SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of TWINRIX Adult. 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.

In regions of low endemicity such as Europe and North America, population-based studies and disease surveillance have shown that infection by either the hepatitis A or B viruses is more prevalent in specific population groups (although not exclusively restricted to) where high risk is defined by lifestyle or occupation; for e.g. persons who travel or move from regions of low endemicity to high endemicity, persons who receive blood or blood-derived products. These groups who have been shown to be at high risk would thus derive considerable benefit from the combination of prophylaxis. Thus the rationale for such a combined vaccine was derived primarily from epidemiological studies of hepatitis A in several of the European states. Furthermore the combined vaccine is seen to be more advantageous in that it reduces the number of injections, offers greater convenience and logistical advantages with respect to immunisation with the two monovalent vaccines.

The formulation of TWINRIX Adult is a combination of two different previously authorised active ingredients, which are the same ingredients as in the vaccines: HAVRIX Adult and ENGERIX-B for Hepatitis A and Hepatitis B prophylaxis respectively, in adults. Twinrix Adult is formulated by pooling bulk preparations of the purified inactivated hepatitis A virus (HA) and purified hepatitis B surface antigen (HBsAg), separately adsorbed onto aluminium salts. 2-Phenoxyethanol is used as preservative. A 1.0ml dose of vaccine contains not less than 720 ELISA units of inactivated HA virus and 20 µg of recombinant HBsAg protein.

2. Chemical, biological and pharmaceutical, aspects

The Twinrix Adult combined vaccine is formulated by pooling bulk preparations of the purified inactivated hepatitis A virus and purified recombinant hepatitis B surface antigen.

Composition of the medicinal product

The formulation is to a large extent a blend of the bulk antigen concentrates, which are already marketed as monovalent vaccines (Havrix and Energix B). The total amount of aluminium (adjuvant) is 0.45 mg per dose. The specification for Aluminium content in the finished product is between 0.35 and 0.65 mg/ml. The amount of aluminium per dose is well below the Ph.Eur limit.

The preservative used for the combined vaccine is 2-Phenoxyethanol, which is also used in Havrix.

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 vials or syringes and packaging

The process is carried out under aseptic conditions using sterile equipment and sterile solutions. Methods of sterilisation of the vials and syringes have been adequately provided. The filled containers

are stored at 2-8°C waiting labelling and packaging. Final bulks and lots of filled final containers (vials and syringes) were tested and shown to comply with the release specifications.

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. This inactivation has been adequately validated.

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

The details were the subject of a recent renewal application for Engerix B which received a positive CPMP opinion

Reagents and other ingredients: Calf serum: The company has documented that appropriate measures are in place to ensure the safety of the material

Specifications have been provided for other reagents/excipients and, where relevant are in accordance with Ph. Eur. (European Pharmacopoeia) requirements.

Control of the intermediate and finished products

Appropriate tests are carried out on both the intermediate products and the final product where relevant, Ph. Eur. and WHO requirements are met. A test for inactivation is described in the monograph for hepatitis A vaccine currently under preparation by the European Pharmacopoeia (Ph. Eur.). At such time as the Ph. Eur. Monograph becomes official, the company agrees to reconfirm that the test has been installed as established therein. The specification for potency of the HBsAg component in Twinrix Adult as well as Engerix B will conform to future requirements of the Ph. Eur. Commission.

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

HBsAg: The potency of the adsorbed antigen is evaluated by a direct quantitative determination of adsorbed HBsAg using an *in vitro* immunological method (Enzyme Immunoassay "Auszyme monoclonal" - Abbott Laboratories). The assay method has been satisfactorily validated.

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.

The stability data provided in support of a shelf-life of 24 months was clarified by the company and considered to be acceptable.

The CPMP on 22 May 1996 considered that the additional information provided as well as the commitments agreed to by the company were acceptable.

Manufacturing authorisations/inspection status

This point has been addressed in section II.1 of this assessment report.

3. Toxicological and pharmacological aspects

Pharmacodynamics

No pharmacodynamic data was submitted. *In vivo* potency tests were carried out in mice, however the commercial lots of HAB will be released following *in vitro* potency tests rather than *in vivo* potency tests.

Toxicology

Neither the active ingredients nor the excipients used in this combination vaccine (HAB) are novel and their respective concentrations are within the ranges currently used in other vaccines.

