EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2013
EMA/CHMP/49887/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tritanrix HB

International non-proprietary name: diphtheria (d), tetanus (t), pertussis (whole cell) (pw) and hepatitis b (rdna) (hbv) vaccine (adsorbed)

Procedure No. EMEA/H/W/003838/0000

Note

This document consists of:

- Assessment report for Tritanrix HB adopted by the CHMP with all information of a commercially confidential nature deleted (pages 3 - 10)
- Assessment history of the European Public Assessment Report (EPAR) of Tritanrix HepB (the product on which the Tritanrix HB application has been based) at the time of adoption of the CHMP Opinion for Tritanrix HB (pages 11 - 38).

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Us
D, DT	diphtheria
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
ERA	environmental risk assessment
EU	European Union
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
IU	international units
MA	marketing authorisation
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
Pw	bordatella pertussis (inactivated, whole cell)
rDNA	recombinant deoxyribonucleic acid
RMP	risk management plan
SmPC	summary of product characteristics
T	tetanus
WHO	World Health Organisation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Biologicals S.A. submitted on 2 October 2013 an application to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation (WHO) for Tritanrix HB in accordance with Article 58 of Regulation (EC) No 726/2004.

The eligibility by the World Health Organisation was agreed-upon on 19 July 2013 and CHMP on 25 July 2013.

Tritanrix HepB, a centrally authorised medicinal product, is not marketed and no longer used in the European Union, and its marketing authorisation in the EU will cease to be valid at the end of 2013 in line with provisions of the 'Sunset clause' (Article 14(5) of Regulation (EC) No 726/2004). For global public health reasons acknowledged by WHO, Tritanrix HB application was submitted to the EMA in order to avoid an interruption in availability of this vaccine outside the European Union where it is still used in several countries.

Tritanrix HB will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication: active immunisation against diphtheria, tetanus, pertussis and hepatitis B in infants from 6 weeks onwards.

The legal basis for this application refers to:

Article 58 of Regulation (EC) No. 726/2004 (by analogy to Directive 2001/83/EEC, this application has been submitted under Article 10(c) of Directive 2001/83/EC).

Information on Paediatric requirement

Not applicable as application is submitted under Article 58 of Regulation (EC) No. 726/2004.

Information relating to orphan market exclusivity

Not applicable as application is submitted under Article 58 of Regulation (EC) No. 726/2004.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed and the evaluation teams were:

CHMP Rapporteur: Daniel Brasseur PRAC Rapporteur: Jean-Michel Dogné

CHMP Co-Rapporteur: Jan Mueller-Berghaus PRAC Co-Rapporteur: Brigitte Keller-Stanislawski

- The application was received by the EMA on 2 October 2013.
- The procedure started on 20 October 2013.
- The PRAC Rapporteur's Assessment Report was circulated to all CHMP members on 13 November 2013 (Annex 1).
- The CHMP Rapporteur's Assessment Report was circulated to all CHMP members on 22 November 2013 (Annex 2).
- The PRAC Assessment overview and advice was adopted by the PRAC on 05 December 2013 (Annex 3).
- The CHMP Rapporteur's updated Assessment Report was circulated to all CHMP members on 12 December 2013 (Annex 4).
- During the meeting on 19 December 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion for Tritanrix HB.

2. Scientific discussion

2.1. Introduction

This application for a CHMP scientific opinion in the context of cooperation with the World Health Organisation in accordance with Article 58 of regulation (EC) No 726/2004 for Tritanrix HB has been submitted by GlaxoSmithKline Biologicals S.A. and by analogy to the legal basis of Article 10c of Directive 2001/83/EC, as amended (so-called "informed consent application").

During its meeting on 22 July 2013 the CHMP decided, after having consulted the World Health Organisation, that Tritanrix HB is considered eligible for an application for a CHMP scientific opinion in accordance with Article 58 of Regulation (EC) No. 726/2004.

The marketing authorisation holder (GlaxoSmithKline Biologicals S.A.) for Tritanrix HepB, which was authorised on 19 July 1996 and approved for active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HBV) in infants from 6 weeks onwards, provided consent to make use of the pharmaceutical, non-clinical and clinical documentation of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved prior to its EU MA ceasing to be valid after applicability of the provisions of the 'Sunset clause' (Article 14(5) of Regulation (EC) No 726/2004) i.e. by the end of 2013.

As a consequence, quality, safety and efficacy of Tritanrix HB are identical to the up-to-date quality, non-clinical and clinical aspects of Tritanrix HepB. The data submitted up to date in the dossier of Tritanrix HepB form the basis of Tritanrix HB dossier, and is to be continued to be updated by the applicant, as appropriate.

2.2. Quality aspects

The quality data in support of the Tritanrix HB application are identical to the up-to-date quality data of the Tritanrix HepB dossier, which have been assessed and approved, including all post-marketing procedures.

2.3. Non-clinical aspects

The non-clinical data in support of the Tritanrix HB application are identical to the up-to-date quality data of the Tritanrix HepB dossier, which have been assessed and approved, including all post-marketing procedures.

2.3.1. Ecotoxicity / environmental risk assessment

The applicant did not submit an environmental risk assessment (ERA). In line with the "Article 58" procedural guidance, an ERA is not required for applications under Article 58. In addition, vaccines are exempt from need to conduct ERA in line with CHMP Guideline on the ERA of medicinal products for human use.

2.4. Clinical aspects

The clinical data in support of the Tritanrix HB application are identical to the up-to-date clinical data of the Tritanrix HepB dossier, which have been assessed and approved, including all post-marketing procedures.

2.5. Pharmacovigilance

The summary of pharmacovigilance system was provided in module 1.8.1 of the dossier including required information according to Article 8(3)(ia) of Directive 2001/83/EC. Documentation also contains a statement signed by the MAH and the QPPV to the effect that the MAH has the necessary means to fulfil the tasks and responsibilities listed in the Title IX of the Directive 2001/83/EC, by analogy and in line with the EMA procedural guideline on "Article 58".

The CHMP considered that the Pharmacovigilance system as described by the applicant is adequate for its intended use.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The PRAC considers by consensus that the risk management system for Diphtheria toxoid, Tetanus toxoid, Inactivated whole-cell pertussis bacteria (Pw), Recombinant DNA yeast-derived hepatitis B surface antigen (HBsAg) (Tritanrix HepB) in the active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HB) in infants from 6 weeks onwards is acceptable.

