ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quintanrix powder and suspension for suspension for injection
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units
Tetanus toxoid[1]	not less than 60 International Units
Inactivated *Bordetella pertussis* [2]	not less than 4 International Units
Hepatitis B surface antigen (rDNA) [2, 3]	10 micrograms
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 micrograms
conjugated to tetanus toxoid as a carrier	5-10 micrograms

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 milligrams Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 milligrams Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection
The liquid diphtheria, tetanus, pertussis (whole cell), hepatitis B (DTPw-HBV) component is a turbid white suspension.
The lyophilised *Haemophilus influenzae* type b (HIB) component is a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quintanrix is indicated for primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B and invasive disease caused by *Haemophilus influenzae* type b and for booster immunisation of young children during the second year of life.

The use of Quintanrix should be determined on the basis of official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination:

The primary vaccination schedule consists of three doses of 0.5 ml to be administered at intervals of at least 4 weeks within the first six months of life in accordance with local official recommendations. The first dose can be administered at 6 weeks of age. The following schedules have been studied in clinical trials: 2-4-6 months, 3-4-5 months and 6-10-14 weeks. The 3-5-12 month schedule was not evaluated.

Quintanrix can be given to children who have received hepatitis B vaccine at birth.

The immunoprophylactic measures for hepatitis B should not be modified for children born to hepatitis B virus carrying mothers. This may require separate administration of hepatitis B vaccine and should follow official recommendations.

Booster vaccination:

After the completion of the primary series, a booster should be administered preferably before the end of the second year of life. Booster administration should be in accordance with official recommendations.

Quintanrix may be used to boost responses to DTP, HBV and HIB antigens if its composition is in accordance with official recommendations for boosting. The booster dose should preferably be given at least 6 months after the last primary dose.

Method of administration

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

4.3 Contraindications

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

Quintanrix is contra-indicated 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 diphtheria, tetanus, hepatitis B and HIB vaccines.

As with other vaccines, the administration of Quintanrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, is not a contraindication for vaccination.

4.4 Special warnings and special precautions for use

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for at least 30 minutes.

If any of the following events occur in temporal relation to receipt of Quintanrix, the decision to give subsequent doses of a 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.

Quintanrix should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. A fine needle can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least two minutes following administration.

Quintanrix should under no circumstances be administered intravascularly.

The vaccine will not prevent infection caused by other pathogens known to infect the liver such as hepatitis A, hepatitis C and hepatitis E virus.

The HIB component of the vaccine does not protect against diseases due to capsular serotypes other than type b of *Haemophilus influenzae* or against meningitis caused by other organisms.

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute a contraindication for the use of Quintanrix. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

HIV infection is not considered as a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the capsular polysaccharide antigen is excreted in the urine a positive urine antigen test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm HIB infection during this period.

Antipyretic treatment should be initiated according to local treatment guidelines.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering 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 the 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

In paediatric vaccination it is often practice to co-administer different injectable vaccines at separate injection sites, during the same session.

Limited data show that there is no interference with the response to Measles-Mumps-Rubella (MMR) and OPV antigens. Although no data are available on the immune response to the Bacille-Calmette-Guérin (BCG) antigen, no interference is expected.

As with other vaccines it may be expected that an adequate response may not be achieved in patients receiving immunosuppressive therapy or patients with immunodeficiency.

4.6 Pregnancy and lactation

As Quintanrix 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

Quintanrix was administered to approximately 1,340 healthy infants from 6 weeks of age as a primary vaccination course in several clinical trials.

In these trials, the most common reactions occurring after vaccine administration were pain at the site of injection, fever (axillary ≥ 37.5°C; rectal ≥ 38°C) and irritability, which were associated with about 50% of the doses administered.

Adverse reactions are listed below.

Frequencies are reported as:
Very common: (>1/10)
Common: (>1/100, <1/10)
Uncommon: (>1/1,000, <1/100)
Rare: (>1/10,000, <1/1,000)
Very rare: (<1/10,000) including isolated reports

Psychiatric disorders:
very common: irritability

Nervous system disorders:
very common: drowsiness
rare: collapse or shock-like state (hypotonic-hyporesponsiveness episode), convulsions

Respiratory, thoracic and mediastinal disorders
rare: bronchitis, coughing

Gastrointestinal disorders:
very common: loss of appetite
rare: vomiting

General disorders and administration site conditions:
very common: pain, redness and swelling, fever (axillary ≥ 37.5°C; rectal ≥ 38°C)
common: induration, fever (axillary > 39°C; rectal > 39.5°C)

Quintanrix was administered as a booster to 435 infants in the second year of life. As shown with other vaccines, the booster dose is potentially associated with an increased incidence of minor adverse events such as fever and local reactions.

Adverse reactions reported after booster vaccination are listed below.

Psychiatric disorders
very common: irritability

Nervous system disorders:
very common: drowsiness

Gastrointestinal disorders:
very common: loss of appetite

General disorders and administration site conditions:
very common: pain, redness and swelling, fever (axillary ≥ 37.5°C; rectal ≥ 38°C)
common: fever (axillary > 39°C; rectal > 39.5°C)
uncommon: induration

Allergic reactions, including anaphylactoid reactions and urticaria, have been reported very rarely following vaccination with DTP, hepatitis B and HIB containing vaccines.

