SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before approval of AMBIRIX. This scientific discussion has been updated until 1 April 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Ambirix is a combined viral vaccine that contains no live viral particles. The hepatitis A virus (HAV) component is inactivated and the hepatitis B virus (HBV) surface antigen component (HBsAg) is a product of recombinant technology. The composition of *Ambirix* is identical to the applicant's licensed vaccine *Twinrix Adult*, given as 3 dose primary schedule to subjects 16 years of age and above.

Ambirix is now proposed for use in children and adolescents from 1-15 years according to a two-dose primary schedule. A different name has been proposed for the product when used in children and adolescents from 1 to 15 years so as to differentiate the two modes of use of the same antigen content vaccine.

2. Chemical, pharmaceutical and biological aspects

Composition

Ambirix is a suspension for injection and will be supplied only in pre-filled syringes, with or without separate needles, in pack sizes of 1, 10 and 50 syringes.

A 1 ml dose of Ambirix contains not less than 720 ELISA Units of purified inactivated HA virus and 20 µg of purified recombinant HBsAg protein.

The total amount of aluminium (Al) is 0.45mg 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 vaccine is formulated in 150 mM sodium chloride to ensure isotonicity and contains trace amounts of neomycin, carried over from the HA virus production process.

The proposed vaccine composition is identical to that of the currently registered *Twinrix Adult* vaccine for which the EU Commission granted a Marketing Authorisation (EU/1/96/020/001-009) on September 20, 1996.

Active substance

The active substances are the same as those already authorised in Twinrix Adult.

Other ingredients

The other ingredients and primary packaging materials are the same as those already authorised in Twinrix Adult.

Product development and finished product

The manufacturing process and specifications remain unchanged compared to Twinrix Adult. The applicant has submitted the currently approved specifications of Twinrix Adult, which will also be applicable to Ambirix. All sites proposed are currently registered for the stated purposes for Twinrix Adult.

Stability of the Product

Given the identical composition and primary packaging materials, a shelf life of 36 months at 2-8 °C, which is the shelf life currently approved for Twinrix adult, can be accepted.

Discussion on chemical, pharmaceutical and biological aspects

Ambirix is in all aspects identical to the already approved product Twinrix Adult. The currently approved specifications and shelf life of Twinrix Adult will also be applicable to Ambirix. All sites proposed are currently registered for the stated purposes for Twinrix Adult. Ambirix will be supplied only in pre-filled syringes, with or without separate needles, in pack sizes of 1, 10 and 50 syringes.

. All follow up measures (FUMs) have been fulfilled except for one, regarding the formulation of the media used in the production of a constituent of Ambirix. The Company has accepted to report on this FUM also in the context of it's Ambirix file application.

Regarding compliance with the Note for Guidance on minimising the risk of Transmitting Animal Spongiform Encephalopathy Agent via Human and Veterinary Medicinal Products (EMEA/410/01-Rev. 1), the Company submitted a Type II variation on 12 December 2000 to its Twinrix Adult marketing authorisation. A positive opinion has been adopted for this variation during the September 2001 CHMP meeting.

3. Toxico-pharmacological aspects

This was entirely cross-referenced to the *Twinrix Adult* dossier since *Ambirix* is identical to this product. There is no new information.

4. Clinical aspects

The data submitted by the company to support the use of Ambirix™, administered in a two-dose schedule, with an interval between doses of 6 to 12 months, in children and adolescents aged from 1 to 15 years inclusive, is reviewed and summarised.

The reports for 7 clinical studies are evaluated. The studies set out to assess the feasibility of the two-dose schedule. There were three pivotal studies , a fourth study which examined a flexible schedule with an interval between doses of 6 to 12 months. During the post-authorisation phase, one comparative study in which Ambirix and Twinrix adult were compared and two studies in which the concomitant administration of a DTPa-IPV/Hib vaccine (Infanrix IPV Hib) and a MMR vaccine (Priorix) were submitted. Investigations included:

- safety, tolerability and immunogenicity,
- evaluation of an inter-vaccination interval of 6 to 12 months.

The design of each study took into consideration the Good Clinical Practice Guidelines in operation at the time of the initiation of the study.

Altogether, 1222 subjects aged ≥ 1 year old were enrolled, of which 983 were assessed for safety and 911 for immunogenicity.

Clinical pharmacology

Since this is a vaccine, there are no relevant data. All immunogenicity data were provided in the discussion of the clinical trials.

