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 µg 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 1 culture 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 component 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 2-8C 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.

3. 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.

1. 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 ≥ 98% 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, 3.5 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 one clinical study. A revised statement and a table in the SPC reflect this clearly.
- The balance between this aspect and the operational benefits 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. RR1).

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.