During post marketing surveillance studies with other hepatitis B containing vaccines, serum sickness like disease and thrombocytopenia have been reported very rarely.

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).

Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code JO7CA10

5.1 Pharmacodynamic properties

The immune response after a three-dose primary vaccination course was evaluated in five trials: 297 infants were evaluated after vaccination at 6, 10 and 14 weeks of age, 685 after vaccination at 2, 4, and 6 months of age and 107 after vaccination at 3, 4 and 5 months of age. Results from different studies show that, overall, 95.5% and 99.9% of subjects had anti-diphtheria and anti-tetanus titres ≥ 0.1 IU/ml one month after completion of the primary vaccination course. At this time, the percentage of infants with anti-PRP titres ≥ 0.15 µg/ml was > 99% and the percentage with anti-HBs titres ≥ 10 mIU/ml was 97.3%. More than 99% of subjects were considered to have responded to the pertussis component of the vaccine, which was defined as the appearance of antibodies in initially seronegative subjects (i.e. subjects with pre-vaccination titres < 15 ELU/ml) or a post-vaccination titre at least equal to pre-vaccination levels in subjects initially seropositive due to maternally-derived antibodies.

Seroprotection and vaccine response rates were similar for the three schedules used, with the exception of anti-HBs. The seroprotection rates for anti-HBs (≥10 mIU/ml) observed with the 6, 10, 14 week schedule was lower as shown in the table below, but is unlikely to be clinically relevant due to the small sample size:

2, 4, 6 months schedule N = 672	3, 4, 5 months schedule N = 107	6, 10, 14 weeks schedule N = 97
98.9%	95.3%	92.8%

Limited information exists on the persistence of the immune response after primary vaccination with Quintanrix as well as on the immunogenicity of booster doses. Results from one pilot study showed that, for 63 infants primed according to a 6, 10, 14 week schedule, > 80% still had antibodies to diphtheria, tetanus, HBs and PRP at levels considered to be protective. Forty-one percent had antibodies to pertussis. Data from clinical trials show that Quintanrix, when given as a booster dose in the second year of life, induces a greater than 10-fold increase in mean antibody titre with respect to prebooster levels for all vaccine components.

It can be expected that hepatitis D will also be prevented by immunisation with Quintanrix as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety testing with the vaccine has been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilised HIB component:
Lactose

Liquid DTPw-HBV component:
Thiomersal
Sodium chloride
Water for injections.

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, the reconstituted Quintanrix vaccine must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution, it is recommended to inject the vaccine promptly. However the stability has been demonstrated for 8 hours at 25°C after reconstitution.

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

Powder in a vial (type I glass) for 1 dose with a stopper (rubber butyl).
0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (rubber butyl)
in the following pack sizes:
- pack size of 1 vial of powder plus 1 vial of suspension
- pack size of 100 vials of powder plus 100 vials of suspension

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Upon storage, a white deposit and clear supernatant may be observed for the DTPw-HBV component. This does not constitute a sign of deterioration.

The DTPw-HBV component should be well shaken in order to obtain a homogeneous turbid white suspension and should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

The vaccine is reconstituted by withdrawing the contents of the vial containing the DTPw-HBV component by means of a syringe and by adding it to the vial containing the HIB powder. After the addition of the DTPw-HBV component to the HIB powder, the mixture should be well shaken until

the powder is completely dissolved. The reconstituted vaccine is a homogeneous turbid white suspension.

Remove and discard the needle used for reconstitution and replace it with a second needle to administer the vaccine. After reconstitution, the vaccine should be injected promptly.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/301/001
EU/1/04/301/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2005

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Quintanrix powder and suspension for suspension for injection, multidose
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units
Tetanus toxoid[1]	not less than 60 International Units
Inactivated *Bordetella pertussis* [2]	not less than 4 International Units
Hepatitis B surface antigen (rDNA) [2, 3]	10 micrograms
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 micrograms
conjugated to tetanus toxoid as a carrier	5-10 micrograms

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 milligrams Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 milligrams Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

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

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection
The liquid diphtheria, tetanus, pertussis (whole cell), hepatitis B (DTPw-HBV) component is a turbid white suspension.
The lyophilised *Haemophilus influenzae* type b (HIB) component is a white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quintanrix is indicated for primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B and invasive disease caused by *Haemophilus influenzae* type b and for booster immunisation of young children during the second year of life.

The use of Quintanrix should be determined on the basis of official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination:

The primary vaccination schedule consists of three doses of 0.5 ml to be administered at intervals of at least 4 weeks within the first six months of life in accordance with local official recommendations. The first dose can be administered at 6 weeks of age. The following schedules have been studied in

clinical trials: 2-4-6 months, 3-4-5 months and 6-10-14 weeks. The 3-5-12 month schedule was not evaluated.

Quintanrix can be given to children who have received hepatitis B vaccine at birth.

The immunoprophylactic measures for hepatitis B should not be modified for children born to hepatitis B virus carrying mothers. This may require separate administration of hepatitis B vaccine and should follow official recommendations.