This advice is based on the following content of the Risk Management Plan:

Table 1. Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis or hepatitis B vaccines • Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause • Hypotonic-hyporesponsive episode (HHE) • Convulsions with or without fever, occurring within 3 days
Important potential risks	• Apnoea in infants born prematurely • Syncope • Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine
Important identified interactions	• None
Missing information	• Data on the immunogenicity and safety of Tritanrix-HB in premature children

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product. The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Table 2. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risks		
Hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis or hepatitis B vaccines	The SmPC contains the following contraindication: "Tritanrix HepB should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis or hepatitis B vaccines"	None
Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause	The following warning and precaution is included in the SmPC: If temperature of ≥ 40.0 C occurs within 48 hours of receipt of Tritanrix-HB, not due to another identifiable cause, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.	None
Hypotonic-hyporesponsive episode	The following warning and precaution is included in the SmPC: If hypotonic-hyporesponsive episode occurs within 48 hours of receipt of Tritanrix-HB, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.	None
Convulsions with fever, occurring within 3 days after vaccine administration	The following warning and precaution is included in the SmPC: If convulsions with or without fever occurs within 3 days of receipt of Tritanrix-HB, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.	None
Potential Risks		
Apnoea in infants born prematurely	The following warning and precaution is included in the SmPC: "The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunization 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."	None
Syncope	The following warning and precaution is included in the SmPC: "Syncope (fainting) can occur following, or even before any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faint"	None
Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine	The SmPC contains the following contraindication: "Tritanrix HepB 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 DT and hepatitis B vaccines"	None
Missing information		
Data on the immunogenicity and safety of Tritanrix HB in premature children	No other risk minimisation measures are in place in addition to the risk minimisation measures taken to inform the prescriber of the potential risk of apnoea in children born prematurely (see potential risk: Apnoea in infants born prematurely). Clinical data on the immunogenicity and safety of Tritanrix-HB in premature children are missing. However, vaccination in premature children is supported by medical literature considering the benefit of vaccination in this group of infants who are at a greater risk of infection compared to infants born at full term (Koblin, 1988; AAP, 2003; Saari, 2003; Omeñaca, 2005; CDC, 2011). This is supported in the SmPC with the following "As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed."	None

The CHMP endorsed this advice without changes.

2.7. User consultation

User testing of the Package Leaflet is not mandatory because the product is to be marketed outside the European Union. Furthermore, the proposed package leaflet is in line with the package leaflet of product Tritanrix HepB, which is currently authorised in the EU. .

3. Benefit-Risk Balance

This application for a CHMP Scientific Opinion according to Article 58 Regulation (EC) No 726/2004 has been submitted by analogy to the legal basis of Article 10c of Directive 2001/83/EC, as an informed consent application of Tritanrix HepB.

As a consequence, quality, safety and efficacy of Tritanrix HB suspension for injection is identical to the up-to-date quality, non-clinical and clinical profile of the reference product Tritanrix HepB suspension for injection.

In line with the assessment of data undertaken in the framework of the Tritanrix HepB initial marketing authorisation application as well as within all post-authorisation procedures, the CHMP considers that the benefit/risk balance for Tritanrix HB is positive.

Furthermore, in order to ensure continuous surveillance of the benefit-risk balance of the product, the periodic safety update reports should be continued to be submitted in line with requirements of the EURD list at the of adoption of the Opinion. Therefore, the PSURs should be submitted every three years and next PSUR should cover the time period from the data lock point of latest PSUR submitted for Tritanrix HepB.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tritanrix HB in the active immunisation against diphtheria, tetanus, pertussis and hepatitis B in infants from 6 weeks onwards is favourable.

This opinion is based upon the risk-benefit scenarios in the populations and conditions of use as documented with clinical data submitted for medicinal product Tritanrix HepB.

RECOMMENDATIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

Official batch release

The CHMP recommends that batch compliance control of individual batches be performed by an independent control laboratory before release on the market in third countries.

OTHER RECOMMENDATIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

Periodic Safety Update Reports

The scientific opinion holder shall submit the first periodic safety update report for this product within 90 calendar days after the data lock point of 18.07.2014. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 3 years until otherwise agreed by the CHMP.

RECOMMENDATIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Scientific Opinion Applications and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Attachments:

Assessment History of the EPAR of Tritanrix HepB

1. Tritanrix HepB EPAR - Initial marketing authorisation: Scientific Discussion (pages 13 – 17).
2. Tritanrix HepB EPAR - Procedural steps taken and scientific information after the authorisation (pages 19 – 28).
3. Tritanrix HepB-H-C-93-P45-39 EPAR – Assessment Report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006 (pages 30 – 38).

Attachment 1

Tritanrix HepB EPAR - Initial marketing authorisation: Scientific Discussion

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Tritanrix HepB. This scientific discussion has been updated until 1 November 2002. For information on changes after 1 November 2002 please refer to module 8B.

1. Introduction

Tritanrix HepB is a tetravalent vaccine against diphtheria, tetanus, pertussis and hepatitis B developed by GlaxoSmithKline (GSK) Biologicals S.A. on the basis of the combination of the existing active ingredients in their diphtheria-tetanus-inactivated whole cell pertussis vaccine (DTP_w) and their recombinant yeast-derived hepatitis B vaccine (Engerix B). Both the DTP_w vaccine and the hepatitis B vaccine have been licensed and used successfully as separate vaccines in EU member states (and in a number of non-EU countries) for a number of years.

This tetravalent vaccine contains not less than 30IU of adsorbed D toxoid, not less than 60 IU of adsorbed T toxoid, not less than 4 IU of P_w and 10 mg of r-HBsAg protein/0.5ml equivalent to one dose. The company applied for two presentations: a 3ml monodose vial containing one dose of vaccine and a 10ml multidose vial containing ten doses of vaccine.

The diphtheria (D) and tetanus (T) toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* by formalin inactivation using established technology. The pertussis (P_W) component is obtained by heat inactivation of phase I cultures of *Bordetella pertussis* bacteria. The surface antigen of the hepatitis B virus (HBsAg) is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene coding for the major surface antigen of the hepatitis B virus.

The following indications are claimed for Tritanrix HepB:

"Tritanrix HepB is indicated for active immunisation against diphtheria, tetanus, pertussis and hepatitis B (HB) in infants from 6 weeks of age onwards."

