ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tritanrix HepB, suspension for injection
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 IU
Tetanus toxoid[1]	not less than 60 IU
Bordetella pertussis (inactivated)[2]	not less than 4 IU
Hepatitis B surface antigen [2,3]	10 micrograms

1	Adsorbed on aluminium hydroxide, hydrated	0.26 milligrams Al^{3+}
2	Adsorbed on aluminium phosphate	0.37 milligrams Al^{3+}
3	Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology	

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tritanrix HepB is indicated for active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HBV) in infants from 6 weeks onwards (see section 4.2).

4.2 Posology and method of administration

Posology

The recommended dose is 0.5 ml.

Primary vaccination:

The primary vaccination schedule consists of three doses within the first six months of life. Where HBV vaccine is not given at birth, the combined vaccine can be administered beginning as early as 8 weeks of age. Where there is a high endemicity of HBV, the practice to administer HBV vaccine at birth should be continued. In these circumstances, vaccination with the combined vaccine should start at 6 weeks of age.

Three vaccine doses must be administered at intervals of at least 4 weeks.

When Tritanrix HepB is given according to the 6-10-14 weeks schedule, it is recommended to administer a dose of HBV vaccine at birth to improve protection.

In the case of children born of known HBV carrier mothers the immunoprophylactic measures for hepatitis B should not be modified. This may require separate vaccination with HBV and DTPw vaccines and also include the administration of HBIg at birth.

Booster vaccination:

A booster dose with Tritanrix HepB will give rise to increased reactogenicity as would be expected for a booster during the second year of life. In consequence, boostering should follow local recommendations.

The administration of a booster dose with trivalent DTP vaccine is recommended before the end of the second year of life. For long-term protection against HBV, a booster dose of HBV vaccine could also be administered after the first year of life. However, the need for this dose is currently not established.

Method of administration

Tritanrix HepB is for deep intramuscular injection, preferably in the anterolateral thigh.

It is recommended that in patients with thrombocytopenia or bleeding disorders the vaccine be administered subcutaneously (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis or hepatitis B vaccines.

The administration of Tritanrix HepB should be postponed in subjects suffering from acute severe febrile illness.

Tritanrix HepB is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances the vaccination course should be continued with DT and HBV vaccines.

4.4 Special warnings and precautions for use

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of adverse reactions) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.

If any of the following events occur in temporal relation to receipt of Tritanrix HepB, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause.
Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
Persistent crying lasting ≥ 3 hours, occurring within 48 hours.
Convulsions with or without fever, occurring within 3 days.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

As for any vaccination, the risk-benefit of immunising with Tritanrix HepB or deferring this vaccination should be weighed carefully in an infant or in a child suffering from a new onset or progression of a severe neurological disorder.
A history of febrile convulsions, a family history of convulsions, a family history of SIDS (Sudden Infant Death Syndrome) and a family history of an adverse reaction following Tritanrix HepB vaccination do not constitute contra-indications.

HIV infection is not considered as a contra-indication for diphtheria, tetanus, pertussis and HBV vaccination. The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patients on immunosuppressive therapy.

Tritanrix HepB should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

TRITANRIX HepB SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

4.5 Interaction with other medicinal products and other forms of interaction

It is current practice in paediatric vaccination to co-administer different vaccines during the same session with injectable vaccines being administered at separate injection sites.

Tritanrix HepB can be administered simultaneously at separate sites or in any temporal relationship with other paediatric vaccines if this fits conveniently in the immunisation scheme.

In clinical studies, Tritanrix HepB has been administered simultaneously with oral polio vaccine (OPV) and *Haemophilus influenzae* type b (Hib) vaccine. In these studies the immune response to the oral polio vaccine has not been investigated, however, previous experience with simultaneous administration of DTP, OPV and HBV vaccines has not shown any interference. In some clinical studies, Tritanrix HepB was used to reconstitute the lyophilised Hib vaccine (Hiberix); no interference in the immune response to any of the antigens was observed as compared to the responses observed following administration of the vaccines at separate sites (see section 6.2).