Immunogenicity

Seven clinical trials evaluated the immunogenicity of *Ambirix* in 911 healthy children (aged ≥ 1 years old) and adolescents proven to be sero-negative at baseline.Antibody titres have been expressed in mIU/ml by reference to a WHO reference serum, for both antigens.

Results for both anti-HAV and anti-HBs have been expressed as seroconversion (SC) and/or seroprotection (SP) rates, at the given time points. Geometric mean titres (GMTs) have also been computed.

Anti-HAV antibody was measured in the primary phases of these trials using a commercial ELISA assay with a cut-off for seronegativity/positivity at 33 mIU/mL. In the follow-up phases to 24 months in two trials, the new EIA used for anti-HAV assays had a cut-off at 15 mIU/ml. The EIA was also used to re-test month 7 samples so as to directly compare with month 24 results. Seropositivity rate (S+/SC) for Anti-HAV was defined as the percentage of subjects with titre greater than the cut-off point.

Anti-HBs antibody was measured in the primary phases by a commercial radioimmunoassay (with a cut-off of 1 mIU/ml) whereas an ELISA that had a cut-off at 3.3 mIU/mL assayed month 24 samples. Seropositivity was defined in both cases as a result above the cut-off. For both assays, seroprotection was defined as ≥ 10 mIU/mL.

All assays were performed blinded to vaccine treatment using validated procedures with adequate controls.

Analyses for each of the studies reported are based upon the "According to Protocol" (ATP) cohorts. ATP results were consistent with "Intention to Treat" (ITT) analyses.

Main studies

Pivotal studies included HAB-075, HAB-076 and HAB-084.

- *Children of 6-11 years*

HAB-076 was an open study that evaluated the immunogenicity of two doses of *Ambirix* at 0 and 6 months in 203 evaluable subjects of 1-11 years of age, of which 132 were ≥ 6 years old.

In subjects ≥ 6 years old, seropositivity rates for anti-HBs antibodies were 73.8% one month after the first dose and 100% after the second dose given at month 6 (i.e. month 7). The anti-HBs seroprotection rates (titers ≥ 10 mIU/ml) at both time points were 34.6% and 98.5% respectively.

Seropositivity rates for anti-HAV antibodies were 99.2% one month after the first dose and 100% after the second dose given at month 6 (i.e month 7).

The GMCs for anti-HAV and anti-HBs antibodies were 11293 mIU/ml and 7622 mIU/ml respectively after completion of the 2 dose schedule.

- *Adolescents*

HAB-084 was an open, randomised study that compared *Ambirix* at the proposed two-dose regimen with a standard course of *Twinrix Paediatric*; with a long term follow up of the immune response. There were 142 subjects in the *Ambirix* group and 148 in the *Twinrix Paediatric* group evaluable for immunogenicity at month 7.

Anti-HBs seropositivity rates increased from 80% in the *Ambirix* group and 58% in the *Twinrix Paediatric* group at one month after the first dose, to 93% and 99% immediately before the last dose at month 6, and to 100% after the last dose of each regimen.

Seroprotection rates increased over time from 43% in the *Ambirix* group and 29% in the *Twinrix Paediatric* group at month 1, to 38% and 86% respectively at month 2 (reflecting the second dose of *Twinrix Paediatric*), and to 68% and 98% immediately before the last dose. Rates were 98% and 100% after the final doses.

GMCs were 4-fold and 15-fold higher at months 2 and 6, respectively, in the *Twinrix Paediatric* group but were very similar between groups after the final dose (4949 and 5054 mIU/ml).

At month 24, 94% and 98% of the subjects who returned were still seropositive for anti-HBs and 93% and 96%, respectively, were seroprotected, with GMCs of 359 and 337 mIU/ml. Data from the *kinetics cohort* showed a decrease in antibody from months 7 to 24 by 93% in both groups.

Anti-HAV seropositivity rates were 99% and 93% at month 1, 100% and 99% at both months 2 and 6, and 100% in both groups at month 7. After the last dose of each regimen, GMCs were 5487 mIU/ml and 4174 mIU/ml in the *Ambirix* and *Twinrix Paediatric* groups respectively.

The immune response elicited by *Ambirix* at month 7 (i.e. after completion of the vaccination course) was non-inferior to that of the three dose *Twinrix Paediatric* vaccine for both antigen components.