The rationale for the production of this new combination is established within the context of the universal vaccination of infants against hepatitis B, as recommended by the WHO EPI (Expanded Program on Immunisation), for simplifying vaccine delivery and reducing the costs. The incorporation of the hepatitis B vaccine in a multivalent formulation with DTP_W is appropriate and technically feasible because both DTP_w and hepatitis B vaccines are adsorbed products that are administered by the intramuscular route and also because their administration schedules includes multiple doses during the first year of life.

The results of pharmacology (potency and immunogenicity) and toxicology tests and the results of the relevant clinical trials needed for the review of this application have been submitted.

2. Part II: Chemical, pharmaceutical, and biological aspects

The data submitted were in compliance with the current requirements.

During the CPMP discussions particular attention was given to the following quality aspects:

Dosage form

The DTP_WHB vaccine contains merthiolate as preservative in both the monodose and multidose preparations. This preservative has been used in DTP vaccines for years, and has been shown to be efficacious. The SB hepatitis B vaccine also contains merthiolate. The combined DTP_WHB vaccine also

contains 2-phenoxyethanol as a residual. The possibility of using 2-phenoxyethanol as the only preservative was discussed.

The possibility of removing the preservative altogether from the single dose presentation was also discussed. Its use was justified by the fact that this preparation is not terminally sterilised and that its intrinsic cloudy appearance (because of the presence of adjuvant) carries the potential to mask evidence of microbial contamination.

Method of preparation

The completeness of adsorption of D, T and Hbs antigens has been demonstrated. Furthermore the Company commits to testing each final bulk for completeness of adsorption as an additional specification.

Control of starting materials

An updated list of specifications for the bulk purified D and T toxoids was considered necessary and has been provided by the company.

Control of the finished product

As to the specifications for the Hepatitis B component, they have been brought in line with those agreed for the company's hepatitis B vaccine Engerix B as presented in the renewal dossier which was reviewed by the CPMP in 1994. An updated list of specifications was considered necessary and was provided by the company. The specification for the potency of the HBsAg on mice is expressed relative to the reference Engerix B; the upper fiducial limit (P=0.95) of the estimated relative potency is reported to be not less than 1.0. The amount of unbound HBsAg is less than 1% of the nominal value according to the updated specification.

The limit for residual ethylene oxide in the Terumo syringes has been set according to the Note for Guidance as published in Volume III of The Rules Governing Medicinal Products in the European Union.

The final potency specifications of the PW components meet EP (European Pharmacopoeia) requirements. Data from the company provided evidence of the conformity of batches of Tritanrix HepB with EP and WHO requirements.

Stability

The stability parameters for the final product were shown to be complete and stability data after 36 months storage at 2-8 have been provided, including pH and sterility. Data presented on batches of the D, T and HB components stored for 36 months at 2-8 ºC, show that there is no release from the adjuvant (desorption) during storage. The stability parameters for the final product also includes tests for the completeness of adsorption. A shelf-life of 24 months for the finished product was accepted at the time of approval. The shelf-life of 24 months was recently extended to 36 months following the submission of additional supporting data.

Part III: Toxico-pharmacological aspects

The active ingredients of the vaccine are well known. The excipients used in this combined vaccine are well known and the amounts are within the limits used for other vaccines. Toxicological tests (which follow the requirements of WHO and the EP) were performed on 5 lots of the combined vaccine DTP_W -HB.

These tests include:

- specific toxicity in guinea pigs for diphtheria and tetanus
- mouse weight gain test for pertussis toxicity

- general safety tests in mice and guinea pigs.

The 5 lots tested were found to comply with the specifications.

As to the potency of this combined vaccine, 5 lots were tested using methods in accordance with Ph.Eur. and the WHO requirements for DTP_W and the mouse potency test developed by the company for lot release of hepatitis B vaccine.

The vaccine was first released for clinical trials on the basis of specifications set up at 2 IU as a mean potency for the pertussis component. The final potency specifications of the P_W component meet EP (European Pharmacopoeia) requirements. This was referred to in the clinical assessment of the dossier.

No other data were submitted or considered necessary.

4. Part IV: Clinical aspects

Clinical trials

The complete results of 6 clinical trials performed by 3 groups in 3 European countries were presented in this application. A total of 872 subjects aged 7 to 20 weeks were included. One study was performed using a pilot lot on a small number of children, the 5 others, for part or all subjects using three production lots of the vaccine.

These clinical trials demonstrate the production of protective levels of antibodies after the primary vaccination series against diphtheria, tetanus and hepatitis B in ≥ 97% of the vaccinees and a response against pertussis in ≥ 92%. These results were considered convincing.

The following trials were provided to address outstanding questions.

- Study DTP_W HB-038; an open randomised study comparing the immunogenicity and reactogenicity of the combined DTP_W -HB vaccine with that of simultaneously administered DTP_W and HB vaccines (different sites). Although this trial was not a double blind study, it nevertheless provides convincing evidence that the combined vaccine is as immunogenic as DTP_W for each of the 3 components of this vaccine and more immunogenic with respect to hepatitis B than the HB vaccine administered at a different site. In this single comparative clinical study the combined vaccine was more reactogenic (see Table of results in SPC) than DTP_W and HB vaccines administered at different sites.
- Study DTP_W HBV-023; an interim report of a double-blind randomised study to evaluate the immunogenicity and reactogenicity of combined tetravalent DTP_W -HB vaccines administered at 1.5, 2.5 and 6 months of age primed at birth with hepatitis B 10 mg component. This study was performed to investigate the use of the vaccine in children younger than 8 weeks of age. It shows that local and general reactogenicity is similar to that observed with the combined vaccine in study DTP_W HB-038.

  Study DTP_W HB-Hib-003; an open randomised trial; sub-analysis of the immunogenicity data for infants who received the first dose of vaccine at 5-6 weeks. The immunogenicity of the DTP_W HB vaccine was considered to be adequate when the first dose is administered at 6 weeks.
- Two additional studies were performed to document the persistence of antibodies after the 3 dose primary vaccination.

These studies suggest that the persistence of antibodies against diphtheria, tetanus and pertussis after DTP_W HB vaccine is not different from that after DTP_W and show that at least 80% of the vaccinees with

the combined vaccine have protective levels of anti-Hbs antibodies during the second year of life. This suggests that a booster dose during the second year of life is warranted at least for the diphtheria tetanus and pertussis components, as it is current practice, but it does not give sufficient evidence as to the necessity of a booster dose for the hepatitis B component.

The limited experience with DTP_W HB as a booster indicates adequate immunogenicity. However, the reported experience is insufficient to evaluate the reactogenicity of a booster. This point is made clear in the SPC.