Booster vaccination:

After the completion of the primary series, a booster should be administered preferably before the end of the second year of life. Booster administration should be in accordance with official recommendations.

Quintanrix may be used to boost responses to DTP, HBV and HIB antigens if its composition is in accordance with official recommendations for boosting. The booster dose should preferably be given at least 6 months after the last primary dose.

Method of administration

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

4.3 Contraindications

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

Quintanrix is contra-indicated 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 diphtheria, tetanus, hepatitis B and HIB vaccines.

As with other vaccines, the administration of Quintanrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, is not a contraindication for vaccination.

4.4 Special warnings and special precautions for use

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events).

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for at least 30 minutes.

If any of the following events occur in temporal relation to receipt of Quintanrix, the decision to give subsequent doses of a 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.

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

fine needle can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least two minutes following administration.

Quintanrix should under no circumstances be administered intravascularly.

The vaccine will not prevent infection caused by other pathogens known to infect the liver such as hepatitis A, hepatitis C and hepatitis E virus.

The HIB component of the vaccine does not protect against diseases due to capsular serotypes other than type b of *Haemophilus influenzae* or against meningitis caused by other organisms.

A history of febrile convulsions,a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute a contraindication for the use of Quintanrix. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

HIV infection is not considered as a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the capsular polysaccharide antigen is excreted in the urine a positive urine antigen test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm HIB infection during this period.

Antipyretic treatment should be initiated according to local treatment guidelines.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering 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 the 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

In paediatric vaccination it is often practice to co-administer different injectable vaccines at separate injection sites, during the same session.

Limited data show that there is no interference with the response to Measles-Mumps-Rubella (MMR) and OPV antigens. Although no data are available on the immune response to the Bacille-Calmette-Guérin (BCG) antigen, no interference is expected.

As with other vaccines it may be expected that an adequate response may not be achieved in patients receiving immunosuppressive therapy or patients with immunodeficiency.

4.6 Pregnancy and lactation

As Quintanrix 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

Quintanrix was administered to approximately 1,340 healthy infants from 6 weeks of age as a primary vaccination course in several clinical trials.

In these trials, the most common reactions occurring after vaccine administration were pain at the site of injection, fever (axillary ≥ 37.5°C; rectal ≥ 38°C) and irritability, which were associated with about 50% of the doses administered.

Adverse reactions are listed below.

Frequencies are reported as:
Very common: (>1/10)
Common: (>1/100, <1/10)
Uncommon: (>1/1,000, <1/100)
Rare: (>1/10,000, <1/1,000)
Very rare: (<1/10,000) including isolated reports

Psychiatric disorders:
very common: irritability

Nervous system disorders:
very common: drowsiness
rare: collapse or shock-like state (hypotonic-hyporesponsiveness episode), convulsions

Respiratory, thoracic and mediastinal disorders
rare: bronchitis, coughing

Gastrointestinal disorders:
very common: loss of appetite
rare: vomiting

General disorders and administration site conditions:
very common: pain, redness and swelling, fever (axillary ≥ 37.5°C; rectal ≥ 38°C)
common: induration, fever (axillary > 39°C; rectal > 39.5°C)

Quintanrix was administered as a booster to 435 infants in the second year of life. As shown with other vaccines, the booster dose is potentially associated with an increased incidence of minor adverse events such as fever and local reactions.

Adverse reactions reported after booster vaccination are listed below.

Psychiatric disorders
very common: irritability

Nervous system disorders:
very common: drowsiness

Gastrointestinal disorders:
very common: loss of appetite

General disorders and administration site conditions:
very common: pain, redness and swelling, fever (axillary ≥ 37.5°C; rectal ≥ 38°C)
common: fever (axillary > 39°C; rectal > 39.5°C)
uncommon: induration

Allergic reactions, including anaphylactoid reactions and urticaria, have been reported very rarely following vaccination with DTP, hepatitis B and HIB containing vaccines.

During post marketing surveillance studies with other hepatitis B containing vaccines, serum sickness like disease and thrombocytopenia have been reported very rarely.

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).

Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code JO7CA10

5.1 Pharmacodynamic properties

The immune response after a three-dose primary vaccination course was evaluated in five trials: 297 infants were evaluated after vaccination at 6, 10 and 14 weeks of age, 685 after vaccination at 2, 4, and 6 months of age and 107 after vaccination at 3, 4 and 5 months of age. Results from different studies show that, overall, 95.5% and 99.9% of subjects had anti-diphtheria and anti-tetanus titres ≥ 0.1 IU/ml one month after completion of the primary vaccination course. At this time, the percentage of infants with anti-PRP titres ≥ 0.15 µg/ml was > 99% and the percentage with anti-HBs titres ≥ 10 mIU/ml was 97.3%. More than 99% of subjects were considered to have responded to the pertussis component of the vaccine , which was defined as the appearance of antibodies in initially seronegative subjects (i.e. subjects with pre-vaccination titres < 15 ELU/ml) or a post-vaccination titre at least equal to pre-vaccination levels in subjects initially seropositive due to maternally-derived antibodies.