In patients receiving immunosuppressive therapy or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Pregnancy and lactation

As Tritanrix HepB is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

- Clinical trials:

  In clinical studies, the most commonly reported adverse events were reactions at the injection site, including redness, swelling and pain.

  General reactions that may occur in temporal association with Tritanrix HepB vaccination are listed below.

  Frequencies are defined as follows:
  Very common (≥1/10)
  Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders:
very common: drowsiness

Respiratory, thoracic and mediastinal disorders:
common: bronchitis
uncommon: respiratory disorder

Gastro-intestinal disorders:
very common: feeding problems
common: gastro-intestinal symptoms such as vomiting and diarrhoea

Infections and infestations:
common: otitis media, pharyngitis
uncommon: pneumonia

General disorders and administration site conditions:
very common: fever, swelling, pain and redness

Immune system disorders:
very rare: allergic reactions including anaphylactic and anaphylactoid reactions and serum sickness like disease

Psychiatric disorders:
very common: unusual crying, irritability

In a prospective comparative study, which compared the administration of the combined DTPw-HBV vaccine with the simultaneous separate administration of DTPw and HBV vaccine, higher incidences of pain, redness, swelling and fever were reported in the group receiving the combined vaccine. The incidences are presented below:

		Group 1 DTPw-HBV (combined)	**Group 2 DTPw (separate)**	**HBV (separate)**
N° of symptom checklists		175	177	177
Local symptoms (%)				
Pain	Total	32.0	15.3	2.8
	Severe*	0.0	0.0	0.0
Redness	Total	38.9	27.1	5.1
	> 2cm	9.1	3.4	0.6
Swelling	Total	30.9	21.5	4.5
	> 2cm	10.9	3.4	0.6
General Symptoms (%)				
Fever ≥ 38°C		53.1	35.0	
Fever > 39.5° C		1.1	0.0	

* reported by the parents as adversely affecting the child's daily activities

For both vaccination groups, the majority of the reactions were short lasting.

- Post marketing surveillance:

  Nervous system disorders:
  Collapse or shock-like state (hypotonic-hyporesponsive episode)

  Respiratory, thoracic and mediastinal disorders:
  Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

- Experience with hepatitis B vaccine:

  Blood and lymphatic system disorders:
  Thrombocytopenia

  Nervous system disorders:
  Convulsions

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.3)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA05.

Tritanrix HepB contains diphtheria (D), tetanus (T) toxoids, inactivated pertussis bacteria (Pw) and the purified major surface antigen of the hepatitis B virus (HBV), adsorbed on aluminium salts.

The D and T toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* by formalin inactivation using established technology. The Pw component is obtained by heat inactivation of phase I culture of *Bordetella pertussis* bacteria.

The surface antigen of the HBV (HBsAg) is produced by culture of genetically-engineered yeast cells *(Saccharomyces cerevisiae)* which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptide and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of the natural HBsAg.

Four different schedules have been studied (6-10-14 weeks, 2-4-6 months; 3-4-5 months and 3-4½-6 months) according to routine vaccination practices in different countries with three doses administered within the first six months of life.

For each component of the vaccine, the following immune responses have been documented one month after completion of the primary vaccination schedule.

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Tritanrix HepB:

Antibody (cut-off)	**6-10-14 weeks**	**2-4-6 months; 3-4-5 months and 3-4½-6 months**
	%	%
Anti-diphtheria (0.1 IU/ml) †	93.1	99.7
Anti-tetanus (0.1 IU/ml) †	100	100
Anti-*B. Pertussis* (vaccine response) ††	97.2	97.7
Anti-HBs (10 mIU/ml) †	97.7*	99.2

* in a subgroup of infants not administered hepatitis B vaccine at birth, 89.9% of subjects had anti-HBs titres ≥ 10 mIU/ml
† cut-off accepted as indicative of protection
†† vaccine response: % of subjects considered to have responded to the *Bordetella pertussis* antigen

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on general safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Thiomersal
Sodium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package, in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in a vial (type I glass) with a plunger stopper (rubber butyl) – pack size of 1.

6.6 Special precautions for disposal and other handling

Tritanrix HepB can be mixed with the lyophilised Hib vaccine (Hiberix).

Upon storage, a white deposit and clear supernatant can be observed.