During the CPMP meeting on 19-20 December 1995, a number of outstanding clinical issues were addressed and oral explanations were given by the company. These explanations were also provided in writing and were found to be acceptable by the Rapporteur. The main issues which were discussed can be summarised as follows:

- Evaluation of the protective efficacy of the pertussis component: a summary of a study was submitted to demonstrate the efficacy of the SB vaccine DTP_W.
- A higher incidence of reactions following administration of the combined vaccine as compared to administration of DTP_W and hepatitis B vaccines separately was reported in the clinical study. A revised statement and a table in the SPC reflect this clearly.
- The balance between this aspect and the operational benefit gained by using the combination has been considered in the light of the proceedings of the WHO Task Force which convened in 1992 and concluded that there was "an important need for a DTP_W-HB vaccine".
- Possible interaction with other routine childhood vaccines: Study DTP_W HB-Hib-003; an open randomised study to evaluate the tolerability and immunogenicity of the DTP_W HB vaccine and the SB tetanus-conjugated Haemophilus influenzae type B vaccine injected either simultaneously at different sites or mixed, showed that there was no interference in the immune response to any of the components.
- Another study showing a lack of interference between Engerix B and OPV is also supported by the US Department of Health and Human Services - ACIP recommendations on Immunisation (MMWR January 28, 1994, vol., 43, no. RR-1)

During the CPMP meeting break-out session on 13 February 1996, a representative from the WHO presented an overview comparing the reactogenicity of other existing DTP vaccines with the combined DTP_WHB vaccine and it was observed that the profile of side effects were reasonably comparable. In conclusion it was noted that although DTP_WHB was slightly more reactogenic than the SB Biologicals DTP_W vaccine in Study 038, its reactogenicity in general, was within the range of other DTP vaccines currently available.

In addition to the post marketing surveillance mentioned in Council Regulation 2309/93, the company will initiate outside the EU additional surveillance in accordance with the involved authorities.

Finally the SPC was revised taking into account the following points:

- The insufficient experience with respect to the immunogenicity of the combined vaccine DTPW HB as a booster
- Vaccination with the combined DTPW and HB vaccine in children born to HB carrier mothers.
- The a.m. revised statement on the reactogenicity profile of this vaccine.

5. Conclusions

During its meeting on 12-13 March 1996 the CPMP considered satisfactory data on quality, safety and efficacy have been submitted by the company to support the Marketing Authorisation for Tritanrix HepB.

Although the CPMP recognised that Tritanrix HepB is more reactogenic than the DTPw vaccine manufactured by the same company, the company provided sufficient evidence in order to demonstrate that the reactogenicity of this combined vaccine is within the range observed for other DTPw vaccines currently used.

Consequently the CPMP has come to the conclusion that the overall benefit/risk analysis was positive and adopted two favourable opinions to accommodate for the monodose and the multidose presentations.

Since the Marketing Authorisation was granted, the CPMP considered at the time of the 5-year renewal that the benefit/risk profile of Tritanrix continued to be favourable and therefore, recommended the renewal of the Marketing Authorisation.

Attachment 2

Tritanrix HepB EPAR - Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
WS/0401	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	25/07/2013	n/a		
IG/0306	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2013	n/a		
IG/0297	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/04/2013	n/a		
II/0063	Replacement of the current screwcaps used for the purified bulk transfer and storage. B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition of sterile and non-frozen biological/immunological ASs	21/02/2013	n/a		
WS/0336	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	17/01/2013	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	To introduce a new method for monitoring homogeneity during filling. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
WS/0201/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To propose new target fill volume controls. To align the volume specifications to be applied at release and during stability evaluation. To revise QC release procedures for final container volume determination. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/01/2012	n/a		
IG/0052/G	This was an application for a group of variations. B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to	18/03/2011	n/a		

	the specification with its corresponding test method B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete paramete				
II/0057	Changes to the manufacturing process of th[illegible] drug substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [illegible] substance in the manufacture of a biologic[illegible]/immu[illegible]ological medicinal product and is not [illegible]lated [illegible]n a pro[illegible]col	21/10/2010	27/10/2010		
IB/0058	Change in a test proce[illegible]re for the master and working seeds of Clo[illegible]idium te[illegible]nd Corynebacterium	11/08/2010	n/a		

	dipheriae. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0059	Change in an in-process test for the active substance. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	11/08/2010	n/a		
WS/0001	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To register an additional building for formulation activities. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products	22/04/2010	22/04/2010		
IB/0056	IB_12_a_Change in spec. of active substance used in manuf. of active subst. - tightening	18/09/2009	n/a		
II/0055	Introduction of new filter equipment during the manufacturing process of tetanus toxoid. Change(s) to the manufacturing process for the active	25/06/2009	02/07/2009		

	substance				
II/0053	Change to the purification process of diphteria (D) and tetanus (T) toxoid. Change(s) to the manufacturing process for the active substance	19/03/2009	25/03/2009		
II/0054	Modification of the purification process for tetanus toxoid. Change(s) to the manufacturing process for the active substance	19/03/2009	25/03/2009		
II/0052	Change in the production process for the whole cell pertussis concentrate produced by Novartis Vaccines & Diagnostics GmbH &Co. Change(s) to the manufacturing process for the active substance	22/01/2009	28/01/2009		
II/0049	Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	27/01/2009	SmPC and PL	
II/0047	Change to the shelf-life specification of thiomersal for the two-dose and multi-dose presentations of Tritanrix HepB. Change(s) to the test method(s) and/or specifications for the finished product	20/11/2008	26/11/2008		
IA/0050	IA_04_Change in name and/or address of a manufacturer of the active substance (no Ph. Eur. cert. avail.)	21/11/2008	n/a	Annex II	
IA/0051	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	18/11/2008	n/a		
II/0048	Extension of the shelf-life for the DTPw bulk, used in the formulation of Tritanrix HepB.	25/09/2008	01/10/2008		