Seroprotection and vaccine response rates were similar for the three schedules used, with the exception of anti-HBs. The seroprotection rates for anti-HBs (≥10 mIU/ml) observed with the 6, 10, 14 week schedule was lower as shown in the table below, but is unlikely to be clinically relevant due to the small sample size:

2, 4, 6 months schedule N = 672	3, 4, 5 months schedule N = 107	6, 10, 14 weeks schedule N = 97
98.9%	95.3%	92.8%

Limited information exists on the persistence of the immune response after primary vaccination with Quintanrix as well as on the immunogenicity of booster doses. Results from one pilot study showed that, for 63 infants primed according to a 6, 10, 14 week schedule, > 80% still had antibodies to diphtheria, tetanus, HBs and PRP at levels considered to be protective. Forty-one percent had antibodies to pertussis. Data from clinical trials show that Quintanrix, when given as a booster dose in the second year of life, induces a greater than 10-fold increase in mean antibody titre with respect to prebooster levels for all vaccine components.

It can be expected that hepatitis D will also be prevented by immunisation with Quintanrix as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

No preclinical safety testing with the vaccine has been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilised HIB component:
Lactose

Liquid DTPw-HBV component:
Thiomersal
Sodium chloride
Water for injections.

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, the reconstituted Quintanrix vaccine must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

After reconstitution,it is recommended to inject the vaccine promptly. However the stability has been demonstrated for 8 hours at 25°C after reconstitution.

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

Powder in a vial (type I glass) for 2 doses with a stopper (rubber butyl).
1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl)
in the following pack sizes:
- pack size of 1 vial of powder plus 1 vial of suspension
- pack size of 100 vials of powder plus 100 vials of suspension.

Powder in a vial (type I glass) for 10 doses with a stopper (rubber butyl).
5 ml of suspension in a vial (type I glass) for 10 doses with a stopper (rubber butyl)
in a pack size of 50 vials of powder plus 50 vials of suspension.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Upon storage, a white deposit and clear supernatant may be observed for the DTPw-HBV component. This does not constitute a sign of deterioration.

The DTPw-HBV component should be well shaken in order to obtain a homogeneous turbid white suspension and should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

The vaccine is reconstituted by withdrawing the contents of the vial containing the DTPw-HBV component by means of a syringe and by adding it to the vial containing the HIB powder. After the addition of the DTPw-HBV component to the HIB powder, the mixture should be well shaken until the powder is completely dissolved. The reconstituted vaccine is a homogeneous turbid white suspension.

Remove and discard the needle used for reconstitution and replace it with a second needle to administer the vaccine. After reconstitution, the vaccine should be injected promptly.

When using a multidose vial, each 0.5 ml dose of the reconstituted suspension 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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/301/003
EU/1/04/301/004
EU/1/04/301/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2005

10. DATE OF REVISION OF THE TEXT

ANNEX II

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Name and address of the manufacturer of the biological active substances

Diphtheria toxoid, tetanus toxoid, pertussis (whole cell):

Chiron-Behring GmbH & Co.
Postfach 1630-35006 Marburg
Germany
Tel: +49 6421 39 29 17
Fax: +49 6421 39 47 20

Haemophilus influenzae type b polysaccharide

GlaxoSmithKline Biologicals S.A.
2100 Gödöllö, Táncsics Mihály út 82
Hungary
Tel: +36 28 511 960
Fax:+ 36 28 511 999

GlaxoSmithKline Biologicals S.A.
89 rue de I'Institut-1330 Rixensart
Belgium
Tel: +32 2 656 81 11
Fax:+32 2 656 80 00

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89 rue de I'Institut-1330 Rixensart
Belgium
Tel: +32 2 656 81 11
Fax:+32 2 656 80 00

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

Official batch release: in accordance with Article 114 of Directive 2001/83/EC, 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 FOR MONODOSE PRESENTATIONS

1. NAME OF THE MEDICINAL PRODUCT

Quintanrix powder and suspension for suspension for injection
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Inactivated *Bordetella pertussis* [2]	≥ 4 IU
Hepatitis B surface antigen (rDNA) [2, 3]	10 µg
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2] conjugated to tetanus toxoid as a carrier	2.5 µg 5-10 µg

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 mg Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

3. LIST OF EXCIPIENTS

Lactose
Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection
1 Vial: Powder
1 Vial: Suspension
1 dose (0.5 ml)
100 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

intramuscular use
Shake well 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

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/1/04/301/001
EU/1/04/301/002

13. MANUFACTURER'S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING FOR MULTIDOSE PRESENTATIONS

1. NAME OF THE MEDICINAL PRODUCT

Quintanrix powder and suspension for suspension for injection, multidose
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Inactivated *Bordetella pertussis* [2]	≥ 4 IU
Hepatitis B surface antigen (rDNA) [2, 3]	10 µg
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 µg
conjugated to tetanus toxoid as a carrier	5-10 µg

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 mg Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

3. LIST OF EXCIPIENTS

Lactose
Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection
1 Vial: Powder
1 Vial: Suspension
2 doses (1 ml)
100 x 2 doses (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

intramuscular use
Shake well 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

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/1/04/301/003
EU/1/04/301/004