The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

Any unused product of waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/014/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 1996.

Date of latest renewal: 19 July 2006.

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Tritanrix HepB, suspension for injection, multidose
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 IU
Tetanus toxoid[1]	not less than 60 IU
Bordetella pertussis (inactivated)[2]	not less than 4 IU
Hepatitis B surface antigen[2,3]	10 micrograms

[1]	Adsorbed on aluminium hydroxide, hydrated	0.26 milligrams Al^{3+}
[2]	Adsorbed on aluminium phosphate	0.37 milligrams Al^{3+}
[3]	Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology	

This is a multidose container. See section 6.5 for the number of doses per vial.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tritanrix HepB is indicated for active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HBV) in infants from 6 weeks onwards (see section 4.2).

4.2 Posology and method of administration

Posology

The recommended dose is 0.5 ml.

Primary vaccination:

The primary vaccination schedule consists of three doses within the first six months of life. Where HBV vaccine is not given at birth, the combined vaccine can be administered beginning as early as 8 weeks of age. Where there is a high endemicity of HBV, the practice to administer HBV vaccine at birth should be continued. In these circumstances, vaccination with the combined vaccine should start at 6 weeks of age.

Three vaccine doses must be administered at intervals of at least 4 weeks.

When Tritanrix HepB is given according to the 6-10-14 weeks schedule, it is recommended to administer a dose of HBV vaccine at birth to improve protection.

In the case of children born of known HBV carrier mothers the immunoprophylactic measures for hepatitis B should not be modified. This may require separate vaccination with HBV and DTPw vaccines and also include the administration of HBIg at birth.

Booster vaccination:

A booster dose with Tritanrix HepB will give rise to increased reactogenicity as would be expected for a booster during the second year of life. In consequence, boostering should follow local recommendations.

The administration of a booster dose with trivalent DTP vaccine is recommended before the end of the second year of life. For long-term protection against HBV, a booster dose of HBV vaccine could also be administered after the first year of life. However, the need for this dose is currently not established.

Method of administration

Tritanrix HepB is for deep intramuscular injection, preferably in the anterolateral thigh.

It is recommended that in patients with thrombocytopenia or bleeding disorders the vaccine be administered subcutaneously (see section 4.4.).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis or hepatitis B vaccines.

The administration of Tritanrix HepB should be postponed in subjects suffering from acute severe febrile illness.

Tritanrix HepB is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances the vaccination course should be continued with DT and HBV vaccines.

4.4 Special warnings and precautions for use

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of adverse reactions) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.

If any of the following events occur in temporal relation to receipt of Tritanrix HepB, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

- Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent crying lasting ≥ 3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

As for any vaccination, the risk-benefit of immunising with Tritanrix HepB or deferring this vaccination should be weighed carefully in an infant or in a child suffering from a new onset or progression of a severe neurological disorder.

A history of febrile convulsions, a family history of convulsions, a family history of SIDS (Sudden Infant Death Syndrome) and a family history of an adverse reaction following Tritanrix HepB vaccination do not constitute contra-indications.

HIV infection is not considered as a contra-indication for diphtheria, tetanus, pertussis and HBV vaccination. The expected immunological response may not be obtained after vaccination of immunosuppressed patients, e.g. patients on immunosuppressive therapy.

Tritanrix HepB should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

TRITANRIX HepB SHOULD UNDER NO CIRCUMSTANCES BE ADMINISTERED INTRAVENOUSLY.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

4.5 Interaction with other medicinal products and other forms of interaction

It is current practice in paediatric vaccination to co-administer different vaccines during the same session with injectable vaccines being administered at separate injection sites.

Tritanrix HepB can be administered simultaneously at separate sites or in any temporal relationship with other paediatric vaccines if this fits conveniently in the immunisation scheme.

In clinical studies, Tritanrix HepB has been administered simultaneously with oral polio vaccine (OPV) and *Haemophilus influenzae* type b (Hib) vaccine. In these studies the immune response to the oral polio vaccine has not been investigated, however, previous experience with simultaneous administration of DTP, OPV and HBV vaccines has not shown any interference. In some clinical studies, Tritanrix HepB was used to reconstitute the lyophilised Hib vaccine (Hiberix); no interference in the immune response to any of the antigens was observed as compared to the responses observed following administration of the vaccines at separate sites. (see section 6.2.).

