

Summary of the risk management plan (RMP) for Tritanrix HB [Diphtheria, tetanus, pertussis (whole cell) and hepatitis B (rDNA) vaccine (adsorbed)]

Overview of disease epidemiology

Diphtheria

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*, spread from person to person through direct contact or after breathing in droplets produced by infected people when coughing or sneezing. Diphtheria usually affects the airways, and, in tropical climates and where the conditions of overcrowding and poor sanitation are present it can also affect the skin. The bacteria produce a toxin that destroys local tissue. The disease typically has a short incubation period (time between exposure to a bacteria, and first signs and symptoms) of 1-5 days and lasts from several days to months if complications occur, such as choking or inflammation of the heart muscle. Systemic complications are due to the diphtheria toxin, which is toxic to all tissues, but has a particularly striking effect on the heart and nervous system.

A diphtheria infection is treated using antibiotics to kill the diphtheria bacteria and antitoxins to neutralise the effects of the toxin produced by the bacteria. Cutaneous diphtheria is treated by thoroughly washing any wounds infected with the diphtheria bacteria with soap and water.

Cases of diphtheria occur almost exclusively in developing countries, although small numbers of cases are reported annually in Europe.

Tetanus

Tetanus is a bacterial disease, and often fatal, caused by *Clostridium tetani*, which is not transmitted from one person to another, but is acquired through environmental exposure. Spores of *Clostridium tetani* (bacterial structures very resistant to environment), which are universally present in the soil, typically enter the body through a wound where they germinate and produce toxins which are responsible for the typical symptoms of tetanus: spasms and persistent contraction of muscles.

The incubation period for tetanus is usually 8 days (ranging 3–21 days).

Tetanus occurs worldwide and is more common in agricultural regions and areas where contact with soil or animal excreta is more likely and immunisation is inadequate. The highest number of cases was reported in the Africa and South-East Asia, areas with the lowest vaccination coverage.

Neonatal tetanus (tetanus infecting newborn babies) is the most common form of the disease in developing countries. Infection occurs through the unhealed umbilical stump, particularly if non-sterile instruments were used to cut the umbilical cord. Tetanus will affect infants who do not have protective passive immunity (transfer of tetanus antibodies from the mother to the fetus), due to a lack of vaccination of the mother.

Pertussis

Pertussis, also known as whooping cough, is a respiratory infection (infection of the sinuses, throat, airways or lungs) caused by bacteria called *Bordetella pertussis*. Pertussis is highly contagious and spreads very easily from person to person in droplets produced by coughing or sneezing. Once in the upper respiratory tract, the bacteria release a toxin that leads to local paralysis, interfering with the clearance of lung secretions. Pertussis is characterised by an uncontrollable and spastic cough which is often followed by vomiting.

Pertussis can be severe in infants and children, but in adults the symptoms tend to be mild and indistinguishable from those of other respiratory infections. However, infected adults can still transmit the disease to susceptible individuals.

Pertussis is endemic worldwide, even in areas with high vaccination rates. Disease rates are highest among young children in countries where vaccination coverage is low, which is primarily in the developing world. In developed countries, the incidence of pertussis is highest among infants too young to be vaccinated.

Pertussis is treated with antibiotics such as azithromycin, clarithromycin and erythromycin.

Hepatitis B

Hepatitis B (HepB) remains a major global health problem and the most serious type of viral hepatitis. It is a potentially life-threatening infection caused by the hepatitis B virus (HBV) that attacks the liver and can cause both acute (short-term) and chronic (long-term) disease. HBV is transmitted from person to person via contact with the blood or other body fluids of an infected person. HBV is not spread by contaminated food or water. The incubation period of the HBV is 120 days on average, but can vary from 45 to 160 days.

HBV can cause an acute illness with symptoms that last several weeks, including jaundice (yellowing of the skin and eyes), dark urine, extreme tiredness, nausea, vomiting and abdominal pain. Acute HepB progresses to a chronic state in 30–50% of people infected during childhood and in less than 5% of people infected during adolescence or adulthood. People with chronic HepB infection often do not have any symptoms, therefore, individuals may not be aware that they have been infected, although they are still able to infect others. Chronic liver infection can later develop into cirrhosis (scarring) of the liver or liver cancer.

There is no specific treatment for acute HepB. Care is aimed at maintaining comfort and adequate nutritional balance. Some people with chronic HepB can be treated with antiviral drugs that can slow the progression of cirrhosis. Vaccination is therefore the only means by which this disease can be controlled.

People who are more at risk of developing infections caused by HBV include people having unprotected sexual contact or sharing needles with an infected person, visiting endemic regions, frequently receiving blood or blood products, occupations involving contact with blood, household contacts of HBV carriers and perinatal (from mother to baby at birth) transmission.

Summary of treatment benefits

Tritanrix-HB is a combination vaccine aimed at protecting people against diseases caused by the bacteria *Corynebacterium diphtheria* (diphtheria), *Clostridium tetani* (tetanus) and I (pertussis) and by the hepatitis B virus (hepatitis B). The bacterial diseases are treated with antibiotics or other treatments but permanent damage or death may still occur despite treatment. There is no specific

treatment for acute hepatitis B. Vaccination is considered to be an effective way to stop the spread and impact of infections caused by these infectious agents.

Tritanrix-HB can be given to children from the age of 6 weeks onwards. The vaccine works by helping the body to produce its own antibodies in order to protect against the diseases these bacteria cause.