	Change(s) to the manufacturing process for the active substance				
IA/0046	IA_05_Change in the name and/or address of a manufacturer of the finished product	18/07/2008	n/a		
IA/0045	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	07/07/2008	n/a		
II/0044	To update section 4.8 of the SPC to bring it in line with the current SPC guideline. Update of Summary of Product Characteristics	19/03/2008	22/04/2008	SmPC	The undesirable effects section was reviewed to bring it in line with the current SPC guideline. The section was restructured so that the adverse events were listed under the appropriate heading. The frequency of all events remained the same but these were aligned in order of decreasing seriousness.
II/0043	Update of Summary of Product Characteristics. Update of sections 4.4 and 4.8 of the SPC to implement the class labelling text on the risk of apnoea following vaccination of very prematurely born infants agreed by the CHMP in July 2007. Update of Summary of Product Characteristics	15/11/2007	06/12/2007	SmPC	Following a review on the risk of apnoea in very premature infants after immunisation the CHMP recommended a class labelling on apnoea for all vaccines in very premature infants. The SPC was updated to include information about the potential risk of apnoea and the need for respiratory monitoring for 48-72h, when the primary immunisation series is administered to very premature infants (born ? 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. Nonetheless, preterm infants should not be withdrawn from the immunisation scheme because the benefit of vaccination outweighs the risk of apnoea.
II/0041	Change(s) to the manufacturing process for the active substance	20/09/2007	24/10/2007	SmPC, Labelling and PL	
II/0042	To update section 4.1 of the SPC to include information about the immune response induced by the 6, 10, 14-week schedule in the assessment of the	21/06/2007	10/08/2007	SmPC, Annex II and PL	The product information was updated to reflect information from clinical studies performed with the 6-10-14 weeks schedule for Tritanrix Hep B. The data showed that when this

	renewal. Section 4.2 was consequently updated to include the administration of a dose of hepatitis B vaccine at birth when the vaccine is given according to this schedule. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) and updated the SPC, annex II and PL according to the latest EMEA/QRD template. Update of Summary of Product Characteristics and Package Leaflet				schedule is to be used, it is recommended to administer a dose of hepatitis B vaccine at birth to improve protection. Other changes were introduced to the product information to bring them in line with the current templates.
II/0040	Change(s) to the manufacturing process for the finished product	16/11/2006	27/11/2006		
R/0039	Renewal of the marketing authorisation.	01/06/2006	13/07/2006	SmPC, Annex II, Labelling and PL	
II/0033	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2005	n/a	Labelling and PL	
IB/0037	IB_37_b_Change in the specification of the finished product - add. of new test parameter	21/09/2005	n/a		
II/0036	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	15/09/2005	26/09/2005		
II/0034	Change(s) to the test method(s) and/or specifications for the finished product	16/03/2005	23/03/2005		
II/0035	Change(s) to the test method(s) and/or specifications for the finished product	16/03/2005	23/03/2005		

IB/0032	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	02/12/2004	n/a		
II/0031	Change(s) to the manufacturing process for the active substance	16/09/2004	21/09/2004		
II/0029	Update of section 4.8 following the assessment of PSUR 10, to include hypotonic-hyporesponsive episodes. The Package Leaflet (PL) was also updated to reflect the information on the SPC. Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	17/06/2004	SmPC and PL	Based on the assessment of PSUR 10 covering the period from 20.07.02 to 19.07.03, the CHMP agreed that the MAH should update section 4.8 (Undesirable effects) to include very rare reports of hypotonic-hyporesponsive episodes. In addition, the CHMP agreed with the MAH proposal to complete the list of local representatives in the PL in order to include the 10 accession countries and amend the declarations of storage conditions in SPC section 6.4 (Special Precautions for storage), PL and labelling in accordance with EMEA/QRD templates.
IA/0030	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/03/2004	n/a		
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/08/2003	03/09/2003	Labelling and PL	
I/0027	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/07/2003	25/07/2003		
II/0021	Change(s) to the test method(s) and/or specifications for the active substance	20/02/2003	04/03/2003		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2002	10/10/2002	PL	
II/0019	Quality: Change(s) to the manufacturing process for the active substance Quality: Change(s) to the manufacturing process for the finished product Change(s) to the test method(s) and/or specifications for the finished product	19/09/2002	25/09/2002		

I/0018	03_Change in the name and/or address of the marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s)	05/11/2001	29/01/2002	SmPC, Annex II, Labelling and PL	
I/0017	01_Change in the name of a manufacturer of the medicinal product	16/11/2001	06/12/2001		
R/0014	Renewal of the marketing authorisation.	26/07/2001	20/11/2001	SmPC, Annex II, Labelling and PL	
II/0015	Quality changes	20/09/2001	08/10/2001		
II/0013	Update of or change(s) to the pharmaceutical documentation	23/08/2001	07/09/2001		
I/0016	01_Change following modification(s) of the manufacturing authorisation(s)	22/08/2001	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2001	17/05/2001	Labelling	
II/0010	New presentation(s)	25/01/2001	03/05/2001	SmPC, Labelling and PL	
II/0009	Update of Summary of Product Characteristics and Package Leaflet	13/10/2000	13/03/2001	SmPC and PL	
II/0011	Change(s) to the test method(s) and/or specification for the finished product	25/01/2001	01/02/2001		
I/0008	25_Change in test procedures of the medicinal product	16/03/2000	n/a		
I/0006	13_Batch size of active substance	29/07/1999	04/08/1999		
I/0007	12_Minor change of manufacturing process of the active substance	29/07/1999	04/08/1999		
II/0005	Change(s) to shelf-life or storage conditions	23/06/1999	23/06/1999		

N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/09/1998	n/a	PL	
I/0002	02_Change in the name of the medicinal product (either invented name of common name)	20/08/1997	12/12/1997	SmPC, Labelling and PL	
I/0003	01_Change in the name of a manufacturer of the medicinal product	31/10/1997	n/a		
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	03/07/1997	25/09/1997	SmPC	

Attachment 3

Tritanrix HepB-H-C-93-P45-39 EPAR – Assessment Report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

1 Recommendation

No further action required.

2 Introduction

The MAH submitted 2 completed paediatric studies for Tritanrix-Hep B, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use. Two short critical expert overviews have also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Tritanrix-Hep B that there is no consequential regulatory action.

3 Scientific Discussion

Information on the pharmaceutical formulation used in the clinical studies

Tritanrix HepB, suspension for injection

Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

Non-clinical aspects

Not applicable.