In patients receiving immunosuppressive therapy or patients with immunodeficiency, an adequate response may not be achieved.

4.6 Pregnancy and lactation

As Tritanrix HepB is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

- Clinical trials:

  In clinical studies, the most commonly reported adverse events were reactions at the injection site, including redness, swelling and pain.

General reactions that may occur in temporal association with Tritanrix HepB vaccination are listed below.

Frequencies are defined as follows:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders:
very common: drowsiness

Respiratory, thoracic and mediastinal disorders:
common: bronchitis
uncommon: respiratory disorder

Gastro-intestinal disorders:
very common: feeding problems
common: gastro-intestinal symptoms such as vomiting and diarrhoea

Infections and infestations:
common: otitis media, pharyngitis
uncommon: pneumonia

General disorders and administration site conditions:
very common: fever, swelling, pain and redness

Immune system disorders:
very rare: allergic reactions including anaphylactic and anaphylactoid reactions and serum sickness like disease

Psychiatric disorders:
very common: unusual crying, irritability

In a prospective comparative study, which compared the administration of the combined DTPw-HBV vaccine with the simultaneous separate administration of DTPw and HBV vaccine, higher incidences of pain, redness, swelling and fever were reported in the group receiving the combined vaccine. The incidences are presented below:

		Group 1 DTPw-HBV (combined)	**Group 2**	
			DTPw	**HBV**
			(separate)	
N° of symptom checklists		175	177	177
Local symptoms (%)				
Pain	Total	32.0	15.3	2.8
	Severe*	0.0	0.0	0.0
Redness	Total	38.9	27.1	5.1
	> 2cm	9.1	3.4	0.6
Swelling	Total	30.9	21.5	4.5
	> 2cm	10.9	3.4	0.6
General Symptoms (%)				
Fever ≥ 38°C		53.1	35.0	
Fever > 39.5° C		1.1	0.0	

* reported by the parents as adversely affecting the child's daily activities

For both vaccination groups, the majority of the reactions were short lasting.

- Post marketing surveillance:

  Nervous system disorders:
  Collapse or shock-like state (hypotonic-hyporesponsive episode).

  Respiratory, thoracic and mediastinal disorders:
  Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

- Experience with hepatitis B vaccine:

  Blood and lymphatic system disorders:
  Thrombocytopenia

  Nervous system disorders:
  Convulsions

This medicinal product contains thiomersal (an organomercuric compound) as a preservative and therefore, it is possible that sensitisation reactions may occur (see section 4.3)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA05.

Tritanrix HepB contains diphtheria (D), tetanus (T) toxoids, inactivated pertussis bacteria (Pw) and the purified major surface antigen of the hepatitis B virus (HBV), adsorbed on aluminium salts.

The D and T toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* by formalin inactivation using established technology. The Pw component is obtained by heat inactivation of phase I culture of *Bordetella pertussis* bacteria.

The surface antigen of the HBV (HBsAg) is produced by culture of genetically-engineered yeast cells *(Saccharomyces cerevisiae)* which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptide and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of the natural HBsAg.

Four different schedules have been studied (6-10-14 weeks, 2-4-6 months; 3-4-5 months and 3-4½-6 months) according to routine vaccination practices in different countries with three doses administered within the first six months of life.

For each component of the vaccine, the following immune responses have been documented one month after completion of the primary vaccination schedule.

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Tritanrix HepB:

Antibody (cut-off)	**6-10-14 weeks**	**2-4-6 months; 3-4-5 months and 3-4½-6 months**
	%	%
Anti-diphtheria (0.1 IU/ml) †	93.1	99.7
Anti-tetanus (0.1 IU/ml) †	100	100
Anti-*B. Pertussis* (vaccine response) ††	97.2	97.7
Anti-HBs (10 mIU/ml) †	97.7*	99.2

* in a subgroup of infants not administered hepatitis B vaccine at birth, 89.9% of subjects had anti-HBs titres ≥ 10 mIU/ml
† cut-off accepted as indicative of protection
†† vaccine response: % of subjects considered to have responded to the *Bordetella pertussis* antigen

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on general safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Thiomersal
Sodium chloride
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Store in the original package, in order to protect from light.

