EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Referral under Article 30 of Directive 2001/83/EC

Havrix and associated names

INN: inactivated hepatitis A virus

Procedure number: EMEA/H/A-30/1527

Note: Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Background information

On 21 August 2023, due to the divergent national decisions taken by Member States concerning the authorisation of Havrix and associated names, GlaxoSmithKline Biologicals SA notified the CHMP/European Medicines Agency of a referral under Article 30 of Directive 2001/83/EC for Havrix and associated names, in order to resolve divergences amongst the nationally authorised product information (PI) and thus harmonise it across the European Union (EU).

# 2. Scientific discussion

## *2.1. Introduction*

Havrix and associated names are a whole Hepatitis A-virion (strain HM175), formaldehyde-inactivated, aluminium-adsorbed vaccine. Havrix exists in 2 strengths: Havrix 1440 Adult and Havrix 720 Junior. They are both presented as a suspension for injection in a vial or a pre-filled syringe for intramuscular injection. Havrix is preservative-free.

The adult strength contains 1440 ELISA units (EL.U) of inactivated hepatitis A viral antigen adsorbed onto 0.5 mg of aluminium as aluminium hydroxide, in a volume of 1.0 ml.

The paediatric strength contains 720 ELISA units (EL.U) of inactivated hepatitis A viral antigen adsorbed onto 0.25 mg of aluminium as aluminium hydroxide, in a volume of 0.5 ml. It is half the adult dose.

Havrix 1440 Adult and Havrix 720 Junior were first authorised in the EU in 1993 and 1997, respectively. They are currently authorised for active immunisation against hepatitis A virus in adults and children in the following 26 European Union (EU) Members States (MSs): Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden, as well as in Iceland and Norway. Worldwide they are authorised in over 85 countries. The marketing authorisation holder (MAH) has performed an analysis of the divergences between the English translations of all national Summary of Product Characteristics (SmPC) of the 26 EU MSs for Havrix 1440 Adult and Havrix 720 Junior. As per the notification, the main divergencies were found in section 4.1, 4.2, 4.4, and 4.8 of the SmPC, but divergencies also exist in sections 4.3, 4.5, 4.6, 4.7, 5.1, 5.2, and 5.3 of the SmPC.

In view of these divergences, concerning the authorisation of the above-mentioned medicinal product the MAH notified the European Medicines Agency (EMA) of a referral procedure under Article 30(1) of Directive 2001/83/EC to harmonise the product information (PI) for its Hepatitis A vaccine Havrix and associated names, across the EU MSs.

In this regard, the MAH provided an overview of the identified divergences, together with the proposed harmonised PI, and supportive data.

## *2.2. Critical Evaluation*

The MAH presented data from 48 clinical studies they had sponsored in subjects from the age of 11 months. Some of the submitted clinical studies were conducted in specific sub-populations: 12 included the paediatric population with subjects aged from 11 months to 19 years with the paediatric strength and 2 included only female subjects from 10 to 25 years of age.

Of all MAH-sponsored studies presented to support the strength and indication of the vaccine as described in the PI, in 39 studies Havrix was administered to more than 6,000 subjects (Havrix 720 Junior and Havrix 1440 Adult), while in 9 Havrix was administered as the control.

In addition, the MAH submitted literature data from over 70 published studies conducted either with Havrix (Havrix 720 Junior and Havrix 1440 Adult) or with the vaccine Vaqta. Of those, 5 studies were conducted with one of the GlaxoSmithKline Biologicals' vaccines as Twinrix, Engerix B or Typherix and Havrix as active comparator. The invented name or MAH of the hepatitis A vaccines used were not specified in two of the submitted literature references.

It should be noted that Havrix and Vaqta are both hepatitis A vaccines (inactivated), whilst Twinrix is a combination vaccine containing a hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (absorbed). Therefore, data obtained with these two vaccines was considered relevant to support the efficacy, immunogenicity and safety of Havrix. The primary objective of the studies conducted with Engerix B, a hepatitis B vaccine, and Typherix, a vaccine to prevent typhoid fever, was to demonstrate the non-inferiority of the vaccines when they are co-administered.

The MAH proposed one combined SmPC covering both adult and paediatric strengths with some strength-specific wordings, and separate package leaflet (PL) for each strength. The CHMP considered this proposal in line with the Policy on combined Summaries of Products Characteristics (SmPCs)[1] and therefore acceptable.

The CHMP considered the available data; the results most relevant to the harmonisation of the Havrix PI are summarised below.

## 2.2.1. Product information

**Section 4.1 – Therapeutic Indications**

Condition covered by the indication:

The first part of the therapeutic indication describing that Havrix is indicated for active immunisation against hepatitis A virus (HAV) infection was nearly identical in all MSs, with slight differences due to linguistic peculiarities. To support the immunogenicity and efficacy of Havrix against HAV infection, the MAH provided studies with Havrix Adult (Table 1) and Havrix Junior (Table 2), studies in which the vaccine was used as an active control (Table 3 and Table 4), clinical development programme with Havrix as an active control, and studies published in the literature (Table 5).

