# SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion for the approval of TWINRIX Paediatric. This scientific discussion has been updated until 01 February 2004. For information on changes after this date please refer to module 8B**

## 1 Introduction

Hepatitis A and hepatitis B virus infections represent the most frequent forms of viral disease of the liver. It is widely accepted that prophylaxis against hepatitis A and hepatitis B in the form of vaccines, is the most efficacious way of offering long-term protection.

A combined Hepatitis A and Hepatitis B vaccine for use in adults and adolescents aged 16 years and over, Twinrix Adult was granted a positive opinion by the CPMP on 22 May 1996 and the European Commission granted a marketing authorisation on 20 September 1996. The Company subsequently submitted an application for a marketing authorization for Twinrix Paediatric, a combined hepatitis A, hepatitis B vaccine for use in the paediatric population.

The Adult and Paediatric Twinrix vaccines differ only in fill volume (1.0 and 0.5 ml respectively) and in product literature particulars. All agreements made by the Company with the Members States with respect to Twinrix Adult were applied for Twinrix Paediatric.

The indication for Twinrix Paediatric is as follows:

"Twinrix Paediatric is indicated for use in non immune infants, children and adolescents from 1 year up to and including 15 years who are at risk of both Hepatitis A and Hepatitis B infection."

## 2 Chemical, biological and pharmaceutical, aspects

**Composition of the medicinal product**
A 0.5 ml dose of Twinrix Paediatric contains not less than 360 ELISA Units of purified inactivated HA virus and 10 μg of purified recombinant HBsAg protein.

The total amount of aluminium (Al) is 0.225mg per dose. (specification 0.35 – 0.65 mg/ml). The amount of aluminium per dose is well below the Ph. Eur. limit.

2-phenoxyethanol is used as preservative. This preservative is also used in Havrix, the Company's Hepatitis A monovalent vaccine.
The composition of Twinrix Paediatric is quantitatively one half, for all ingredients, that of the adult vaccine. The dose volume of the paediatric vaccine is 0.5 ml that of the adult vaccine, 1.0 ml.

Since Twinrix Paediatric and Twinrix Adult are identical in every respect except the quantitative composition, the pharmaceutical report of Twinrix Paediatric differed from that of Twinrix Adult only in respect of changes requested as a result of the company responding to the CPMP Consolidated List of Questions for the adult vaccine..

**Method of preparation**

The manufacture of the vaccine consists of :

- preparation of adsorbed HBsAg concentrate
- preparation of adsorbed HAV antigen concentrate
- pooling of the adsorbed antigens and addition of the excipients
- filling into sterile vials or syringes and packaging

Information on manufacture of the active ingredients (HBsAg and HAV antigen) is given below. With respect to manufacture of the finished product, the vaccine is formulated by pooling bulk preparations of purified inactivated hepatitis A virus (HA) and purified recombinant hepatitis B surface antigen (HBs Ag) separately adsorbed onto aluminium salts, resulting in the final bulk which is filled in final

containers. The formulation is, to a large extent, a blend of the bulk antigen concentrates which are used for the monovalent vaccines Havrix and Engerix B

Formulation and filling are carried out under aseptic conditions using sterile equipment and sterile solutions.

The filled containers are stored at 2-8° C waiting labelling and packaging. Final bulks and lots of filled final containers (vials and syringes) are tested for compliance with the release specifications. Consistency of production is shown by the consecutive production lots meeting the release control test specifications (see below).

**Manufacture and control of the starting materials**

HA Ag: HA Ag is produced on human diploid MRC-5 cells. After virus propagation the cells are washed and following cell disruption the virus is harvested. Virus inactivation is based on the principles used in the production of inactivated polio vaccine. Inactivation has been adequately validated.

HBsAg: HBsAg is produced by culture, in a selective medium, of genetically engineered yeast cells

Reagents and other ingredients: The company has documented that appropriate measures are in place to ensure the safety of the calf serum used in production of the HAV antigen. Specifications have been provided for all other reagents/excipients used in production of the vaccine and these are, where relevant, in accordance with Ph.Eur monographs.

**Control of the intermediate and finished product**

Appropriate tests are carried out on both the intermediate products and the final product. Where relevant, Ph. Eur. and WHO requirements are met.

HAV assay: Potency of the adsorbed vaccine is evaluated by an ELISA method. The method has been adequately validated.

HBsAg assay: The potency of the adsorbed antigen is evaluated by a direct quantitative determination of adsorbed HBsAg using an in vitro immunological method..