6.5 Nature and contents of container

1 ml of suspension in a vial (type I glass) for 2 doses with a plunger stopper (rubber butyl) – pack size of 1.

5 ml of suspension in a vial (type I glass) for 10 doses with a plunger stopper (rubber butyl) – pack size of 1.

Not all pack-sizes may be marketed

6.6 Special precautions for disposal and other handling

Tritanrix HepB can be mixed with the lyophilised Hib vaccine (Hiberix).

Upon storage, a white deposit and clear supernatant can be observed.

The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and visually inspected for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.

Any unused product of waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/96/014/002
EU/1/96/014/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 1996.
Date of latest renewal: 19 July 2006.

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89,
1330 Rixensart
Belgium

Novartis Vaccines and Diagnostics GmbH & Co. KG
Emil-von-Behring-Str. 76,
D-35041 Marburg
Germany

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89,
1330 Rixensart
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

PSUR: The Marketing Authorisation Holder will continue to submit Periodic Safety Update Reports on a 2 years basis.

Official batch release: in accordance with Article 114 of Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MONODOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Tritanrix HepB – Suspension for injection
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Bordetella pertussis (inactivated)[2]	≥ 4 IU
Hepatitis B surface antigen[2,3]	10 µg

[1] adsorbed on aluminium hydroxide, hydrated 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate 0.37 mg Al^{3+}
[3] produced in yeast cells (*Saccharomyces cerevisiae)* by recombinant DNA technology

3. LIST OF EXCIPIENTS

Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 vial
1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/014/001

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MONODOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tritanrix HepB – Suspension for injection
DTPw-HBV vaccine
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIDOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Tritanrix HepB – Suspension for injection
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Bordetella pertussis (inactivated)[2]	≥ 4 IU
Hepatitis B surface antigen[2,3]	10 µg

[1] adsorbed on aluminium hydroxide, hydrated 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate 0.37 mg Al^{3+}
[3] produced in yeast cells (*Saccharomyces cerevisiae)* by recombinant DNA technology

3. LIST OF EXCIPIENTS

Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
2 doses (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/014/003

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MULTIDOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tritanrix HepB – Suspension for injection
DTPw-HBV vaccine
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 ml)

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIDOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT

Tritanrix HepB – Suspension for injection
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Bordetella pertussis (inactivated)[2]	≥ 4 IU
Hepatitis B surface antigen[2,3]	10 µg

[1] adsorbed on aluminium hydroxide, hydrated 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate 0.37 mg Al^{3+}
[3] produced in yeast cells (*Saccharomyces cerevisiae)* by recombinant DNA technology

3. LIST OF EXCIPIENTS

Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
10 doses (5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/014/002

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MULTIDOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tritanrix HepB – Suspension for injection
DTPw-HBV vaccine
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses (5 ml)

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tritanrix HepB suspension for injection
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

Read all of this leaflet carefully before your child starts receiving this vaccine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Tritanrix HepB is and what it is used for
2. Before your child receives Tritanrix HepB
3. How Tritanrix HepB is given
4. Possible side effects
5. How to store Tritanrix HepB
6. Further information

1. WHAT TRITANRIX HepB IS AND WHAT IT IS USED FOR

Tritanrix HepB is a vaccine used in children to prevent four diseases: diphtheria, tetanus (lockjaw), pertussis (whooping cough) and hepatitis B. The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

- **Diphtheria**: Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and even death.

- **Tetanus** (Lockjaw): Tetanus bacteria enter the body through cuts, scratches or wounds in the skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure/dung or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and even death. The muscle spasms can be strong enough to cause bone fractures of the spine.

- **Pertussis** (Whooping cough): Pertussis is a highly infectious illness. The disease affects the airways causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a "whooping" sound, hence the common name "whooping cough". The cough may last for 1-2 months or longer. Pertussis can also cause ear infections, bronchitis which may last a long time, pneumonia, fits, brain damage and even death.