A similar persistence of the immune response was observed with *Ambirix* and *Twinrix Paediatric* up to month 24:

- At month 24, 94% and 98% of the subjects who returned were still seropositive for anti-HBs and 93% and 96%, respectively, were seroprotected, with GMCs of 359 and 337 mIU/ml.

- At month 24, all subjects were still seropositive for anti-HAV, with GMCs of 943 and 725 mIU/ml.

A similar decline in anti-HAV and anti-HBs antibody titres was observed in both groups between months 7 and 24.

HAB-082 was an open, randomised study that compared the immunogenicity of two doses of *Ambirix* when given at either six or twelve months apart, with a long term follow up of the immune response. There were 106 subjects in the *Ambirix* 0, 6 month group and 102 in the 0, 12 month group evaluable for immunogencity at month 7 or month 13.

The immune response elicited by *Ambirix* was demonstrated to be non-inferior for the 0,12 month schedule, versus the 0,6 month schedule.

Seropositivity rates for anti-HAV antibodies immediately prior to the second dose of vaccine were, respectively 95 % (0, 6 schedule) and 84 % (0, 12 schedule). All subjects except one (in the 0, 12 schedule) were seropositive after completion of the vaccination course. The GMCs for the two groups were 5992 and 8472 mIU/ml respectively after the second doses.

At month 24, all subjects in the previous 0, 6 month group and 80/81 in the 0, 12 month group were seropositive, with GMCs at 744 and 1075 mIU/ml, representing decreases in anti-HAV between the second dose and month 24 of the study by 91% and 83% in the two initial groups.

Seroprotection rates against HBV immediately prior to the second dose of vaccine were 59 % and 51 %, respectively for the 0, 6 and 0, 12-month schedule. After the second dose, 98 % (0, 6) and 97 % (0, 12) of subjects had antibody titres of ≥ 10 mIU/ml. The GMCs for the two groups were 2791 and 4340 mIU/ml respectively after the second doses.

At month 24, 93% and 99% were still seropositive, 91% and 94% were seroprotected, and GMCs were 248 and 570 mIU/ml, representing decreases in anti-HBs between the second dose and month 24 of the study by 95% and 92% in the two initial groups.

The persistence of anti-HAV and anti-HBs antibodies at month 24 was shown to be similar following a 0, 6 or a 0, 12 month schedule.

HAB-075 was a double-blind study in which *Ambirix* (67 subjects) was compared with an experimental combined hepatitis A and B vaccine containing a higher antigen content (55 subjects) in 11-18 year-olds at 0 and 6 months. Both vaccines were administered in a schedule of 0 and 6 months.

In both groups, all subjects were seropositive for anti-HAV antibodies and were seroprotected against hepatitis B after the second dose (i.e at month 7). The immune response observed with Ambirix at intermediate time-points was consistent with that seen in previous studies described above.

Long-term antibody persistence

In adolescents, seropositivity with respect to both viral components and seroprotection to HBV was almost uniformly maintained at month 24. Anti-HBs and anti-HAV GMCs were similar to those seen after the *Twinrix Paediatric* regimen. These findings and the kinetics of decreases in antibody, were comparable with the results of HAB-039, a previously reported trial in which *Twinrix Paediatric* was administered to 1-6 year-olds.

Additional Studies submitted after initial approval:

HAB-120 was an open multi-centre comparative trial that primarily compared the reactogenicity of *Ambirix* (at 0, 6 months) with *Twinrix Paediatric* (at 0, 1, 6 months) in subjects aged 1 to 11 years (inclusive). For an early assessment of grade 3 solicited symptoms, a descriptive interim safety analysis was performed at one month after the first vaccine dose. Eligible subjects were not known to be seropositive for antibodies to hepatitis A virus (anti-HAV), hepatitis B core antigen (anti-HBc) or hepatitis B virus (anti-HBs) and or to have detectable hepatitis B surface antigen (HBsAg). In this study 249 healthy children received Ambirix, while 250 were vaccinated with Twinrix paediatric. Randomisation employed a standard validated program and stratification by age group (1 to 5 year olds *vs* 6 to 11 year olds) and by centre.
In both the ATP and total cohorts, the GMT for anti-HBsAg antibody was higher (with no overlap of 95% CI) in the group that received three doses of *Twinrix Paediatric* rather than *Ambirix*. However, the GMTs in both groups were so very high that this difference is not likely to be of any clinical significance.
Following a CHMP request, the MAH provided the proportion of children achieving anti-HBs levels ≥ 100 mIU/ml for the two age groups (1-5 years old and 6-11 years old) and for the overall study cohort. The proportion of children with anti-HBs levels ≥ 100 mIU/ml was confirmed to be similar in both vaccine groups and close to 100% in the two age cohorts.