The general safety test in mice and guinea pigs was performed on a total of 8 lots of HAB vaccine. No abnormality was observed and the lots complied with the specifications laid down in Ph. Eur. In line with the trend to reduce the use of animals in testing of medicinal products and in line with the Ph. Eur. recommendations, the general safety test is no longer conducted for routine QC release.

The product is subject to EC Batch Release Protocols in accordance with EC Guidelines III/5861/93 and III/3382/93: 'Control Authority Batch Release of Hepatitis A Vaccine and Hepatitis B Vaccine (rDNA)' respectively.

**Stability**

Adsorbed HA Ag and adsorbed HBsAg concentrates can be prepared in advance and stored at 2° C to 8° C for a given period of time before pooling to form the final vaccine.

Stability data supporting a shelf life of 24 months for the final filled product was provided. at the time of approval. Additional data supporting the extension of the shelf-life to 36 months at +2 – +8 ˚C were submitted later on and approved.

## 3 Toxico-pharmacological aspects

No formal toxicology studies were presented or considered necessary at the time of approval, by the CPMP.

## 4 Clinical aspects

A pilot study compared the combined vaccine Twinrix Adult (pilot lot) with Havrix (hepatitis A vaccine) and Engerix-B (hepatitis B vaccine) given at different sites or mixed in the same syringe. It was an open randomised study in which healthy adults received 3 doses at 0, 1 and 6 months. The 3 groups were:

- Group 1 received Twinrix (1 ml)
- Group 2 received Havrix (1 ml) in one arm and Engerix B (1 ml) in the other arm
- Group 3 received Havrix and Engerix B in the same syringe (2 ml)

Blood samples were taken at time 0, 1, 2, 6 and 7 months. The results showed satisfactory immunological response. Administering the vaccines together did not compromise the Geometric Mean antibody Titre (GMT) for HAV. All vaccinees were also shown to achieve protective levels of anti-HBs.

The incidence of adverse reactions were observed to be lower for Twinrix Adult than for the two monovalent vaccines mixed in a single syringe, and not significantly different from the incidence observed when the two monovalent vaccines were administered simultaneously.

The clinical evaluation of the lot-to-lot consistency of the production methods was performed on data from 6 clinical trials carried out using the adult presentation of the combined Hepatitis A and Hepatitis B vaccine. These data had previously been provided with the Twinrix Adult application.

As identical methods were used for the production of the paediatric presentation, the results from the studies in adults were considered to be applicable also to the paediatric presentation they demonstrated that production lots are consistent with respect to both the reactogenicity profile and the immune response, which they induce.

**Efficacy**

Two studies were carried out in children and adolescents to evaluate the reactogenicity and immunogenicity of the combined Hepatitis A and Hepatitis B vaccine at the paediatric dosage level. The same lots as for adults were assessed; one lot in children aged 1-6 years and two lots in children aged 6-15 years A total of 180 subjects were vaccinated and analysed for reactogenicity; 168 (93.3%) of these were included in the analysis of immunogenicity. The reasons for exclusion of the subjects have been documented in the individual study reports.

Results show an immune response at least as good as that seen during the adult studies for both components. All children had satisfactory anti-HAV antibody levels by month 2. Almost 100% showed an anti-HBs titre ≥10 mIU/ml (=seroprotection) at the sixth month timepoint, just prior to administration of the third vaccine dose. In both cases substantial increases in antibody titre response occurred after the third dose.

Although no long term follow-up data were submitted in the original application., The applicant contended that since the immunogenicity results seen in these two studies were at least as good as those seen in the adult studies, the persistence of protection which was shown in adult studies (18 month follow-up in adult volunteers for Twinrix Adult) could be extrapolated to the childhood setting..

The lack of long-term immunogenicity data was considered and discussed by the CPMP and it was agreed that long-term immunogenicity data in relation to the persistence of immune response in the relevant patient group should be provided as a follow-up measure. Data which have subsequently been submitted in fulfillment of this follow-up measure support the application of similar recommendations for boosting after a standard primary course of Twinrix Paediatric as are adopted after standard courses of Twinrix Adult or of age appropriate Havrix and Engerix B.

The data submitted were derived from five studies in which the immunization schedule was 0,1 and 6 months. Three of the trials were follow-up reports on trials submitted in the original dossier for approval of Twinrix Adult (two studies) and Twinrix Paediatric (one study). The remaining two reports contained long-term data on antibody titres in adults following Havrix or Engerix B.

