI should behave differently in different ethnic populations. Information on ethnicity of the subjects enrolled in the clinical trials is not available.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Vaccination of persons who have previously experienced undesirable effects produced by the immune system, including allergies, previously triggered by the product or any components hereof (contraindication) (Known hypersensitivity to the active substances, to any of the excipients or to formaldehyde that may be present as traces (contraindication))	Severe hypersensitivity reactions are always a risk when injecting a vaccine. Persons with known severe hypersensitivity to any components of the vaccine are at increased risk	Previous severe hypersensitivity/anaphylactic reaction after vaccination is stated as a contraindication in the SmPC and PIL

Risk	What is known	Preventability
Vaccination of persons suffering from neurological diseases that are not stabilised (contraindication) (Administration to persons suffering from progressive neurological disease (contraindication))	The pertussis antigen in TdaP Vaccine SSI can potentially worsen the neurologic disease	The condition is stated as a contraindication in the SmPC and PIL
Vaccination of persons suffering from acute severe fever (contraindication) (Administration to persons suffering from acute severe febrile illness (contraindication))	Severe fever can interfere with the immune response to vaccination	Severe fever at time of vaccination is stated as a contraindication in the SmPC and PIL
Vaccination of persons who have experienced problems of the nervous system (encephalopathy) within 7 days after previous vaccination with a vaccine against pertussis (contraindication) (Administration to persons who have experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine (contraindication))	Historically, pertussis vaccines have been associated with undesirable effects to the nervous system	Previous nervous system disorder after pertussis vaccination is stated as a contraindication in the SmPC and PIL
Primary immunisation (Primary immunisation)	TdaP Vaccine SSI is a booster vaccine. Booster vaccines are vaccines that are administered to enhance the effect of primary vaccinations. Usually booster vaccines do not contain as much antigen as vaccines for primary use. If a booster vaccine is used as a primary vaccine, the vaccine may be less effective	Precaution/warning is stated in the SmPC and PIL
Administration of the vaccine into a blood vessel (Intravascular administration)	Vessel damage may occur. Also, blood clots may form when injecting the vaccine directly into the lumen of the blood vessel	Aspirating (to draw back the plunger) before injecting the vaccine can prevent injection of vaccine into the blood vessel. However, due to lack of supporting evidence, this practice is not recommended. Precaution/warning is stated in the SmPC and PIL
Vaccination of persons whose immune system's ability to fight infectious diseases is compromised or entirely absent (Vaccination of immunocompromised individuals)	Vaccines may be less effective in these persons	These persons also have an increased risk of vaccine preventable diseases and may have more severe illness if infected. Therefore, vaccination is still important in this group. Precaution/warning is stated in the SmPC and PIL

Risk	What is known	Preventability
Previous collapse or shock-like state occurring within 48 hours of vaccination with a vaccine against pertussis (Previous occurrence of hypotonic-hyporesponsive episode (HHE) within 48 hours of vaccination with a pertussis-containing vaccine)	The risk connected to vaccination of persons who previously have experienced collapse or shock-like state is unknown. This is not a contraindication, further vaccinations should be considered carefully	Precaution/warning is stated in the SmPC and PIL
Previous high fever (> 40˚C) without any other identifiable cause occurring within 48 hours of vaccination with a vaccine against pertussis (Previous occurrence of fever > 40°C within 48 hours of vaccination with a pertussis-containing vaccine not due to any other identified cause)	The risk connected to vaccination of individuals who have had previous occurrence of fever > 40°C is unknown. This is not a contraindication, further vaccinations should be considered carefully	Precaution/warning is stated in the SmPC and PIL
Previous persistent crying lasting more than 3 hours or more occurring within 48 hours of vaccination with a vaccine against pertussis (Previous occurrence of persistent, inconsolable crying lasting more than 3 hours, within 48 hours of vaccination with a pertussis-containing vaccine)	The risk connected to vaccination of persons who previously have experienced persistent, inconsolable crying is unknown. This is not a contraindication, further vaccinations should be considered carefully	Precaution/warning is stated in the SmPC and PIL
Previous convulsions with or without fever occurring within 3 days of vaccination (Previous occurrence of convulsions with or without fever, occurring within 3 days of vaccination with a pertussis-containing vaccine)	Infants and young children, who have had prior convulsions after vaccination, whether febrile or afebrile, appear to be at increased risk for convulsions following diphtheria/tetanus/pertussis vaccination than children and infants without these histories. Previous occurrence is not a contraindication, further vaccinations should be considered carefully	Precaution/warning is stated in the SmPC and PIL
TdaP Vaccine SSI should be administered with caution in persons treated with medicine that prevents the blood from clotting or in persons with bleeding disorders (Administration to persons treated with anticoagulants or with coagulation disorders)	The recommended route of administration of TdaP Vaccine SSI (in the muscle) can cause bleeding in these persons	Injection in the subcutis can be considered in such cases to reduce the bleeding. Precaution/warning is stated in the SmPC and PIL