HAB-085 was an open and non-comparative study that was planned to evaluate the immunogenicity of Ambirix when the first dose was administered concomitantly with a DTaP-IPV/Hib vaccine. A single lot of each vaccine was used throughout the study. For the concomitant administration, injections were given into opposite thighs. The second dose of Ambirix was given into the same thigh as the first dose. Blood samples were obtained at months 0, 1 and 7. Safety data were collected in a similar fashion to that described for HAB-120.
The primary efficacy variable was designated as the proportion of previously seronegative subjects with anti-HAV antibody ≥ 33 mIU/ml and with anti-HBs antibody ≥ 10 mIU/ml one month after the second dose (i.e. the combined response rate).
The ATP cohort for analysis of immunogenicity included all previously seronegative subjects for whom assay results were available for antibody against at least one antigen after vaccination.
All 60 subjects enrolled completed the study. Of these, 53 subjects were eligible for the immunogenicity analysis. The data do not suggest that there should be any detrimental effect of *Ambirix* on responses to DTaP-IPV/Hib vaccines when given in the second year of life. Similarly, such vaccines would not be expected to interfere with responses to the HAV and HBsAg antigens in *Ambirix*.

HAB 087 was an open clinical study that was designed to investigate concomitant administration of *Ambirix* and Measles-Mumps-Rubella (MMR) vaccine to healthy infants aged 12-15 at time of the

first dose of each vaccine. The plan was to enrol 60 eligible healthy children in order to obtain 50 evaluable subjects. Eligible subjects had to have completed the primary course of DTP and OPV at least 30 days before study entry.
The primary endpoint was the proportion of subjects with anti-HAV antibody titres ≥ 33 mIU/ml and with anti-HBs antibody titres ≥ 10 mIU/ml one month after the second dose, calculated at month 7 for all initially seronegative subjects. Patient cohorts were defined as in HAB-085. Out of 57 enrolled patients, 52 completed the study. Out of these, 37 were included in the ATP analysis of immunogenicity. For the ATP immunogenicity cohort, all subjects were seroprotected for anti-HBs, such that all subjects had at least 100 mIU/ml antibody. This applies also to the seroprotection regarding anti-HAV with a GMT value of 11016 mIU/ml. Concerning the immunogenicity results of the concomitantly administrated MMR vaccine, all subjects were seropositive for anti-measles, anti-mumps and anti-rubella antibodies after *Priorix* was given at the same time as *Ambirix*, this is also the case for the total cohort at month 1.

Discussion on immunogenicity

- Dose and dose regimen

Pooled data from all subjects of 1-15 years who received *Ambirix* at 0, 6 months, showed that this regimen resulted in uniform seropositivity with respect to HAV and HBsAg, and that almost all (98%) subjects were also seroprotected against HBV.

In adolescents, *Ambirix* at 0, 6 months gave 100% seropositivity for both viruses and an HBV seroprotection rate of 98% after the second dose, compared with 100% for all three parameters after a standard three-dose regimen of *Twinrix Paediatric*.

In adolescents, final seropositivity and seroprotection rates and GMCs were comparable when the second dose was delayed for up to 12 months. The pre-second dose seropositivity/seroprotection rates and GMCs were similar or only slightly higher for 6 months *vs* 12 months, indicating that a delay in the second dose is not likely to have a huge impact on susceptibility to infection.

In study HAB-075 in adolescents, there was some advantage for the higher strength vaccine (*eg*. for seropositivity at month 6, and higher HBV seroprotection rates at months 2 and 6), but the differences *vs Ambirix* were not marked and the dose that has been proposed is considered to be supported.

Throughout the administration period, Ambirix is expected to provide the same degree of protection as Twinrix Paediatric against HAV, but not against HBV. As expected, a higher proportion of subjects were seroprotected against hepatitis B by month 2 following two doses of *Twinrix Paediatric* (at months 0 and 1) than after a single dose of *Ambirix* (at month 0), when measured at the same time point. This finding of lower intervening seroprotection rates for *Ambirix* compared with the three-dose regimen of *Twinrix Paediatric* before the final dose is likely to be applicable throughout the 1-15 year age range.