13. MANUFACTURER'S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING FOR MULTIDOSE PRESENTATIONS

1. NAME OF THE MEDICINAL PRODUCT

Quintanrix powder and suspension for suspension for injection, multidose
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	≥ 30 IU
Tetanus toxoid[1]	≥ 60 IU
Inactivated *Bordetella pertussis* [2]	≥ 4 IU
Hepatitis B surface antigen (rDNA) [2, 3]	10 µg
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 µg
conjugated to tetanus toxoid as a carrier	5-10 µg

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 mg Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 mg Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

3. LIST OF EXCIPIENTS

Lactose
Thiomersal
Sodium chloride
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and suspension for suspension for injection
1 Vial: Powder
1 Vial: Suspension
50 x 10 doses (5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

intramuscular use
Shake well 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

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/1/04/301/005

13. MANUFACTURER'S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MONODOSE PRESENTATIONS

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

DTPw HBV for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MONODOSE PRESENTATIONS

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

HIB for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MULTIDOSE PRESENTATIONS

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

DTPw HBV for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 ml)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MULTIDOSE PRESENTATIONS

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

HIB for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MULTIDOSE PRESENTATIONS

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

DTPw HBV for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses (5 ml)

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS FOR MULTIDOSE PRESENTATIONS

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

HIB for Quintanrix
I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 doses

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before your child starts receiving this medicine.
- Keep this leaflet until your child has finished the complete vaccination course. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for your child and should not be passed on to others.

In this leaflet:

Quintanrix powder and suspension for suspension for injection
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

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

Diphtheria toxoid[1]	not less than 30 International Units
Tetanus toxoid[1]	not less than 60 International Units
Inactivated *Bordetella pertussis* [2]	not less than 4 International Units
Hepatitis B surface antigen (rDNA) [2, 3]	10 micrograms
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 micrograms
conjugated to tetanus toxoid as a carrier	5-10 micrograms

[1] adsorbed on aluminium hydroxide, hydrated	Total: 0.26 milligrams Al^{3+}
[2]adsorbed on aluminium phosphate	Total: 0.40 milligrams Al^{3+}

[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

- The other ingredients in the vaccine are: lactose, thiomersal (preservative), sodium chloride and water for injections.

Marketing authorisation holder and Manufacturer: GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

1. WHAT QUINTANRIX IS AND WHAT IT IS USED FOR

Quintanrix is a white slightly milky liquid obtained by mixing the vial containing the diphtheria (D), tetanus (T), whole cell pertussis (Pw) and hepatitis B (HBV) liquid (DTPw-HBV) with the vial containing the *Haemophilus influenzae* type b (HIB) powder. Both components are presented in a glass vial for 1 dose and must be mixed together before your child receives the vaccine.

Quintanrix is available in the following pack sizes:
- pack size of 1 vial of powder plus 1 vial of liquid
- pack size of 100 vials of powder plus 100 vials of liquid.

Not all pack sizes may be marketed.

Quintanrix is a vaccine used in children to prevent five infectious diseases: diphtheria, tetanus (lockjaw), pertussis (whooping cough), hepatitis B and *Haemophilus influenzae* type b (a type of bacteria). The vaccine works by causing the body to produce its own protection (antibodies) against these infectious 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**: Infection with the hepatitis B virus may cause the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people. Signs of the disease may not be seen for 6 weeks to 6 months after infection. Sometimes people who have been infected do not look or feel ill. Others have signs of mild flu, but some people can become very ill. They may be extremely tired, and have dark urine, pale faces, yellowish skin and/or eyes (jaundice), and other signs of the disease possibly requiring hospitalisation.

  Most adults fully recover from the disease. But some people, particularly children, who may not have shown signs of the disease can remain infected. They are called hepatitis B virus carriers. Hepatitis B carriers can infect others throughout their lives. Hepatitis B carriers are at risk of serious liver disease, such as cirrhosis (liver scarring) and liver cancer.

- ***Haemophilus influenzae* type b (HIB)**: HIB infection most frequently causes brain inflammation (swelling). There will be some type of serious complications such as: mental retardation, cerebral palsy, deafness, epilepsy or partial blindness. HIB infection also causes inflammation of the throat. It occasionally causes death by suffocation. Less commonly, the bacteria can also infect the blood, heart, lungs, bones, joints, and tissues of the eyes and mouth.

Vaccination is the best way to protect against these diseases. The vaccine cannot cause diphtheria, tetanus (lockjaw), pertussis (whooping cough), hepatitis B or *Haemophilus influenzae* type b infections.

The hepatitis B and *Haemophilus influenzae* type b components of Quintanrix can only help to protect your child against infections with hepatitis B or *Haemophilus influenzae* type b viruses. It cannot protect your child against other infections that can affect the liver or against infections due to other bacteria than *Haemophilus influenzae* type b or against meningitis caused by other organisms.

2. BEFORE YOUR CHILD RECEIVES QUINTANRIX

In the following cases, Quintanrix should not be given to your child. You must tell your doctor:

- if your child has experienced any health problems after previous administration of a vaccine.

- if your child has previously had any allergic reaction to Quintanrix, or any ingredient contained in this vaccine. The active substances and other ingredients in Quintanrix are listed at the beginning 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), hepatitis B or *Haemophilus influenzae* type b diseases.
- if your child experienced problems of the nervous system (such as repetitive fits, decrease of consciousness) 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). In these cases, the vaccination will be postponed until your child has recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- if your child has any known allergies.

