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Summary of the risk management plan (RMP) for Vaxelis

(diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus* type b conjugate vaccine (adsorbed))

This is a summary of the risk management plan (RMP) for Vaxelis, which details the measures to be taken in order to ensure that Vaxelis is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Vaxelis, which can be found on Vaxelis's EPAR page.

Overview of disease epidemiology

Vaxelis is a vaccine used in babies and toddlers aged from six weeks to protect against the following infectious diseases:

- **Diphtheria**

Diphtheria is a highly contagious disease that affects the throat and skin, and can damage the heart and other organs. Diphtheria is caused by a toxin produced by the bacterium *Corynebacterium diphtheriae*. Diphtheria infects the upper respiratory tract and spreads from person to person through coughing or close contact.

Diphtheria affects 1 to 10 in every 100 million persons in highly vaccinated populations. The elderly, who often have not received booster vaccines, are most at risk. Five to 10 in every 100 infected persons may die. All deaths from diphtheria in the world are generally in children under 5 years in countries with lower levels of vaccination.

- **Tetanus**

Tetanus is an infectious disease caused by a toxin produced by the bacterium *Clostridium tetani.* Bacteria in the environment infect people through open wounds or newborns born in non-hygienic conditions. Tetanus is not transmitted from person to person.

Tetanus affects 1 to 4 in every 10 million persons in highly vaccinated populations, where the elderly, who often have not received booster vaccination, are most at risk. Eight to 20 in every 100 infected persons may die, with higher risk for the youngest and oldest patients without hospital care.

- **Pertussis (whooping cough)**

Pertussis is an infection caused by the bacterium *Bordetella pertussis*, which is transmitted from person to person through coughing or sneezing. The disease causes lung and throat inflammation, with fits of coughs, difficulty catching breath, and whooping upon inbreathing. Coughing fits can lead to vomiting and severe complications, sometimes fatal in the very young. An increase in the number of people with pertussis has been recorded in several countries in recent years, as a result of several

factors: gradual loss of vaccine protection, incomplete vaccinations, increased detection of the disease and possible evolution of the bacterium.

About 1 or 2 out of every 100 infected persons die from pertussis in the world. Almost all deaths occur in very young unvaccinated children.

- **Invasive *Haemophilus influenzae* type b (Hib) disease**

Invasive Hib disease results from infection with the bacterium *Haemophilus influenzae* type b. The bacterium is transmitted from person to person through coughing or close contact and it can remain in the body without causing disease for up to 6 months. The bacterium commonly infects young children, elderly and immunocompromised individuals. Infection results in brain inflammation (meningitis) as well as inflammation of other organs including the lungs (pneumonia) or the epiglottis.

Between 2 and 40 in every 10 million were affected by Hib disease in the US in 2011 and the EU in 2006. Among children under 5 years of age, 1 and 10 in every million were affected in the US and EU. In the US in 2011 and European countries in 2006, 140 and 85 per 1,000 persons with Hib disease died, respectively.

- **Poliomyelitis**

Poliomyelitis (polio, a disease that affects the nerves and can lead to muscle weakness or paralysis) is caused by poliovirus infection spreading to the nervous system. The virus is transmitted from person to person through contact with infected faeces or oral fluids. In about 1 in every 1000 infected persons, the virus migrates to the nervous system and causes muscle paralysis. Five to 10 in every 100 persons with poliomyelitic paralysis may die. In other cases, the paralysis can lead to disability.

Europe and the US are officially considered free of poliomyelitis. Poliomyelitis continues to spread in Afghanistan, Nigeria and Pakistan, from where it has spread to previously polio-free countries in Africa and the Middle-East. There is no treatment for poliomyelitis or poliovirus infection.

- **Hepatitis B**

Hepatitis B virus (HBV) (which causes a viral liver infection) is transmitted from person to person through blood or body fluids or from mother to child during delivery. HBV can result in severe liver disease and liver failure. While 95% of patients recover, HBV can persist in the liver, leading to loss of liver function (cirrhosis) and liver cancer. Acute HBV infection commonly affects adults aged 20-40 years in Europe and the US, with 2-4 new cases per million infected in 2011-2012. Severe HBV infection results in 5-10 deaths per 1,000 people while cirrhosis or cancer results in 15-25 deaths per 100 cases.

Summary of treatment benefits

Vaxelis is a vaccine used for primary and booster vaccinations in babies and toddlers from the age of 6 weeks and should be used in accordance with official recommendations.

Vaxelis has been studied in two main studies involving more than 2,500 infants and toddlers over six weeks of age who were given either two or three doses of the vaccine during their first six months of life. They then received a booster dose shortly after their first birthday. The effects of Vaxelis were compared with those of another vaccine, Infanrix hexa, designed to protect against the same six diseases as Vaxelis. In these studies, children also received other vaccines according to local vaccination schedules to protect against other childhood diseases such as rotavirus gastroenteritis, measles, mumps, rubella and varicella. The main measure of effectiveness was the production of antibodies at levels known to be protective against diphtheria, tetanus, poliomyelitis, hepatitis B and *H. influenzae* type b infections and expected to protect against pertussis.

Both studies showed that Vaxelis produces satisfactory levels of antibodies to protect against all of these six diseases in between 90 and 100% of children who completed the course of vaccination with Vaxelis.

Unknowns relating to treatment benefits

Vaxelis has not been studied in babies under 6 weeks of age; severely premature infants (born at up to 28 weeks of pregnancy); patients with low immunity (immunocompromised patients) or children above 15 months of age.