- **Hepatitis B**: Hepatitis B is caused by the hepatitis B virus. It causes the liver to become inflamed and swollen . The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people.

Vaccination is the best way to protect against these diseases. None of the components in the vaccine are infectious.

2. BEFORE YOUR CHILD RECEIVES TRITANRIX HepB

Tritanrix HepB should not be given:

- if your child has previously had any allergic reaction to Tritanrix HepB, or any ingredient contained in this vaccine. The active substances and other ingredients in Tritanrix HepB are listed at the end of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- if your child has previously had an allergic reaction to any vaccine against diphtheria, tetanus, pertussis (whooping cough) or hepatitis B diseases.
- if your child experienced problems of the nervous system within 7 days after previous vaccination with a vaccine against pertussis (whooping cough) disease.
- if your child has a severe infection with a high temperature (over 38°C). A minor infection such as a cold should not be a problem, but talk to your doctor first.

Take special care with Tritanrix HepB:

- if your child has experienced any health problems after previous administration of a vaccine.
- if after previously having Tritanrix HepB or another vaccine against pertussis (whooping cough) disease, your child had any problems, especially:
  - ♦ A high temperature (over 40°C) within 48 hours of vaccination
  - ♦ A collapse or shock-like state within 48 hours of vaccination
  - ♦ Persistent crying lasting 3 hours or more within 48 hours of vaccination
  - ♦ Seizures/fits with or without a high temperature within 3 days of vaccination
- if your child is suffering from an undiagnosed or progressive disease of the brain or uncontrolled epilepsy. After control of the disease the vaccine should be administered
- if your child has a bleeding problem or bruises easily
- if your child has a tendency to seizures/fits due to a fever, or if there is a history in the family of this

Using other medicines or vaccines
Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Important information about some of the ingredients of Tritanrix HepB
This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction. Tell your doctor if your child has any known allergies.

3. HOW TRITANRIX HepB IS GIVEN

Your child will receive a total of three injections with an interval of at least one month between each one. Each injection is given on a separate visit. You will be informed by the doctor or nurse when you should come back for subsequent injections.

If additional injections are necessary, the doctor will tell you.

If your child misses a scheduled injection, talk to your doctor and arrange another visit.

Make sure your child finishes the complete vaccination course of three injections. If not, your child may not be fully protected against the diseases.

The doctor will give Tritanrix HepB as an injection into the thigh muscle. Your child will remain under medical supervision for 30 minutes after each injection.

The vaccine should never be given into a vein.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tritanrix HepB can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Tritanrix HepB were as follows:

- Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
  - pain or discomfort at the injection site
  - redness or swelling at the injection site
  - fever (more than 38°C)
  - drowsiness, irritability, unusual crying
  - feeding problems

- Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
  - infection of the middle ear
  - bronchitis
  - sore throat and discomfort when swallowing
  - gastrointestinal symptoms such as vomiting and diarrhoea

- Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
  - pneumonia (serious lung infection)
  - respiratory disorder

- Very rare (side effects which may occur in less than 10,000 doses of vaccine):
  - allergic reactions, including anaphylactic and anaphylactoid reactions. These may be local or widespread rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's surgery. However, you should seek immediate treatment in any event.
  - serum sickness like disease (a hypersensitivity reaction to the administration of a foreign serum with symptoms like fever, swelling, skin rash, enlargement of the lymph nodes)

After the marketing of Tritanrix HepB, the following additional side effects have been reported on a few occasions:

- collapse or periods of unconsciousness or lack of awareness have been reported within 2 to 3 days after vaccination
- in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination

Tritanrix HepB contains a hepatitis B component, to provide protection against disease caused by hepatitis B virus. The following undesirable events have occurred very rarely following the administration of hepatitis B containing vaccines:

- seizures or fits
- bleeding or bruising more easily than normal

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRITANRIX HepB

Keep out of the reach and sight of children.