Clinical aspects

Introduction

The MAH submitted reports for and synopsis for:

- Study DTP-HBV-006 (2 reports) (Thailand)
    - **208139/00** final study report
        - The immunogenicity and reactogenicity of combined tetravalent diphtheria, tetanus, whole cell pertussis, hepatitis B (DTPwHBV) candidate vaccine in healthy infants.
    - **208139/003** erratum annex and additional report on 18 month booster
        - The immunogenicity and reactogenicity of combined tetravalent diphtheria, tetanus, whole-cell pertussis, hepatitis B (DTPwHBV) candidate vaccine in healthy infants. This annex: results of the booster dose administered at 18 months of age.
- Study DTP-HBV-028 (1 report) (Thailand)
    - **208139/018** Month 30, Years 4 and 5 long term follow-up
    - **208139/051** Year 6 long term follow-up
    - **208139/054** Year 7 Annex 2 Development Phase II

- An open randomised study in healthy infants vaccinated at birth with Engerix™-B (10 μg) to evaluate the immunogenicity and the reactogenicity of the following GlaxoSmithKline (GSK) Biologicals' vaccines:
    - combined DTP-HB vaccine (10 μg HBsAg)
    - combined DTP-HB vaccine (5 μg HBsAg)
    - simultaneous administration of Engerix™-B (10 μg) vaccine in right thigh and whole-cell DTP vaccine in left thigh

  when administered at 2, 4 and 6 months of age.

Clinical studies

Clinical study: 208139/003 (DTP-HBV-006) - (Thailand)

Description

This open, randomized feasibility study with 160 healthy infants at 2 to 3 months of age started in Thailand on 11/02/1992. It was performed to evaluate the immunogenicity and reactogenicity of two formulations of a combined DTPwHBV vaccine, against a commercial DTPw vaccine starting at 6-12 weeks of age. An amendment (22/06/1993) to the protocol of the study DTPw-HBV-006 was approved to evaluate a booster dose administered at 18 months of age (annex report).

Methods

- **Objectives**

The primary objective of the study was to evaluate and compare the antibody responses elicited by the hepatitis B component of two formulations of a combined DTPwHBV vaccine when administered according to a 0, 2, 4 month schedule. Other objectives include the evaluation of the antibody responses to diphtheria and tetanus toxoid and whole cell B. pertussis components and the reactogenicity of the formulations. A control group was included which received a commercial DTPw vaccine. The aim of the annex report study was to evaluate the immunogenicity and reactogenicity of booster vaccination at 18 months of age. Reactions to vaccinations were subjectively evaluated.

- **Study design**

160 infants were randomized to receive either one of the two formulations of SmithKline Beecham Biologicals' combined diphtheria, tetanus, whole-cell pertussis, hepatitis B candidate vaccine (DTP_WHBV) (Groups 1 and 2) or a commercial DTPw vaccine (Berna) (Group 3) according to a 0,2,4 month schedule. Antibody titers were measured in blood samples obtained just before vaccination and 4 weeks after the third dose. For ethical reasons group 3 received a hepatitis B vaccination course, according to a 0, 1 and 6 months schedule after the primary vaccination. An amendment (annex report) was approved to administer a booster dose at 18 months of age. The annex report provides the results of blood samplings taken at 18, 19 and 30 months of age as well as solicited and unsolicited symptoms reported following the booster vaccination.

- **Study population / Sample size**

160 healthy infants of 2 to 3 months of age

- **Treatments**

Group 1 received the combined DTP_WHBV vaccine lot 15707A2 with 0.5 ml dose (containing 075 mg of aluminium) and a booster dose of SB Bio's DTP_WHBV lot 15724B2, 0.5ml at 18 months of age.

Group 2 received the combined DTP_WHBV vaccine lot 15720A2 with 0.6 ml dose (containing 0.676 mg of aluminium) and the same booster dose as group 1.

Group 3 received commercial DTP_W Berna with 0.5 doses and a booster dose Berna-DTP_W vaccine both without hepatitis B. A hepatitis B vaccine course according to a 0, 1 and 6 months schedule was given for ethical reasons.

- **Outcomes**

The immunogenicity outcomes were titers of antibodies against the hepatitis B surface antigen (anit-HBs), diphtheria toxoid (anti-diphtheria), tetanus toxoid (antit-tetanus) and whole-cell B. pertussis bacteria (anti-B. Pertussis) were measured in pre and post III vaccination serum samples. For the booster dose serum antibody titers against vaccine antigen components assessed in blood samples taken before the booster dose, one month after the booster dose and one year later (18, 19 and 30 months of age)

Concerning the safety outcomes the reactogenicity was evaluated after each dose administered, involving 30 minutes observing for adverse events and parent reports of symptoms of local, general and possible other reactions. The investigator evaluated subjectively the feverishness of the infants based on parent's comments. No objective measurements were taken for any reaction.

- **Endpoints**

The presence of **anti-HBs** titers was determined using radioimmunoassay (AUSAB, Abbott) and titers were calculated in mIU/ml as described by Hollinger, et al, titered against a WHO reference standard. The assay cut-off used for this study was 1 mIU/ml. (titers ≥ 10 mIU/ml)

Anti-diphtheria and anti-tetanus titers were measured by Elisa and expressed in international units per ml (IU/mil), with respect to a reference serum. The assay cut-off was 0. IU/ml. (titers ≥ 0.1IU/ml)

Anti-B. pertussis antibody titers were determined by ELISA Units (EI.U/ml). The assay cut-off was 15 EL.U/ml. (post-vaccination titer ≥ pre- vaccination titer)

For the booster the same assay cut-offs were used.

- **Statistical Methods**

All analyses were descriptive only. The demographics were analysed for age and sex. The reactogenicity data are presented in terms of type, incidence and intensity. The immunogenicity analysis was performed on data from sera collected at pre and post III vaccination for those subjects who conformed to specific criteria with respect to vaccination. Further statistical comparisons were not made nor were additional details were given.

Results

- **Recruitment / number analyzed**

160 healthy infants of 2 to 3 months of age were enrolled. 133 subjects were eligible for inclusion in the immunogenicity analysis. Compliance for the booster dose at 18 months: 119 subjects (mean age of the infants at this moment was 17.7 months)

- **Efficacy results**

For the primary study the immunogenicity results were as follows. One month after the full vaccination course, all of the subjects in group 1 and all except for one subject (97.6%) in group 2 had protective levels of anti-HBs. At this time, all subjects in all three groups had protective levels of antibodies against diphtheria and tetanus as well as satisfactory levels of pertussis antibodies.