Summary of safety concerns

Important identified risks

No important risks with the use of this vaccine have been identified at the present time.

Important potential risks

Risk	What is known
Allergic reactions (hypersensitivity, including anaphylactic reactions) 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.	Allergic reactions such as rash, itching, redness of skin, difficulty in breathing, shock, swelling of the face, swelling of the skin around eyes and lips, have been reported with other vaccines containing the components of Vaxelis. As with all injectable vaccines, appropriate medical treatment and healthcare providers should be readily available for immediate treatment of a rare severe allergic reaction (anaphylactic reaction) following the administration of this vaccine. Vaxelis must not be given to an individual who has experienced allergic reactions with Vaxelis or with other vaccines containing the same components or constituents.
Seizures (fits) with or without fever	Febrile convulsion is a seizure associated with a significant rise in body temperature. High fever can be associated with febrile convulsions in young children from 6 months of age. The majority of febrile convulsions occur in the second year of life, with highest incidence around 18 months of age. Seizures are signs of underlying central nervous system disorders that result in the over-stimulation of nerve cells in the brain. In case of convulsions with or without fever, within 3 days of vaccination, doctors should carefully consider whether to give further doses. People who have had febrile convulsions in the past should be carefully followed up after vaccination with Vaxelis because convulsions may occur within 2 to 3 days after vaccination.
Low responsiveness - low muscle tone episode (hypotonic-hyporesponsive episode)	There may be sudden onset of reduced muscle tone and low responsiveness together with a change in skin colour following vaccination with Vaxelis. This event has not been reported with Vaxelis and most events have been reported with a type of pertussis vaccine called ‘whole-cell’ pertussis. This occurs normally within 48 hours after vaccination and symptoms usually last for up to 30 minutes, but may take up to 10 days to resolve fully. This event, which has been observed most frequently

Risk	What is known
	after the first dose of the primary immunisation, has no long-term after-effects. Nevertheless, caution is needed when using Vaxelis in children with a history of such reaction.
Brain disorder (encephalopathy/encephalitis)	Encephalopathy is a disorder of the function or structure of the brain. Encephalitis is an inflammation (swelling) of the brain. Encephalopathy and encephalitis have been reported with pertussis-containing vaccines, and as with all pertussis-containing vaccine, individuals should not be given Vaxelis if they have had unexplained encephalopathy (*e.g.*, coma, decreased level of consciousness, prolonged fits) within 7 days of a pertussis-containing vaccine. In case individuals develop encephalitis or encephalopathy during the immunisation schedule, Vaxelis should be discontinued and the vaccination should be continued with other diphtheria, tetanus, hepatitis B, poliomyelitis and Hib vaccines.
Stopped breathing or prolonged breathlessness (in premature children born at up to 28 weeks of pregnancy [apnoea (in premature infants less than or equal to 28 weeks gestation)]	Apnoea has been reported with all childhood vaccines. The child may stop breathing or suffer breathlessness for more than 20 seconds or take a shorter pause when breathing. This usually occurs 3 days after vaccination. When giving the primary vaccination to very premature infants (born at up to 28 weeks of gestation) and to those with a history of immaturity of the airways, doctors should consider the potential risk of apnoea and the need for monitoring breathing during 48-72 hours after vaccination. As the benefit of vaccination is high in this group of infants, vaccination should not be denied or delayed.
Major limb swelling	Extensive limb swelling is swelling that starts at the injection site and extends to one or both joints. These reactions start within 24 to 72 hours after vaccination, may be associated with erythema (redness of skin), warmth, pain to touch or pain at the injection site. The reactions usually settle down on their own within 3 to 5 days. The risk appears to be dependent on the number of previous doses of a pertussis-containing vaccine, with a greater risk after the 4th and 5th doses.

Missing information

Risk	What is known
Children below 6 weeks of age	Vaxelis has not been studied in babies under 6 weeks of age, because Vaxelis is not intended for use in infants below 6 weeks.
Children born prematurely at less than 28 weeks of pregnancy (Premature infants less than 28 weeks of gestation at the time of birth)	Vaxelis has not been studied in children born prematurely at less than 28 weeks of pregnancy. Data available showed that the immune responses to Vaxelis in these preterm infants were generally similar to those of the overall study population. However, a lower immune response may be observed and the level of clinical protection is unknown.
Patients with low immunity (immunocompromised	The immune response of the vaccine may be reduced in patients taking immunosuppressive treatment (treatment that reduces or halts the immune system activity of the body) or those with a weak immune.

Risk	What is known
patients)	Therefore it is recommended to postpone vaccination until the end of such treatment or disease. However, Vaxelis is recommended in human immunodeficiency virus (HIV) patients even if the immune response may be lower. Vaxelis has not been studied in patients who have a weak immune system or who lack immune response to fight against infections.
Use in children above 15 months of age	Although Vaxelis has not been studied in children above 15 months, the use of Vaxelis in children older than 15 months of age according to official recommendations (e.g. in catch up scenarios) is supported by clinical evidence of the immunogenicity of similar pertussis vaccines. However it is difficult to define a specific age cut off when appropriate booster vaccines should be considered.
Persistence of pertussis antibodies after vaccination, which is expected to indicate protection against the infection	It is not known how long the antibodies against pertussis remain in the body. No study has been required to address this missing information; however the company is planning to assess the long term persistence of pertussis antibodies in children that were part of the two EU main studies, when they reach 4 to 5 years of age.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Vaxelis can be found on Vaxelis's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

None

Studies which are a condition of the marketing authorisation

Not applicable.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 02-2016.