**Since the Marketing Authorisation was granted**, an update regarding the need for a booster dose of hepatitis B vaccine and regarding the persistence of anti-HAV and anti HBs antibodies has been approved.

Since the data on long-term antibody levels are compared with trials with Havrix and Engerix B, these early trials are summarised below.

*Study with Havrix:*

- HAV-058: The study commenced in 1990, this was a two-lot consistency study of HAV 720 EL.U vaccine in adults of 18-29 years. The report describes additional long-term follow up from month 60 to month 96; 45 subjects returned at the last timepoint and 40 of these were evaluable.

*Study with Engerix B:*

- HBV-006: The study commenced in 1985 and initially randomised 300 adults (mean 24 years) to receive:
    - three doses of recombinant HBsAg at one of 10, 20 or 40 µg per dose at 0, 1 and 6 months (all Lot L) or
    - three doses at one of 10 or 20 µg per dose (all Lot N) or
    - three doses of the licensed plasma-derived HBsAg vaccine (20 µg per dose)

Of these 300, 269 were initially seronegative and remained evaluable in the initial analysis; 168 of these had not received a booster and were available for follow-up at month 60. Data from months 7 and 60 were available for 165 subjects.

*Study with Twinrix Adult*

- HAB-028: This study commenced in 1993 as a three-lot consistency study with Twinrix Adult. Of the 150 subjects of 17-39 years initially vaccinated, 58 returned at month 60. Serological data are presented for 44 of these who met the protocol requirements for evaluability and also for all the 58 subjects.
- HAB-032: This study also commenced in 1993 as a three-lot consistency study with Twinrix Adult. Of the 157 subjects of 17-43 years initially vaccinated, 92 returned at month 60. Serological data are presented for 69 of these who met the protocol requirements for evaluability and also for all the 92 subjects.

*Study with Twinrix Paediatric*

- HAB-039: This study commenced in 1994 as a single lot, open study of Twinrix Paediatric administration in children of 1-6 years. The study proposed follow-up for up to 48 months. Of the 60 children immunised at baseline, 43 returned at month 48 and 40 of these children met the evaluability criteria for assessment of immune responses.

The conclusions from these studies were the following

*HAV:*

- The GMT at one month after the second dose of Havrix (total 2880 ELISA IU) in study 058 was less than observed at one month after the third dose of Twinrix in the two studies in adults (028, 032) and one study in children (039). In the latter studies, three doses of 720 ELISA IU was given to adults and three doses of 360 ELISA IU were given to children. At 36 and 48 months, GMCs in the Twinrix studies ranged from approximately 50-110% of that reported in 058.
- All adults and children followed to 60 and 48 months, respectively, in the Twinrix studies remained seropositive, as did all those followed in study 058 after Havrix.

*HbsAg:*

- In study 006, the GMTs at month 7 were very similar for the two groups given 20 µg antigen (2067 and 2106 mIU/mL), falling to 120 and 218 mIU/mL, respectively, at month 60. In the

Twinrix studies in adults (028 and 032), GMCs at month 60 were 320 and 115 mIU/mL. In the study in children (039), the GMC for those followed to month 48 was 308 mIU/mL.

- In study 006 at month 60, all subjects who were seronegative at baseline, received recombinant HBsAg at months 0, 1 and 6, and returned for evaluation were still seropositive. The seroprotection rates at month 60 were 96% and 100% in the 20 µg dose groups. In the Twinrix studies in adults (028 and 032), 93-96% were seroprotected at month 60 and 98-100% were seropositive. In the study in children (039), all children followed to month 48 were seropositive and 98% were seroprotected.

**Safety**

In summary, in the original application, a total of 538 doses of vaccine were administered to 180 subjects and data were available for all doses administered. Adverse events were reported in approximately 45% of administrations in all subject groups. There was no increased incidence of ADR reports with successive vaccine injections. Although there was a slight trend towards decreased frequency, particularly of local reactions, with increasing age; the number were small.

Local adverse reactions were reported after approximately 30% of injections whereas systemic reactions were reported after approximately 21% of doses. The majority of these were reported as mild. The most common local side effect was soreness. This usually resolved within 24 hours. Virtually all reported cases of soreness resolved spontaneously by day 3. Other local side effects were redness and swelling.

In terms of systemic effects, the most commonly reported was fatigue (11%) followed by headache (8%), then malaise (7%). Fever was reported following less than 4% of all doses; temperature > 39°C was reported with an overall incidence of <0.5%.