Do not use Tritanrix HepB after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C)
Store in the original package in order to protect from light.
Do not freeze. Freezing destroys the vaccine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tritanrix HepB contains

- The active substances contained in 1 dose (0.5 ml) are:

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Bordetella pertussis (inactivated)[2]	≥ 4 IU
Hepatitis B surface antigen[2,3]	10 µg

[1] adsorbed on aluminium hydroxide, hydrated 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate 0.37 mg Al^{3+}
[3] produced in yeast cells (*Saccharomyces cerevisiae)* by recombinant DNA technology

- The other ingredients in Tritanrix HepB are: thiomersal, sodium chloride and water for injections.

What Tritanrix HepB looks like and contents of the pack

Suspension for injection.

Tritanrix HepB is a white, slightly milky liquid presented in a glass vial for 1 dose (0.5 ml).

Tritanrix HepB is available in pack of 1.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last approved in
Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

The following information is intended for medical or healthcare professionals only:

Tritanrix HepB can be mixed with the lyophilised Hib vaccine (Hiberix).

Upon storage, a white deposit and clear supernatant can be observed. This does not constitute a sign of deterioration.

The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the container.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Tritanrix HepB suspension for injection, multidose
Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

Read all of this leaflet carefully before your child starts receiving this vaccine.
- Keep this leaflet . You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This vaccine has been prescribed for your child. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Tritanrix HepB is and what it is used for
2. Before your child receives Tritanrix HepB
3. How Tritanrix HepB is given
4. Possible side effects
5. How to store Tritanrix HepB
6. Further information

1. WHAT TRITANRIX HepB IS AND WHAT IT IS USED FOR

Tritanrix HepB is a vaccine used in children to prevent four diseases: diphtheria, tetanus (lockjaw), pertussis (whooping cough) and hepatitis B. The vaccine works by causing the body to produce its own protection (antibodies) against these diseases.

- **Diphtheria**: Diphtheria mainly affects the airways and sometimes the skin. Generally the airways become inflamed (swollen) causing severe breathing difficulties and sometimes suffocation. The bacteria also release a toxin (poison), which can cause nerve damage, heart problems, and even death.

- **Tetanus** (Lockjaw): Tetanus bacteria enter the body through cuts, scratches or wounds in the skin. Wounds that are especially prone to infection are burns, fractures, deep wounds or wounds contaminated with soil, dust, horse manure/dung or wood splinters. The bacteria release a toxin (poison), which can cause muscle stiffness, painful muscle spasms, fits and even death. The muscle spasms can be strong enough to cause bone fractures of the spine.

- **Pertussis** (Whooping cough): Pertussis is a highly infectious illness. The disease affects the airways causing severe spells of coughing that may interfere with normal breathing. The coughing is often accompanied by a "whooping" sound, hence the common name "whooping cough". The cough may last for 1-2 months or longer. Pertussis can also cause ear infections, bronchitis which may last a long time, pneumonia, fits, brain damage and even death.

- **Hepatitis B**: Hepatitis B is caused by the hepatitis B virus. It causes the liver to become inflamed and swollen. The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people.

Vaccination is the best way to protect against these diseases. None of the components in the vaccine are infectious.

2. BEFORE YOUR CHILD RECEIVES TRITANRIX HepB

Tritanrix HepB should not be given:

- if your child has previously had any allergic reaction to Tritanrix HepB, or any ingredient contained in this vaccine. The active substances and other ingredients in Tritanrix HepB are listed at the end of the leaflet. Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.
- if your child has previously had an allergic reaction to any vaccine against diphtheria, tetanus, pertussis (whooping cough) or hepatitis B diseases.
- if your child experienced problems of the nervous system within 7 days after previous vaccination with a vaccine against pertussis (whooping cough) disease.
- if your child has a severe infection with a high temperature (over 38°C). A minor infection such as a cold should not be a problem, but talk to your doctor first.

Take special care with Tritanrix HepB:

- if your child has experienced any health problems after previous administration of a vaccine.
- if after previously having Tritanrix HepB or another vaccine against pertussis (whooping cough) disease, your child had any problems, especially:
  - ♦ A high temperature (over 40°C) within 48 hours of vaccination
  - ♦ A collapse or shock-like state within 48 hours of vaccination
  - ♦ Persistent crying lasting 3 hours or more within 48 hours of vaccination
  - ♦ Seizures/fits with or without a high temperature within 3 days of vaccination
- if your child is suffering from an undiagnosed or progressive disease of the brain or uncontrolled epilepsy. After control of the disease the vaccine should be administered
- if your child has a bleeding problem or bruises easily
- if your child has a tendency to seizures/fits due to a fever, or if there is a history in the family of this

Using other medicines or vaccines
Please tell your doctor if your child is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

Important information about some of the ingredients of Tritanrix HepB
This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction. Tell your doctor if your child has any known allergies.