Table 3B: Immunogenicity: anti-HBs titers (analyzable group)

Group	Blood sample	N	Subjects with protective titer n	Subjects with protective titer %	GMT (mIU/ml)	CL 95% lower limit	CL 95% upper limit
1	Pre	52	12	23.1	11	7	19
	Post	42	42	100.0	234	149	367
2	Pre	52	15	28.8	10	7	15
	Post	42	41	97.6	416	256	676

Table 3C: Immunogenicity: anti-diphtheria titers (analyzable group)

Group	Blood sample	N	Subjects with protective titers n	Subjects with protective titers %	GMT (IU/ml)	CL 95% lower limit	CL 95% upper limit
1	Pre	52	22	42.3	0.092	0.07[illegible]	0.[illegible]6
	Post	42	42	100.0	3.941	2.[illegible]61	[illegible].429
2	Pre	52	18	34.6	0.084	[illegible].067	[illegible].106
	Post	42	42	100.0	3.[illegible]92	2.[illegible]34	[illegible].888
3	Pre	29	10	34.5	0.088	[illegible].065	0.119
	Post	24	24	10[illegible]	2.741	1.772	4.239

Table 3D: Anti-tetanus antibody titres of subjects included in the analysis of immunogenicity

Group	Timing	N	Subjects with Seropositive titres n	%	GMT	CL 95% lower	CL 95% upper	Min titre	Max titre
1	Pre B (m 18)	38	34	89.5	0.285	0.207	0.393	<0.1	3.360
	Post B (m 19)	38	38	100.0	9.652	7.950	11.717	1.551	20.139
	Post B (m 30)	28	27	96.4	1.020	0.717	1.451	<0.1	[illegible]
2	Pre B (m 18)	36	35	97.2	0.347	0.261	0.459	<0.1	4.[illegible]19
	Post B (m 19)	35	35	100.0	10	8.601	12.761	2.[illegible]3	2.[illegible]549
	Post B (m 30)	25	25	100.0	1.000	0.737	1.357	0.27[illegible]	5.144
3	Pre B (m 18)	22	21	95.5	0.673	0.391	1.1[illegible]8	[illegible]1	28.838
	Post B (m 19)	21	21	100.0	29	19.39[illegible]	42.057	3.5[illegible]5	169.760
	Post B (m 30)	11	11	100.0	3.024	1.69[illegible]	[illegible]94	[illegible]69	9.376

For the booster dose amendment the immunogenicity results were as follows. % subjects greater than assay cut-off.

	Pre-booster Group 1, 2, 3	1 year after Group 1, 2, 3
Antibody titers	68.4%, 69.4% and 54.5%	96.4%, 100.0%, 81.8%
Antitetanus	89.5%; 97.2% and 95.5%	96-100% in all groups
Anti-BPT	2.1%, 77.8 and 68.2%	100%, 100%, 90, 9%

- **Safety results**

No serious adverse experiences were reported in this study and reactions were not essentially different from what is usually reported following vaccination with DTPw. Local reactions were reported by approximately 10% of the subjects, general reactions in approximately 55% (more in group 1 and 2). After the booster dose the only reported solicit symptom was fever in 77.8%, 62.2%, 64% in the 3 groups, but no fever was scored as severe.

Conclusion

In conclusion, the results of the primary study indicate that both formulations of the DTPw-HBV candidate vaccine were safe when administered to these healthy infants, with the first dose administered between 2 to 3 months of age, according to a 0, 2, 4 month schedule. The immunological response to the diphtheria, tetanus and B. pertussis antigens in the combined vaccines were similar to those obtained with the commercial DTPw vaccine. The response to the hepatitis B component of the combined candidate vaccines meets the criteria proposed by a WHO task force (May, 1992) that a combined vaccine could be judged acceptable if the minimum protective level for hepatitis B is achieved in more than 95% of the vaccinees.

The conclusion for the booster doses amendment states that the SmithKline Beecham Biologicals's combination DTPwHBV vaccine is both safe and immunogenic and elicits similar results as those obtained

with commercially available DTPw vaccine when used as a booster dose to vaccinate previously primed 18-month children.

Clinical Expert statement

GlaxoSmithKline has reviewed the results of this study and has concluded that they are in accordance with the approved SPC for Tritanrix^{Tm}-HepB.

Rapporteur's conclusion study DTP-HBV-006

The quality of this trial seems to be rather poor: the statistical analysis of this open label feasibility study was seriously limited and the method for retrieving safety results was also far from quality research design. Nevertheless the conclusion of the MAHs is endorsed in so far that the outcome of this trial does not alter the risk – benefit analysis of Tritanrix-HepB. Furthermore the data found do not contest the existing SPC, so no changes are needed as the MAH expert advices.

Clinical Study: 208139/(018/051/054) (DTP-HBV-028) - (Thailand)

Description

This clinical phase III study is a long term follow-up of the primary study DTPw-HBV-028. In the primary study subjects got a 3-dose primary vaccination course with DTPw-HBV, DTPw and HBV vaccines and a booster of the same vaccines at 18 months of age, followed by a booster of DTPw Vaccine at 4 years of age. The aim of this study (018, 051, 054) is to evaluate the long term persistence of antibodies against hepatitis B, diphtheria, tetanus and Bordetella pertussis. Report number 018 stands for the follow-up at Month 30 and at years 4 and 5, report number 051 stands for the follow-up at year 6 and report number 054 for the year 7 follow-up at development phase III.

Methods

- **Objectives**

The objective of this long-term follow-up was to evaluate the long-term persistence of antibodies against hepatitis B (anti-HBs), diphtheria (anti-diphtheria), tetanus (anti-tetanus) and *Bordetella pertussis* (anti-BPT) in subjects who had completed the 3-dose primary vaccination course with DTPw-HBV vaccine and DTPw and HBV vaccines and received two booster doses of the same vaccines as the primary study.

- **Study design**

The primary study was an open, randomised study with three groups. All infants received a dose of hepatitis B vaccine, Engerix™-B, at birth. In the primary study,

Group 1 received DTPw-HBV vaccine (10 µg HBsAg)

Group 2 received DTPw-HBV vaccine (5 µg HBsAg)

Group 3 received DTPw vaccine and HBV as concomitant injections.

A booster dose of the same vaccine that was given in the primary study was administered at **18 months** of age. At **4 years** of age, all subjects who returned for a follow-up visit received a booster dose of DTPw vaccine. During each of the follow-up visits at 30 months, 4, 5, 6 and 7 years of age, a blood sample was taken to evaluate long-term persistence. Reactogenicity and safety were evaluated for primary vaccination and for the 18 months' booster.