Risk	What is known	Preventability
Serious allergic reaction that is rapid in onset (Anaphylactic/hypersensitivity reactions)	Serious allergic reactions are always a risk when injecting a vaccine. Persons with known severe hypersensitivity to any components of the vaccine are at increased risk. Also, caution should be taken when vaccinating persons with known allergies, as the theoretical risk of a serious allergic reaction might be raised. Therefore, as a general precaution it is advised that the patient is kept under surveillance for 15-20 minutes after vaccination.	Previous severe allergic reaction after vaccination is stated as a contraindication in the SmPC. Management principles consist of the control of serious allergic reactions and its life-threatening effects. Less severe reactions to the vaccine are usually self-limiting and do not require special treatment. Anti-histamines may be required. The precaution/warning is stated in the SmPC and PIL. The frequency of this adverse event is stated in the SmPC and PIL
Long lasting itching nodules at the site of injection (Injection site granuloma)	Aluminium-containing vaccines can cause itching nodules in the skin. The route of administration of such vaccines (in the muscle and not in the subcutis) reduces the risk of nodule formation.	Information in the SmPC and PIL regarding the recommended route of administration (in the muscle and not in the subcutis) can ensure correct administration. The frequency of this adverse event is stated in the SmPC and PIL

Important potential risks

None

Important missing information

Risk	What is known
Use in persons older than 55 years of age (Use in persons older than 55 years of age)	No adults above 55 years of age were included in the clinical trials, however, it is generally considered safe to vaccinate adults of all ages with inactivated vaccines such as TdaP Vaccine SSI, although such vaccines may be less effective in these persons
Use in pregnant or lactating women (Use in pregnant or lactating women)	There are no or limited information on the use of TdaP Vaccine SSI in pregnant women and the effect on breastfed infants after administration of TdaP Vaccine SSI to the mothers has not been studied. As with other inactivated vaccines, harm to the foetus is not anticipated. Nor is it anticipated that vaccination of the breastfeeding mother with inactivated TdaP Vaccine SSI is harmful to the infant
Use in persons whose immune system's ability to fight infectious diseases is compromised or entirely absent (Use in immunocompromised individuals)	The use of TdaP Vaccine SSI in immunocompromised persons has not been studied. It is generally accepted that administration of inactivated vaccines to immunocompromised individuals can be considered safe; however, the vaccines may be less effective in these persons

VI.2.5 Summary of additional risk minimisation measures by safety concern

There are no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

There are no planned studies in the post authorisation development plan.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	Final date (SSI) 04-07-2011	None	First version.
2.0	Final date (SSI) 30-01-2012	**Important identified risks:** Hypersensitivity reactions, headache, myalgia, pain, itching, redness or swelling at the injection site, fatigue, fever, malaise and granuloma or sterile abscess at the injection site. **Important potential risks:** Anaphylactic reactions, urticarial reactions, irritability **Important missing information:** Use in children less than 5 years, use in persons older than 52 years, use in pregnant and lactating women and use in immunocompromised patients	Newly identified safety concerns (headache, myalgia, pain and itching at the injection site and fatigue) were reported in clinical trials.
3.0	Final date (SSI) 27-04-2012	The use of TdaP Vaccine SSI for primary vaccination was added as an Important potential risk	The use for primary vaccination was added during assessment from the Danish Medicines Agency since it is stated in the proposed SmPC that TdaP Vaccine SSI is not intended for primary vaccination.
4.0	Final date (SSI) 16-05-2012	The use of TdaP Vaccine SSI for primary vaccination was removed as an Important potential risk	The use for primary vaccination was deleted following request from the Danish Medicines Agency since off-label primary vaccination use is not likely and only one case in more than 16 million doses has been observed for other SSI booster vaccines.

Version	Date	Safety Concerns	Comment
5.0	Final date (SSI) 10-06-2013	**Important identified risks** 1. Known hypersensitivity to the active substances, to any of the excipients or to formaldehyde that may be present as traces (contraindication) 2. Administration to persons suffering from progressive neurological disease (contraindication) 3. Administration to persons suffering from acute severe febrile illness (contraindication) 4. Administration to persons who have experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine (contraindication) 5. Primary immunisation 6. Intravascular administration 7. Vaccination of immunocompromised individuals 8. Previous occurrence of hypotonic-hyporesponsive episode (HHE) within 48 hours of vaccination with a pertussis-containing vaccine 9. Previous occurrence of fever > 40°C within 48 hours of vaccination with a pertussis-containing vaccine not due to any other identified cause 10. Previous occurrence of persistent, inconsolable crying lasting more than 3 hours, within 48 hours of vaccination with a pertussis-containing vaccine 11. Previous occurrence of convulsions with or without fever, within 3 days of vaccination with a pertussis-containing vaccine 12. Administration to persons treated with anticoagulants or with coagulation disorders 13. Anaphylactic/hypersensitivity reactions 14. Injection site granuloma **Important potential risks** None **Important missing information** 1. Use in persons older than 55 years of age 2. Use in immunocompromised individuals 3. Use in pregnant and lactating women	Extensively revised due to new guidelines for format and content of Risk Management Plans (GVP Module V). Identified and potential risks are selected according to section 4.3 Contraindications and section 4.4 Special warnings and precautions for use in the SmPC. Additionally, adverse events which are either potentially life-threatening or may affect the vaccinated person's life are included as important identified risks.