No other toxicity studies were performed. The general safety tests in mice and guinea pigs were performed on a total of 8 lots of HAB vaccine. No abnormality was observed and the lots comply with the specifications laid down in Ph.Eur

No other data was submitted or considered necessary.

4. Overview of the Part IV of the dossier: clinical aspects

Efficacy

Data have been provided for 998 subjects aged 17-60 years all of whom received Twinrix Adult in the recommended dose schedule (the majority were under 40 years of age). One pilot lot and three production lots were used.

A pilot study used a pilot lot and compared Twinrix Adult with Havrix and Engerix B given at different sites or mixed in the same syringe. It was an open randomized study in which healthy subjects received 3 doses at 0, 1 and 6 months.

The three groups were:

- Group 1; received Twinrix Adult (1 ml)
- Group 2; received Havrix (1 ml) in one arm and Engerix B (1ml) 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 responses. Administering the vaccines together did not compromise the Geometric Mean antibody Titre (GMT) for HAV - in fact it was seen to be significantly higher than when they were given separately at different sites. All vaccines were shown to achieve protective levels of anti-HBs.

The adverse reaction profile was observed to be greater in terms of local effects for the vaccines mixed in a single syringe (Group 3: 2ml dose) compared with the single injection of 1ml vaccine doses.

The remaining clinical studies included a total of 843 individuals and compared lots of Twinrix Adult. All studies were carried out to the same protocol. The subjects included were healthy males and females in the age range of 18-60 years. Pregnant females and patients with liver enzymes twice the upper limit of normal were excluded. Only subjects seronegative for hepatitis A and hepatitis B were to be included in the studies. Immune response was measured by rate of seroconversion and GMT.

Immunogenicity data were available for 784 of the 843 subjects enrolled. With regard to the hepatitis A component, a titre above cut-off was seen in 94% of subjects after the first dose, 99.5% after the second dose and 100% after the third dose. For hepatitis B, 71% of the subjects had seroconverted after dose 1, 97% after dose 2 and 99.7% after dose 3.

Since the Marketing Authorisation was granted, a new vaccination schedule 0,7, 21 days with a fourth dose at 12 months has been approved when, for exceptional circumstances, a travel is anticipated. 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 also been approved.
Data are provided hereafter:

Twinrix Adult given at new schedule (days 0, 7, 21 and month 12)

HAB-049: This open study of 1997-99 in adults (18-48 years; 50% each gender) compared Twinrix Adult given at days 0, 7, 21 plus month 12 with a combination regimen of Havrix at day 0, Engerix B at days 0, 7 and 21 and both mono-component vaccines at month 12. Of the 479 subjects immunised at

baseline, 239 received Twinrix. There were 430 subjects boosted at 12 months (210 Twinrix) and immunological data were available for 362 (183 Twinrix) evaluable subjects.
The primary efficacy variable was the rate of seropositivity re HAV and seroprotection re HBsAg at day 28 (one week after the third injection).

Day 28 immune responses

- For antibody to HAV in the 403 evaluable subjects at this timepoint, all subjects were seropositive after three doses of Twinrix and 190/192 (99%) were seropositive after a single dose of Havrix at day 0. Although Havrix contains twice the viral antigen content of Twinrix (1440 *vs* 720 ELISA IU), the GMC after Twinrix was significantly higher at 845 mIU/mL, compared with 512 mIU/mL after Havrix. At three months from baseline, seropositivity rates were 100% for Twinrix and 98% for Havrix, with GMCs at 628 and 219 mIU/mL, respectively. At months 1, 2 and 3, the lower 95% CIs around the differences in seropositive rates were within -4%. In the ITT cohort, the findings at months 1, 2 and 3 were entirely consistent with the results from the evaluable patient subset.
- For antibody to HBsAg at day 28, 82% in the Twinrix group were seroprotected after three doses within 21 days, compared with 84% after three doses of Engerix B at the same timepoints. The GMCs were not significantly different at 65 and 98 mIU/mL, respectively. At three months from baseline, based on 390 subjects, 95% in the Twinrix group and 91% in the Engerix B group were seroprotected; GMCs were 183 and 131 mIU/mL, respectively. At months 1, 2 and 3, the 95% CIs around the differences in seroprotection rates were within -10%. In the ITT cohort, the findings at months 1, 2 and 3 were entirely consistent with the results from the evaluable patient subset.