- **Study population / Sample size**

Number of subjects enrolled in the primary study: 124

- **Treatments**

The study vaccine was given at 2-4-6 months of age, the booster at 18 months of age. At 4 years of age, all subjects received a booster dose of the local DTPw vaccine under the EPI program. Lot numbers of these DTPw vaccines were not recorded. All vaccines were administered intramuscularly in the anterolateral thigh. Following vaccines were given:

- GSK Biologicals' candidate combined DTPw-HBV(10 µg) vaccine: one dose (0.5ml)
- 2. GSK Biologicals' candidate combined DTPw-HBV (5 µg) vaccine: one dose (0.5 ml),
- 3. GSK Biologicals' recombinant hepatitis B vaccine (EngerixTM-B), given at birth: one dose (0.5 ml)

The reference vaccine was given at 2-4-6 months of age during the primary vaccination course and at 18 months of age during the booster study. All vaccines were administered intramuscularly in the anterolateral thigh. Following vaccines were given:

- Left thigh: GSK Biologicals' DTPw vaccine: one dose (0.5 ml), Lot numbers 13114E7/M (primary) and 13119B9 (18 months)
- Right thigh: GSK Biologicals' recombinant hepatitis B vaccine (Engerix™-B): one dose (0.5 ml), Lot numbers 1080A2 (primary) and 11086A2 (18 months)

- **Duration of the Study**

Long-term follow-up: up to Year 7.

- **Criteria for evaluation**

Anti-HBs antibody concentrations ≥ 10 mIU/ml, anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/ml by enzyme linked immunosorbent assay (ELISA) were considered as protective. Anti-BPT antibody concentrations were determined by ELISA with an assay cut-off of 15 IU/ml determining seropositivity.

NOTE: Anti-HBs antibodies were measured by a Radioimmunoassay (AUSAB RIA -Abbott) until availability of the test kit (i.e. up to Year 5 and partially up to Year 6 time point. Due to the unavailability of this assay, a new assay, an Enzyme-linked Immunosorbent assay (AUSAB EIA from Abbott Laboratories), was used for testing Year 6 and Year 7 blood samples.

- **Statistical Methods**

Analyses were performed on the total vaccinated cohort, ATP cohort and the kinetic cohort. The following analyses were performed for blood samples taken at Months 18 and 30 and at Years 4, 5, 6 and 7: Seroprotection rates for anti-HBs, anti-diphtheria and anti-tetanus antibodies and their exact 95% confidence intervals (CIs) were calculated. Seropositivity rates and their exact 95% CIs were tabulated for anti-BPT antibodies. GMCs and their 95% CIs were calculated for anti-HBs, anti-diphtheria, anti-tetanus and anti-BPT antibodies. Difference/similarity between groups was not evaluated and therefore similarity/comparability is based on clinical judgement.

Results

- **Number of subjects**

In group 1 and 3 the proportion male/female is significantly higher in comparison than group 2, from 30 months throughout the entire study.

Number of subjects:	Group 1	Group 2	Group 3	Total
Number of subjects enrolled in the primary study	41	42	41	**124**
Number of subjects in the total vaccinated cohort (TVC) at Month 18	30	30	33	**93**
Number of subjects in the according to protocol (ATP) Cohort at Month 18	20	23	29	**72**
Number of subjects in the TVC at Month 30	25	23	31	**79**
Number of subjects in the ATP Cohort at Month 30	18	20	27	**65**
Number of subjects in the TVC at Year 4	18	23	28	**69**
Number of subjects in the ATP Cohort at Year 4	15	17	25	**5**
Number of subjects in the TVC at Year 5	14 (17*)	19 (22*)	21 (25*)	**5** **(64*)**
Number of subjects in the ATP Cohort at Year 5	12 (15*)	15 (17*)	19 (23*)	**4** **(5*)**
Number of subjects in the TVC at Year 6	15	19	25	**59**
Number of subjects in the ATP Cohort at Year 6	14	15	23	**52**
Number of subjects in the TVC at Year 7	11	18	17	**46**
Number of subjects in the ATP Cohort at Year 7	10	1	2	**39**

(*) Year 5 time point there were a total of 10 subjects in the TVC and 9 subjects in the ATP who had immunogenicity results but did not have demography results or visit dates.

- **Efficacy results**

Hepatitis B results: approximately 5½ years after the last dose of HBV given in the second year of life, the percentage of subjects with anti-HBs antibody seroprotection rates was 90.9% (95%CI: 58.7; 99.8) and 81.3% (95%CI: 54.4; 96.0) in Groups 1 and 3 respectively and 55.6% (95%CI: 30.8; 78.5) in Group 2. Also anti-HBs GMCs continued to be higher in Groups 1 and 3 than in Group 2. Subjects in Group 2 (who received half the dosage of HBsAg as the other two groups at both primary and booster vaccination time points in the first two years of life) had the lowest anti-HBs GMCs.

D, T and Pw results: three years after the DTPw booster (given at Year 4), at least 94.1% of all subjects had seroprotective levels of anti-diphtheria and anti-tetanus antibodies and at least 88.0% of subjects were seropositive for anti-BPT antibodies. The anti-diphtheria and anti-BPT antibody GMCs were comparable in all three groups. The point estimate of the anti-tetanus antibody GMC was lower in Group 1 as compared to Group 2 and Group 3 but the CIs largely overlapped between groups.

- **Effectiveness results**

Not assessed in this study.

- **Safety results**

Not assessed in this study.

Conclusion

Long-term persistence of anti-HBs antibodies after primary vaccination with DTPw-HBV (10 µg HBsAg) was high (90% of the vaccinees continued to have seroprotective antibody concentrations of anti-HBs antibodies at Year 7) and comparable to that after vaccination with HBV (10 µg HBsAg) vaccine administered separately but concomitantly from the DTPw vaccine. Majority of subjects (at least 81.3%) in the three groups continued to have seroprotective/seropositive antibody levels to the diphtheria, tetanus and whole cell pertussis antigens, at Year 7, i.e. three years after the last booster dose at Year 4.

Clinical Expert statement

GlaxoSmithKline has reviewed the results of this study and has concluded that they are in accordance with the approved SPC for Tritanrix™-HepB.

Rapporteur's conclusion study DTP-HBV-028

Although this is an open label clinical trial (no blinding), the conclusion of the MAH is endorsed and although only immunogenicity data are evaluated and the effectiveness and the safety was not assessed in this study. The data found do not contest the existing SPC, so no changes are needed as the MAH expert advices.

Discussion on clinical aspects

Not applicable.

4 Rapporteur's Overall Conclusion and recommendation

Overall conclusion

The data found in the studies do not contest the currently approved SPC, so no changes are needed as the MAH expert advices.

Recommendation

No further action required.

5 Request for supplementary information

Not applicable