Only one serious adverse event was reported amongst the 180 subjects participating in the paediatric studies. An 8-year-old child experienced headache, fever, photophobia, conjunctivitis and lymphadenopathy, two days after the first vaccine dose. The symptoms resolved within four days. The child was withdrawn from the study.

Unsolicited symptoms were mostly mild and no patterns were evident. Intercurrent infections (upper respiratory tract infection, otitis media, chicken pox) were the most common reported.

There were no deaths reported in any of the studies.

**Post marketing data**

The following reactions have been reported very rarely in temporal association with Twinrix vaccination:

- Body as a whole: flu-like symptoms (fever, chills, headache, myalgia, arthralgia), fatigue, allergic reactions including anaphylactic and anaphylactoid reactions and serum sickness like disease
- Cardiovascular general: syncope, hypotension
- Central and peripheral nervous system: dizziness, paraesthesia
- Gastro-intestinal system: nausea, vomiting, decreased appetite, diarrhoea, abdominal pain
- Liver and Biliary system: abnormal liver function tests
- Neurological disorders: convulsions
- Platelet, bleeding and clotting: thrombocytopenia, thrombocytopenic purpura
- Skin and appendages: rash, pruritis, urticaria
- White cell and reticuloendothelial system: lymphadenopathy

All these changes have been included in the product information.

In addition, the following very rarely reported reactions have been included in the product information within a section relating specifically to post-marketing experience with the monovalent vaccines:

- Central and peripheral nervous system: cases of peripheral and/or central neurological disorders, and may include multiple sclerosis, optic neuritis, myelitis, Bell's palsy, polyneuritis such as Guillain-Barre syndrome (with ascending paralysis), meningitis, encephalitis, encephalopathy
- Skin and Appendage: erythema exsudativum multiforme
- Vascular extracardiac: vasculitis

**Other studies**

The applicant resubmitted summary reports of all six studies submitted in support of Twinrix Adult. The results from these studies were similar to those seen in children and supported the applicants contention that the immune response seen following vaccination of adults could be extrapolated to the childhood setting.

**Postmarketing Surveillance**

GSK Biologicals has taken the appropriate steps to ensure that the SPC text will reflect information on the Company's database.

## 5 Conclusions

Twinrix Paediatric is a combined Hepatitis A and Hepatitis B vaccine. The formulation of Twinrix Paediatric is a combination of two active substances used in different previously authorised vaccines: Havrix and Engerix-B, for the prevention of Hepatitis A and Hepatits B infections respectively. A few outstanding pharmaceutical issues were identified during the evaluation procedure. Following a company response on these points, the CPMP during their meeting on 15-17 October 1996 concluded that the company had satisfactorily resolved these issues.

The clinical data submitted with this application for the combined hepatitis A and B vaccine Twinrix Paediatric was considered to be sufficient for approval of the indication "Twinrix Paediatric is indicated for use in non immune infants, children and adolescents from 1 year up to and including 15 years who are at risk of both hepatitis A and hepatitis B infection." The proposed amendments of the SPC text were also considered to be satisfactory and were adopted by the CPMP during this meeting.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Twinrix Paediatric "for use in non immune infants, children and adolescents from 1 year up to and including 15 years who are at risk of both hepatitis A and hepatitis B infection." was favourable and therefore recommended the granting of the marketing authorisation.

Nevertheless the lack of long-term immunogenicity was considered and discussed by the CPMP and it was agreed that long-term immunogenicity data in relation to the persistence of immune response in the relevant patient group should be provided as a follow-up measure. This information has meanwhile been provided as summarised above and these data submitted by the Company are considered by the CPMP, to adequately support the current SPC text.

Additional information requested by the CPMP on pharmaceutical and clinical aspects has been provided. Where information is in the course of being generated, the Company has committed to provide this to the CPMP within the specified time frame.

The overall benefit/risk analysis remains favourable following the renewal of the Marketing Authorisation in November 2001.

Since the Marketing Authorisation was granted, an update regarding the need for a booster dose of hepatitis B vaccine and regarding the persistence of anti-HAV and anti HBs antibodies has been approved.
In addition, at the time of the 5-year renewal, the CPMP considered that the benefit/risk profile of Twinrix paediatric continued to be favourable and therefore, recommended the renewal of the Marketing Authorisation. Since then, new safety data have been received which led to amendments in the product information.