However, the final protection rates are indistinguishable. *Ambirix* should therefore be used only when there is a relatively low risk of hepatitis B infection during the vaccination course. It is recommended that *Ambirix* should be administered in settings where completion of the two-dose vaccination course can be assured.

It is pointed out that the epidemiology of Hepatitis B infection in Europe is such that rapid protection is generally not needed in the target age group for *Ambirix* (1-15 years). That is, the peak incidence of hepatitis B infection in the EU is 20 to 30 acute cases per 100,000, and this occurs in the 20-30 years age group, in which the majority of infections are acquired through sexual activity and parenteral drug abuse. Therefore, rapid protection against hepatitis B infection in 1 to 15 year-olds should only be required in somewhat exceptional circumstances. These might include subjects travelling to areas of high endemicity, those housed in certain types of institutions, and subjects in close contact with HBsAg carriers.

Clinical safety

Symptoms were recorded as general and local. Solicited general symptoms included fatigue, salivary gland swelling, rash, fever, gastrointestinal symptoms including loss of appetite, drowsiness, irritability/fussiness, meningism and headache. Local symptoms included redness, soreness/pain and swelling.

Patient exposure

In total, 983subjects aged ≥ 1 years received at least one of the two allotted doses of *Ambirix* and were evaluable for safety. There were 295 children of 6-11 years of age, and 459 adolescents.

Adverse events

- Children 1-5 years

In HAB 120:

The main reported local adverse events in the age group of 1-5 years of age were pain (approximately 33 % of injections) redness (approximately 17% of injections) and swelling (approximately 13%of injections) at the injection site. The number and severity of these events did not increase after the second dose. In terms of systemic effects, the most commonly reported was irritability/fussiness (18% of doses) followed by drowsiness (12% of doses). Loss of appetite was reported in less than 10 % of all doses, while fever was reported following approximately 7% of all doses.

In HAB 85

Pain at the injection site was reported following 11.7-15% of *Ambirix* doses, while redness ocurred after 3.3-5% of the injections. One subject showed a swelling after the first (1,7%), but not after the second dose. The most frequently reported solicited general symptom following all doses was irritability but no general symptom was of grade 3. Fever was reported much more frequently following dose 1 (concomitant - 25% vs 1.7%). There were 17 subjects who reported a total of 25 unsolicited symptoms during the 30-day follow-up period, all of which were considered general in nature and none was of grade 3 or was determined by the investigator to have a probable/suspected relationship to the study vaccine. Six subjects reported one SAE each. These were determined by the investigators to have no relationship to vaccination. These included instances of gastroenteritis, gastritis, bronchitis and hypoglycaemia after the first dose of vaccine but all subjects received the second dose as planned.

In HAB 87, which was performed in children 12 to 15 months of age, 45.9% of doses were followed by general symptoms and 47.7% of doses were followed by local symptoms (solicited and unsolicited) during the 4-day follow-up period after vaccination.
The breakdown for local symptoms by vaccine shows no appreciable difference between the two doses of Ambirix but a higher rate than with Priorix. In the 4-day follow-up period, redness (31.2%) and pain (27.5%) were commonest and more subjects reported solicited local symptoms at the Ambirix than at the Priorix injection site. However, none were grade 3. Over the 4-day follow-up period, irritability (49.1%) and loss of appetite (40.4%) were the most prevalent solicited general symptoms reported by subject. Fever was reported by 15.8% of subjects but only one case was grade 3 and determined by the investigator to have a probable relationship to vaccine.

- Children 6-11 years

In HAB-076,

Local adverse reactions were reported after approximately 49% of injections whereas systemic reactions were reported after approximately 28% of doses. The most common local side effect was

pain at the injection site (47% of doses). Only 4 cases of pain graded as severe were reported, which all resolved within the four-day follow up period. Other local side effects were redness and swelling.

In terms of systemic effects, the most commonly reported was fatigue (15% of doses) followed by headache (11% of doses). Fever was reported following less than 5% of all doses; temperature > 39°C was reported with an overall incidence of <0.3%.

No increase was observed in the reactogenicity profile with the subsequent dose.

- Adolescents

In HAB-084, in comparison with *Twinrix Paediatric*, overall differences between regimens were 55% *vs* 43% for local and 37% *vs* 29% for general reactions but the by-subject rates were very similar between groups. These differences were mainly due to the higher incidence of local pain (51% *vs* 39% for all doses) and the higher rate of fatigue (29% *vs* 19%) with *Ambirix*.