In the following cases, your doctor can determine the right time and scheme of vaccination for your child. Tell your doctor:

- if after previously having Quintanrix 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 (floppiness) 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 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
- if your child is taking any other medicine or has recently received any other vaccine. Your doctor will be able to tell you what to do if Quintanrix is to be given with another vaccine or medicine.

Important information about some of the ingredients of Quintanrix

This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction. Tell you doctor if your child has any known allergies.

3. HOW QUINTANRIX 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. The first injection can be given from the age of 6 weeks onwards. You will be informed by the doctor or nurse when you should come back for subsequent injections.
The doctor or nurse will give Quintanrix as an injection into the muscle.

Your doctor will advise on the possible need for extra doses.

If your child misses the visit scheduled for the second or third injection, talk to your doctor and arrange another visit as soon as possible.

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 vaccine should never be given into a vein.

4. POSSIBLE SIDE EFFECTS

Any vaccine can have some side effects.

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

- **Very common** (more than 1 per 10 doses of vaccine):
  - Pain, redness or swelling at the injection site
  - Fever (more than 37.5°C)
  - Irritability
  - Loss of appetite
  - Drowsiness

- **Common** (less than 1 per 10 but more than 1 per 100 doses of vaccine):
  - Induration (hard lump)
  - Fever (more than 39°C)

- **Rare** (less than 1 per 1000 but more than 1 per 10 000 doses of vaccine):
  - Bronchitis
  - Coughing
  - Vomiting
  - Collapse (floppiness) or periods of unconsciousness or lack of awareness
  - Fits

Bleeding or bruising more easily than normal due to a drop in a type of blood cell called platelets have been reported very rarely (less than 1 per 10,000 doses of vaccine) with the hepatitis B component of Quintanrix.

As with all injectable vaccines, there is an extremely small risk of allergic 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.

If these events continue or become severe, tell your doctor.

This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Do not be alarmed by this list of possible side effects. It is possible that your child will have no side effects from vaccination.

5. STORING QUINTANRIX

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.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the pack. The date for last use corresponds to the last day of the month mentioned.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

Luxembourg/Luxemburg
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

България
ГлаксоСмитКлайн ЕООД
ул. Димитър Манов бл.10
София 1408
Тел. + 359 2 953 10 34

Magyarország
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

Malta
GlaxoSmithKline Malta
Tel: + 356 21 225736

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Eesti
GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Österreich
GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Ελλάδα
Allen Φαρμακευτική Α.Ε
Τηλ: + 30 210 68 82 100

Polska
GlaxoSmithKline Pharmaceuticals S.A.
Tel.: + 48 (22) 576 9000

España
GlaxoSmithKline S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

Portugal
Smith Kline & French Portuguesa, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 1 39 17 84 44
diam@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Ireland
GlaxoSmithKline (Ireland) Ltd
Tel: + 353 (0)1 4955000

Slovenija
GlaxoSmithKline d.o.o.
Tel: + 386 1 280 25 00
gqq41253@glaxowellcome.co.uk

Ísland
GlaxoSmithKline ehf.
Tel: +354-530 3700

Italia
GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος
GlaxoSmithKline Cyprus Ltd
Τηλ: + 357 22 89 95 01

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 7312687
lv-epasts@gsk.com

Lietuva
GlaxoSmithKline Lietuva UAB
Tel. +370 264 90 00
info.lt@gsk.com

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 49 10 33 11
recepcia.sk@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 31 67 09 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

This leaflet was last approved on:

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

Upon storage, a white deposit and clear supernatant may be observed for the DTPw-HBV component. This does not constitute a sign of deterioration.

The DTPw-HBV component should be well shaken in order to obtain a homogeneous turbid white suspension and should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

The vaccine is reconstituted by withdrawing the contents of the vial containing the DTPw-HBV component by means of a syringe and by adding it to the vial containing the HIB powder. After the addition of the DTPw-HBV component to the HIB powder, the mixture should be well shaken until the powder is completely dissolved. The reconstituted vaccine is a homogeneous turbid white suspension.

Remove and discard the needle used for reconstitution and replace it with a second needle to administer the vaccine. After reconstitution, the vaccine should be injected promptly.

Quintanrix should not be given to subjects with hypersensitivity to the active substances or to any of the excipients.

Quintanrix is contra-indicated 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 diphtheria, tetanus, hepatitis B and HIB vaccines.

As with other vaccines, the administration of Quintanrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, is not a contraindication for vaccination.

If any of the following events occur in temporal relation to receipt of Quintanrix, the decision to give subsequent doses of a 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 with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

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

Quintanrix should under no circumstances be administered intravascularly.

PACKAGE LEAFLET

Read all of this leaflet carefully before your child starts receiving this medicine.
- Keep this leaflet until your child has finished the complete vaccination course. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for your child and should not be passed on to others.