At day 28, 82% in the Twinrix group and 83% in the comparative group were both seropositive with regard to HAV and seroprotected with regard to HBsAg.

Responses to the booster dose at month 12

- For antibody to HAV, 96% in the Twinrix group and 95% in the Havrix group were still seropositive before boosting and all subjects were seropositive at month 13. The pre-dose and post-dose GMCs were significantly higher in the Twinrix group at 373 and 170 mIU/mL and at 9571 and 5205 mIU/mL, respectively. Results for the ITT cohort reflected these findings.

- For antibody to HBsAg, 94% in the Twinrix group and 92% in the Engerix B group were seroprotected pre-boosting and all met this criterion at month 13. The pre-dose GMCs were significantly higher in the Twinrix group (209 and 106 mIU/mL) but the post-dose GMCs were comparable at 26,000 and 29,200 mIU/mL. Results for the ITT cohort reflected these findings.

At month 13, 90% in the Twinrix group and 88% in the comparative group were both seropositive with regard to HAV and seroprotected with regard to HBsAg.

Long-term antibody persistence

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 were 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

The most common local reaction was soreness at the site of injection (43%). Other main local side effects included redness (17%) and swelling (11%). These reactions were defined as severe in 1-2% of the subjects. There were no clinically significant differences between lots except for one lot which showed significantly less redness ($p<0.03$).

Systemic side effects were observed in approximately 17% of subjects. The most common side effects were headache (9%), fatigue (10%), malaise (5%) and nausea (3%). Fever was rarely reported. Systemic side effects were judged to be severe in approximately 1% of the cases. There were no

differences in the incidence of systemic side effects between groups in the pilot study or between lots in the main studies.

No deaths were reported. Administration of the vaccine to previously seropositive individuals was not found to be hazardous.

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 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

A study involving the measurement of liver enzymes from subjects was carried out. Two participants were noted to have an increase in either AST or ALT greater than two-fold. These were withdrawn from the study and follow-up blood samples showed that the levels returned to normal. No symptoms were recorded in association with the elevated enzymes.

The clinical programme also included testing for both anti-HAV antibodies and neutralising antibodies. The results showed that the antibodies elicited by vaccination had neutralising activity.

An additional study was also performed on healthy seronegative subjects over the age of 40 years. The reactogenicity profile was found to be similar to that found in young adults. Although the GMT was observed to be lower than in the young, seroconversion rate was found to be the same. No additional safety hazards were observed in this age group. These results have been seen before with the component vaccines.

Long term immunogenicity and safety profile of this combination vaccine has been studied in the follow-up of 2 studies, over a period of 18 months. The kinetics of decline of both anti-HAV and anti-HAB after administration of Twinrix Adult are observed to be similar to those observed for the monovalent vaccines.

5. Conclusions

The formulation of Twinrix Adult is a combination of two different previously authorised active ingredients, which are the same active ingredients in the vaccines: Havrix Adult and Engerix-B, for the prevention of Hepatitis A and Hepatitis B prophylaxis respectively.

The clinical data submitted with this application for the combined hepatitis vaccine Twinrix Adult was considered to be sufficient for the approved indication of: "TWINRIX Adult is indicated for use in non immune adults and adolescents of 16 years of age and above who are at risk of both hepatitis A and hepatitis B infection.".

A number of outstanding pharmaceutical points were identified during the evaluation procedure. Additional information was submitted by the company and further addressed by way of oral explanations during the CPMP break-out session on 20 May 1996. These outstanding points were considered by the CPMP to be sufficiently addressed. The company also committed itself to submit additional information on chemical, pharmaceutical and biological aspects as requested by the CPMP.

Thus the CPMP concluded that the overall benefit/risk analysis was favourable and granted two positive opinions for Twinrix Adult to accommodate for the monodose syringe and vial presentations.

Since the Marketing Authorisation was granted, a new vaccination schedule 0,7, 21 days with a fourth dose at 12 months has been approved when, for exceptional circumstances, a travel is anticipated. 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 also been approved.

In addition, at the time of the 5-year renewal, the CPMP considered that the benefit/risk profile of Twinrix adult 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.

At the request of the CPMP, following the results of a retrospective analysis conducted in Germany of immunogenicity in 104 subjects who had received a full course of Twinrix Adult between 1997-2000, the Twinrix adult product information was updated in order to reflect the factors that may lead to a sub-optimal immune response to the HbsAg component of the vaccine.