3. HOW TRITANRIX HepB IS GIVEN

Your child will receive a total of three injections with an interval of at least one month between each one. Each injection is given on a separate visit. You will be informed by the doctor or nurse when you should come back for subsequent injections.

If additional injections are necessary, the doctor will tell you.

If your child misses a scheduled injection, talk to your doctor and arrange another visit.

Make sure your child finishes the complete vaccination course of three injections. If not, your child may not be fully protected against the diseases.

The doctor will give Tritanrix HepB as an injection into the thigh muscle. Your child will remain under medical supervision for 30 minutes after each injection.

The vaccine should never be given into a vein.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Tritanrix HepB can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Tritanrix HepB were as follows:

- Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
  - pain or discomfort at the injection site
  - redness or swelling at the injection site
  - fever (more than 38°C)
  - drowsiness, irritability, unusual crying
  - feeding problems

- Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
  - infection of the middle ear
  - bronchitis
  - sore throat and discomfort when swallowing
  - gastrointestinal symptoms such as vomiting and diarrhoea

- Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
  - pneumonia (serious lung infection)
  - respiratory disorder

- Very rare (side effects which may occur in less than 10,000 doses of vaccine):
  - allergic reactions, including anaphylactic and anaphylactoid reactions. These may be local or widespread rashes that may be itchy or blistering, swelling of the eyes and face, difficulty in breathing or swallowing, a sudden drop in blood pressure and loss of consciousness. Such reactions may occur before leaving the doctor's surgery. However, you should seek immediate treatment in any event.
  - serum sickness like disease (a hypersensitivity reaction to the administration of a foreign serum with symptoms like fever, swelling, skin rash, enlargement of the lymph nodes)

After the marketing of Tritanrix HepB, the following additional side effects have been reported on a few occasions:

- collapse or periods of unconsciousness or lack of awareness have been reported within 2 to 3 days after vaccination
- in babies born very prematurely (at or before 28 weeks of gestation) longer gaps than normal between breaths may occur for 2-3 days after vaccination

Tritanrix HepB contains a hepatitis B component, to provide protection against disease caused by hepatitis B virus. The following undesirable events have occurred very rarely following the administration of hepatitis B containing vaccines:

- seizures or fits
- bleeding or bruising more easily than normal

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRITANRIX HepB

Keep out of the reach and sight of children.

Do not use Tritanrix HepB after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C)
Store in the original package in order to protect from light.
Do not freeze. Freezing destroys the vaccine.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Tritanrix HepB contains

- The active substances contained in 1 dose (0.5 ml) are:

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Bordetella pertussis (inactivated)[2]	≥ 4 IU
Hepatitis B surface antigen[2,3]	10 µg

[1] adsorbed on aluminium hydroxide, hydrated 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate 0.37 mg Al^{3+}
[3] produced in yeast cells (*Saccharomyces cerevisiae)* by recombinant DNA technology

- The other ingredients in Tritanrix HepB are: thiomersal, sodium chloride and water for injections.

What Tritanrix HepB looks like and contents of the pack

Suspension for injection, multidose.

Tritanrix HepB is a white, slightly milky liquid presented in a glass vial for 2 doses (1 ml) or in a glass vial for 10 doses (5 ml).

Tritanrix HepB is available in the following pack sizes:
For 2 doses: pack size of 1
For 10 doses: pack size of 1

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

The following information is intended for medical or healthcare professionals only:

Tritanrix HepB can be mixed with the lyophilised Hib vaccine (Hiberix).

Upon storage, a white deposit and clear supernatant can be observed. This does not constitute a sign of deterioration.

The vaccine should be well shaken in order to obtain a homogeneous turbid white suspension and be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the container.

When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.