In this leaflet:

Quintanrix powder and suspension for suspension for injection, multidose
Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (adsorbed)

- The active substances contained in 1 doses (0.5 ml) of Quintanrix are:

Diphtheria toxoid[1]	not less than 30 International Units
Tetanus toxoid[1]	not less than 60 International Units
Inactivated *Bordetella pertussis* [2]	not less than 4 International Units
Hepatitis B surface antigen (rDNA) [2, 3]	10 micrograms
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 micrograms
conjugated to tetanus toxoid as a carrier	5-10 micrograms

[1] adsorbed on aluminium hydroxide, hydrated — Total: 0.26 milligrams Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 milligrams Al^{3+}
[3] produced in *Saccharomyces cerevisae* cells by recombinant DNA technology

- The other ingredients in the vaccine are: lactose, thiomersal (preservative), sodium chloride and water for injections.

Marketing authorisation holder and Manufacturer: GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart
Belgium

1. WHAT QUINTANRIX IS AND WHAT IT IS USED FOR

Quintanrix is a white slightly milky liquid obtained by mixing the vial containing the diphtheria (D), tetanus (T), whole cell pertussis (Pw) and hepatitis B (HBV) liquid (DTPw-HBV) with the vial containing the *Haemophilus influenzae* type b (HIB) powder. Both components are presented in a glass vial for 2 doses or for 10 doses and must be mixed together before your child receives the vaccine.

Quintanrix is available in the following pack sizes:

For 2 doses :
- pack size of 1 vial of powder plus 1 vial of liquid
- pack size of 100 vials of powder plus 100 vials of liquid

For 10 doses:
- pack size of 50 vials of powder plus 50 vials of liquid

Not all pack sizes may be marketed.

Quintanrix is a vaccine used in children to prevent five infectious diseases: diphtheria, tetanus (lockjaw), pertussis (whooping cough), hepatitis B and *Haemophilus influenzae* type b (a type of bacteria). The vaccine works by causing the body to produce its own protection (antibodies) against these infectious 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**: Infection with the hepatitis B virus may cause the liver to become swollen (inflamed). The virus is found in body fluids such as blood, semen, vaginal secretions, or saliva (spit) of infected people. Signs of the disease may not be seen for 6 weeks to 6 months after infection. Sometimes people who have been infected do not look or feel ill. Others have signs of mild flu, but some people can become very ill. They may be extremely tired, and have dark urine, pale faces, yellowish skin and/or eyes (jaundice), and other signs of the disease possibly requiring hospitalisation.

  Most adults fully recover from the disease. But some people, particularly children, who may not have shown signs of the disease can remain infected. They are called hepatitis B virus carriers. Hepatitis B carriers can infect others throughout their lives. Hepatitis B carriers are at risk of serious liver disease, such as cirrhosis (liver scarring) and liver cancer.

- ***Haemophilus influenzae* type b (HIB)**: HIB infection most frequently causes brain inflammation (swelling). There will be some type of serious complications such as: mental retardation, cerebral palsy, deafness, epilepsy or partial blindness. HIB infection also causes inflammation of the throat. It occasionally causes death by suffocation. Less commonly, the bacteria can also infect the blood, heart, lungs, bones, joints, and tissues of the eyes and mouth.

Vaccination is the best way to protect against these diseases. The vaccine cannot cause diphtheria, tetanus (lockjaw), pertussis (whooping cough), hepatitis B or *Haemophilus influenzae* type b infections.

The hepatitis B and *Haemophilus influenzae* type b components of Quintanrix can only help to protect your child against infections with hepatitis B or *Haemophilus influenzae* type b viruses. It cannot protect your child against other infections that can affect the liver or against infections due to other bacteria than *Haemophilus influenzae* type b or against meningitis caused by other organisms.

2. BEFORE YOUR CHILD RECEIVES QUINTANRIX

In the following cases, Quintanrix should not be given to your child. You must tell your doctor:

- if your child has experienced any health problems after previous administration of a vaccine.
- if your child has previously had any allergic reaction to Quintanrix, or any ingredient contained in this vaccine. The active substances and other ingredients in Quintanrix are listed at the beginning 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), hepatitis B or *Haemophilus influenzae* type b diseases.
- if your child experienced problems of the nervous system (such as repetitive fits, decrease of consciousness) 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). In these cases, the vaccination will be postponed until your child has recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- if your child has any known allergies.

In the following cases, your doctor can determine the right time and scheme of vaccination for your child. Tell your doctor:

- if after previously having Quintanrix 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 (floppiness) 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 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
- if your child is taking any other medicine or has recently received any other vaccine. Your doctor will be able to tell you what to do if Quintanrix is to be given with another vaccine or medicine.

Important information about some of the ingredients of Quintanrix

This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction. Tell you doctor if your child has any known allergies.

3. HOW QUINTANRIX 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. The first injection can be given from the age of 6 weeks onwards. You will be informed by the doctor or nurse when you should come back for subsequent injections.
The doctor or nurse will give Quintanrix as an injection into the muscle.

Your doctor will advise on the possible need for extra doses.

If your child misses the visit scheduled for the second or third injection, talk to your doctor and arrange another visit as soon as possible.

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 vaccine should never be given into a vein.

4. POSSIBLE SIDE EFFECTS

Any vaccine can have some side effects.