Clinical studies have been performed to evaluate the safety of Tritanrix-HB and the ability of this vaccine to cause the production of antibodies (protection against disease). The studies involved the administration of Tritanrix-HB to approximately 10,717 healthy children as primary vaccination. Furthermore, approximately 653 healthy children received a booster dose of Tritanrix-HB in the second year of life.

Further studies have confirmed that Tritanrix-HB can also be safely administered with Hibrix (vaccine against *Haemophilus influenza* type B disease [Hib]). The studies involved 22,879 healthy children where Tritanrix-HB/Hib was given as the primary vaccination (first 3 doses of the vaccine given in the first 6 months of life) and 3,864 subjects where Tritanrix-HB/Hib was given as booster vaccination (extra dose given during the second year of life).

Unknowns relating to treatment benefits

During its development, Tritanrix-HB has been studied in healthy children from 6 weeks to 2 years of age, which adequately reflects the current indication for this vaccine.

Children with a disease or a treatment which affects the immune system (immunodeficient children and children with sickle cell disease for example) were excluded from the clinical studies. Information on the use of Tritanrix HB in these children is thus limited but there is also no evidence of a safety concern. Although the vaccine should be considered for use in these children, they may develop a lower level of immune (protective) response compared with other children.

Children born prematurely were also excluded from the clinical studies. However, the vaccine should be considered for use in these children as the benefit of vaccination is high in this group of infants who are at a greater risk of infection compared with infants born at full term.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity)	Allergic reactions may occur after less than 1 in 10,000 doses of the vaccine. People may develop allergic reactions to any type of vaccine and/or its components. Symptoms can occur from several minutes to hours after the vaccine is administered. Anaphylaxis, a systemic allergic reaction, that can cause low blood pressure, breathing difficulties, shock and loss of consciousness, may occur. Anaphylaxis is a life-threatening emergency that requires	In case of signs of allergic reactions after administration of diphtheria, tetanus, pertussis or hepatitis B vaccines any further vaccination with these vaccines should be avoided. Vaccination should be preceded by a review of the medical history and a clinical examination. Appropriate medical treatment and supervision should be available in case of a rare anaphylactic event following administration of the vaccine.

Risk	What is known	Preventability
	immediate medical treatment.	
High fever (temperature of $\geq 40.0^{\circ}\text{C}$)	High fever can occur after vaccination and usually is reversible with a medicine that reduces fever (antipyretic).	The use of a medicine that reduces fever (e.g. paracetamol), before or immediately after vaccination, can prevent a fever reaction from occurring.
Convulsions (fits) with or without fever	Children with a convulsion disease or who have had convulsions in the past are at higher risk. During a fit, there is a small chance that the child may be injured. Most children recover completely and there is no evidence that convulsions cause brain damage. Although febrile convulsions (fits associated with fever) are common from 3 months to 6 years of age and most children will grow out of them without any long-term effects, a small proportion of children who have had a convulsion associated with fever will later be diagnosed with epilepsy.	This reaction usually occurs between the age of 6 months and 6 years with a peak at 18 months. The use of a medicine that reduces fever (e.g. paracetamol), before or immediately after vaccination, can prevent a fever reaction from occurring.
Collapse, periods of unconsciousness or lack of awareness, and paleness or bluish skin discoloration. (Hypotonic-hyporesponsive episode)	A hypotonic-hyporesponsive episode can occur within 48 hours of receipt of Tritanrix-HB. Most episodes occur within 12 hours after vaccination with a peak at <6 hours. In most cases the episode is of short duration without complications and children return to their pre-vaccination state after 6 to 24 hours.	It is important that procedures are in place to avoid injury from fainting in older infants/toddlers.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Interruption in breathing (apnoea) in children that are born prematurely (before or at 28 weeks of pregnancy)	Apnoea occurs more often in children that are born prematurely or have a low birthweight at the time of vaccination because the brain and breathing systems in these children are not yet fully developed. In most children the disorder will cease to occur once their brain and breathing system is fully developed. When Tritanrix-HB is administered to a child that was born prematurely, it is important that the doctor monitors the child carefully for breathing difficulties following vaccination. If breathing difficulties occur touching the skin of the child can improve breathing. Alternatively medication or breathing support can be used. As this group of infants is at greater risk of infection than other infants, the benefit of vaccination is high and vaccination should not be suspended or delayed.
Fainting (Syncope)	If a patient faints after vaccination, he or she generally recovers within a few minutes. However, syncope can potentially cause serious harm due to fall-related injury. As Tritanrix-HB is indicated before the age of 2 years, the risk of falling and injury after a syncope is low. Syncope occurs at a lower frequency in infants and toddlers compared with older children and adolescents. Syncope can occur following, or even before, <u>any</u> vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from fainting.
Brain disorder (Encephalopathy)	Tritanrix-HB is contraindicated if the child has experienced an encephalopathy of unknown origin, occurring within 7 days following vaccination with a pertussis-containing vaccine. Most affected children will recover without long-term complications.

Missing information

Risk	What is known
Use of the vaccine in children born prematurely (Data on the immunogenicity and safety of Tritanrix-HB in premature children)	Children born prematurely were excluded from the Tritanrix-HB clinical studies and only limited information on vaccination of Tritanrix-HB in premature children is available. However, as supported by the medical literature, the vaccine should be considered for use in these children as the benefit of vaccination is high in this group of infants who are at a greater risk of infection compared with infants born at full term.

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, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Tritanrix HB can be found in the Tritanrix HB's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

There are no studies that are a condition of the marketing authorisation.

Studies which are a condition of the marketing authorisation

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This summary was last updated in 01-2014.