In HAB-082, administration of two doses of the same antigen content vaccine at either a 6 or 12 month interval did not result in notably different rates for local and general reactions after the first or second doses.

In HAB-075, local and general reaction rates were higher in the higher strength vaccine group after the second dose (51% and 76% subjects for local; 30% and 48% subjects for general reactions) but not the first dose. These differences between groups were due to the incidence of soreness (45% *vs* 76%) and the higher rates of headache (14% *vs* 36%) and fatigue (19% *vs* 31%) after the second dose of the higher strength vaccine.

Serious adverse events

23 subjects ≥ 1 years old vaccinated with *Ambirix* reported a SAE during the primary course of the seven studies... One case was determined by the investigator to have a probable relationship to the study vaccine(s). This involved a case of febrile convulsions plus unrelated rhinopharyngitis.

Withdrawals due to Adverse Events

Two subjects from the *Twinrix Paediatric* group dropped out of the study due to an adverse event. One subject was withdrawn due to erythematous rashes considered to be probably vaccine-related, and one was withdrawn due to purpura presumed to be allergic but not vaccine-related.

Discussion on clinical safety

- Children (1-5 years)

The solicited local and systemic symptoms for the 1-5 years age cohort only show no notable excess of any local or systemic reaction in the Ambirix group in this age group. The analyses did not raise any additional concerns regarding the safety of Ambirix in children aged 1-5 years. It appears that the safety profile of Ambirix in 1-5 year old children is similar to that of Twinrix Paediatric.

- Children (6-11 years)

Local reaction rates, predominantly pain at the injection site, were the most frequently reported symptoms. However, the majority of local symptoms were mild to moderate in intensity and did not show a difference between the first and second dose. General symptoms were uncommonly reported (frequency <16% of all doses for each solicited symptom).

- Ambirix vs Twinrix Paediatric

Local and general reaction rates were higher for *Ambirix vs Twinrix Paediatric* after the first and second doses of the two regimens in adolescents, mainly due to the incidences of local pain and fatigue, although there was no difference between regimens in the by-subject analysis.

In children 1 – 11 years of age, incidence of local and general symptoms after vaccination with Ambirix or Twinrix Paediatric was similar, with Ambirix being non-inferior to Twinrix Paediatric in terms of percentage of subjects reporting solicited local or general symptoms considered as severe.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

As Ambirix is in all aspects identical to the already licensed Twinrix Adult vaccine, and is produced and released in exactly the same way, the quality of this product is considered acceptable.

Preclinical pharmacology and toxicology

This was entirely cross-referenced to the *Twinrix Adult* dossier since *Ambirix* is identical to this product. There is no new information.

Immunogenicity

SC, SP rates and GMTs at one month following completion of the 2 dose primary course were within the ranges seen in children vaccinated with Twinrix™ Paediatric in the 3-dose regime. However as expected a higher proportion of subjects are protected by month 2, following two doses of Twinrix™ Paediatric (at months 0 and 1) than after a single dose of Ambirix™, when measured at the same time point. Thus if more rapid protection against hepatitis B is required, the three dose regime with Twinrix™ Paediatric would be the preferred option.

Extending the inter-vaccination interval from 6-12 months did not appreciably change the immune response to the second dose of vaccine.

Safety

In the target age group (1 to 15 yrs old), the incidence of local and general symptoms was overall similar after *Ambirix* and *Twinrix Paediatric*, the only exceptions being a higher incidence of pain and fatigue (both on a per dose basis) after *Ambirix*. However, by-subject rates for all symptoms including pain and fatigue were overall similar to those of the *Twinrix Paediatric* vaccine.

Benefit/risk assessment

Based on the review of the data submitted in the registration file, additional information provided by the applicant in response to the Consolidated List of Questions and the data that was submitted after the initial approval, the CHMP considers that *Ambirix* may be approved for use in non immune children and adolescents from 1 years up to and including 15 years for protection against hepatitis A and hepatitis B infection. Protection against hepatitis B infections may not be obtained until after the second dose.

Therefore Ambirix should be used only when there is a relatively low risk of hepatitis B infection during the vaccination course.

It is recommended that Ambirix should be administered in settings where completion of the two- dose vaccination course can be assured. The approved two-dose regimen is for immunisation at months 0 and months 6-12.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Ambirix in the prophylaxis of non-immune children and adolescents from 1 years up to and including 15 years against hepatitis A and hepatitis B infection, is favourable.