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

- **Very common** (more than 1 per 10 doses of vaccine):
  - Pain, redness or swelling at the injection site
  - Fever (more than 37.5°C)
  - Irritability
  - Loss of appetite
  - Drowsiness

- **Common** (less than 1 per 10 but more than 1 per 100 doses of vaccine):
  - Induration (hard lump)
  - Fever (more than 39°C)

- **Rare** (less than 1 per 1000 but more than 1 per 10 000 doses of vaccine):
  - Bronchitis
  - Coughing
  - Vomiting
  - Collapse (floppiness) or periods of unconsciousness or lack of awareness
  - Fits

Bleeding or bruising more easily than normal due to a drop in a type of blood cell called platelets have been reported very rarely (less than 1 per 10,000 doses of vaccine) with the hepatitis B component of Quintanrix.

As with all injectable vaccines, there is an extremely small risk of allergic 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.

If these events continue or become severe, tell your doctor.

This medicinal product contains thiomersal as a preservative and it is possible that your child may experience an allergic reaction.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Do not be alarmed by this list of possible side effects. It is possible that your child will have no side effects from vaccination.

5. STORING QUINTANRIX

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.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the pack. The date for last use corresponds to the last day of the month mentioned.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

Luxembourg/Luxemburg
GlaxoSmithKline s.a./n.v.
Tél/Tel: + 32 2 656 21 11

България
ГлаксоСмитКлайн ЕООД
ул. Димитър Манов бл.10
София 1408
Тел. + 359 2 953 10 34

Magyarország
GlaxoSmithKline Kft.
Tel.: + 36-1-2255300

Česká republika
GlaxoSmithKline s.r.o.
Tel: + 420 2 22 00 11 11
gsk.czmail@gsk.com

Malta
GlaxoSmithKline Malta
Tel: + 356 21 225736

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
info@glaxosmithkline.dk

Nederland
GlaxoSmithKline BV
Tel: + 31 (0)30 69 38 100
nlinfo@gsk.com

Deutschland
GlaxoSmithKline GmbH & Co. KG
Tel: + 49 (0)89 360448701
produkt.info@gsk.com

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Eesti
GlaxoSmithKline Eesti OÜ
Tel: +372 667 6900
estonia@gsk.com

Österreich
GlaxoSmithKline Pharma GmbH.
Tel: + 43 1 970 75-0
at.info@gsk.com

Ελλάδα
Allen Φαρμακευτική Α.Ε
Τηλ: + 30 210 68 82 100

Polska
GlaxoSmithKline Pharmaceuticals S.A.
Tel.: + 48 (22) 576 9000

España
GlaxoSmithKline S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

Portugal
Smith Kline & French Portuguesa, Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

France
Laboratoire GlaxoSmithKline
Tél: + 33 1 39 17 84 44
diam@gsk.com

România
GlaxoSmithKline (GSK) SRL
Tel: +40 (0)21 3028 208

Ireland
GlaxoSmithKline (Ireland) Ltd

Slovenija
GlaxoSmithKline d.o.o.

Tel: + 353 (0)1 4955000

Ísland
GlaxoSmithKline ehf.
Tel: +354-530 3700

Italia
GlaxoSmithKline S.p.A.
Tel:+ 39 04 59 21 81 11

Κύπρος
GlaxoSmithKline Cyprus Ltd
Τηλ: + 357 22 89 95 01

Latvija
GlaxoSmithKline Latvia SIA
Tel: + 371 7312687
lv-epasts@gsk.com

Lietuva
GlaxoSmithKline Lietuva UAB
Tel. +370 264 90 00
info.lt@gsk.com

Tel: + 386 1 280 25 00
gqq41253@glaxowellcome.co.uk

Slovenská republika
GlaxoSmithKline Slovakia s.r.o.
Tel: + 421 (0)2 49 10 33 11
recepcia.sk@gsk.com

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige
GlaxoSmithKline AB
Tel: + 46 31 67 09 00
info.produkt@gsk.com

United Kingdom
GlaxoSmithKline UK
Tel: + 44 (0)808 100 9997
customercontactuk@gsk.com

This leaflet was last approved on:

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

Upon storage, a white deposit and clear supernatant may be observed for the DTPw-HBV component. This does not constitute a sign of deterioration.

The DTPw-HBV component should be well shaken in order to obtain a homogeneous turbid white suspension and should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. Any unused vaccine or waste material should be disposed of in accordance with local requirements.

The vaccine is reconstituted by withdrawing the contents of the vial containing the DTPw-HBV component by means of a syringe and by adding it to the vial containing the HIB powder. After the addition of the DTPw-HBV component to the HIB powder, the mixture should be well shaken until the powder is completely dissolved. The reconstituted vaccine is a homogeneous turbid white suspension.

Remove and discard the needle used for reconstitution and replace it with a second needle to administer the vaccine. After reconstitution, the vaccine should be injected promptly.

Quintanrix should not be given to subjects with hypersensitivity to the active substances or to any of the excipients.

Quintanrix is contra-indicated 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 diphtheria, tetanus, hepatitis B and HIB vaccines.

As with other vaccines, the administration of Quintanrix should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, is not a contraindication for vaccination.

If any of the following events occur in temporal relation to receipt of Quintanrix, the decision to give subsequent doses of a 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 with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

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

Quintanrix should under no circumstances be administered intravascularly.