[1] Policy on Combined Summaries of Product Characteristics (europa.eu)

**Table 1 – Overview of the most relevant studies supporting the immunogenicity of Havrix 1440**

| Study No. *Country(ies)* | Vaccine(s) (Dose) | Population Age** | Number Enrolled & vaccinated | Number Safety analysis* | Number *Havrix* ATP immuno* | Design and objectives |
|---|---|---|---|---|---|---|
| **HAV-107** [208109/116] *Austria* | *Havrix* 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-40 years | 150 | 150 | 140 | Double-blind, randomised (1:1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-112** [208109/108] *Belgium* | *Havrix* 1440 EL.U 0.5 mg Al, 2 lots | Adults 18-40 years | 194 | 193 | 177 | Double-blind, randomised (1:1); 0, 12 months schedule **Objectives:** Immunogenicity, safety and reactogenicity, and kinetics of antibody production in a subset of the population |
| **HAV-123** [208109/114] *Belgium* | *Havrix* 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-40 years | 119 | 119 | 92 | Double-blind, randomised (1:1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-168** [208109/168] *Belgium* | • *Havrix* 1440 EL.U 0.5 mg Al<br>• HAV 1440 EL.U 0.5 mg Al | Adults 18-40 years | 200 | 100 | 97 | Double-blind, randomised (1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-185** [208109/185] *Belgium* | HAV 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-40 years | 708 | 705 | 676 | Double-blind, randomised (1:1:1), 3 groups; 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-099** [208109/123] *Finland* | *Havrix* 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-40 years | 151 | 151 | 145 | Comparative, double-blind, randomised (1:1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-101** [208109/124] *Denmark* | *Havrix* 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-40 years | 162 | 161 | 102 | Comparative, double-blind, randomised (1:1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-104** [208109/061] *Iceland* | *Havrix* 1440 EL.U 0.5 mg Al, 3 lots | Adults 18-50 years | 150 | 150 | 129 | Comparative, double-blind, randomised (1:1:1); 0, 6 months schedule **Objectives:** Immunogenicity, safety and reactogenicity |

**Table 2 - Overview of paediatric studies supporting the efficacy of Havrix from 1 year of age**

| Study No.<br>*Country(ies)* | Vaccine(s)<br>(Dose) | Population<br>Age** | Number<br>Enrolled &<br>vaccinated | Number<br>Safety<br>analysis* | Number<br>*Havrix*<br>ATP immuno* | Design and objectives |
|---|---|---|---|---|---|---|
| **HAV-129**<br>[208109/134],<br>*Taiwan* | *Havrix* 720 EL.U 0.25 mg Al | Adolescents<br>10-18 years | 120 | 120 | 109 | Open, single-group; 0, 6 months schedule<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-162,**<br>**HAV-187**<br>[208109/162 &<br>/187]<br>*Thailand* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Havrix* 360 EL.U 0.25 mg Al | Children &<br>adolescents<br>2-18 years | 460 | 230 | 230 | Open, randomised (1:1)<br>• *Havrix* 720 at 0, 6 months<br>• *Havrix* 360 at 0, 1 and 6 months<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-204**<br>[208109/204],<br>*Chile* | • *Havrix* 720 EL.U 0.25 mg Al | Children<br>1-2 years | 120 | 120 | 116 | Open, single-group; 0, 6 months schedule<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-210**<br>[208109/210]<br>*US, Australia* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Infanrix*<br>• *OmniHIB* | Children<br>11-25 months | 1084 | 1084 | 881 | Open, comparative, multicentre, 5 groups<br>• 11-13 months: *Havrix* at 0, 6 months<br>• 15-18 months: *Havrix* at 0, 6 months<br>• 15-18 months: *Havrix* + *Infanrix* + *OmniHIB* at Day 0 and *Havrix* at Month 6<br>• 15-18 months: *Infanrix* + *OmniHIB* at Day 0 and *Havrix* at Months 1 and 7<br>• 23-25 months: *Havrix* at 0, 6 months<br>**Primary objective:** Non-inferiority of *Havrix* in children 11-13 months and 15-18 months to *Havrix* in children 23-25 months |
| **HAV-115**<br>[208109/111],<br>*Thailand* | • *Havrix* 1440 EL.U 0.5 mg Al<br>• *Havrix* 720 EL.U 0.25 mg Al | Adolescents<br>12-18 years | 202 | 101**** | 100**** | Open, randomised (1:1); dose-range, 0, 6 months schedule<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-117B**<br>[208109/113],<br>*Argentina* | *Havrix* 720 EL.U 0.25 mg Al | Children<br>2-11 years | 60 | 60 | 52 | Open, single-group; 0, 6 months schedule<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-118**<br>[208109/126],<br>*France* | *Havrix* 720 EL.U 0.25 mg Al | Children<br>2-11 years | 54 | 54 | 22 | Open, single-group; 0, 12 months schedule<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-122**<br>[208109/125]<br>*Italy* | *Havrix* 720 EL.U 0.25 mg Al | Children<br>2-11 years | 81 | 81 | 53 | Open, randomised (1:1); 0, 6 months schedule<br>• Group 1: Blood sample Days 0 and 15, Months 6 and 7<br>• Group 2: Blood Day 0, Months 1, 6, and 7<br>**Objectives:** Immunogenicity, safety and reactogenicity |
| **HAV-231**<br>[208109/231]<br>*US* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *MMRII*<br>• *Varivax* | Children<br>12-13 months | 1241 | 1241 | 854 | Open, randomised (1:1:1), controlled, 3 groups<br>• *Havrix* at Day 0 and Month 6-9<br>• *Havrix* + *MMRII* + *Varivax* at Day 0 and *Havrix* at Month 6-9<br>• *MMRII* +*Varivax* at Day 0, *Havrix* at Day 42 and *Havrix* at Month 7.5-10.5<br>**Co-primary objective:** Non-inferiority of *Havrix* co-administered with *MMRII* and *Varivax*, compared with *Havrix* given alone; non-inferiority of *MMRII* and *Varivax*, co-administered with *Havrix* compared with *MMRII* and *Varivax* given alone |
| **MMRV-054 PRI**<br>[110058]<br>*US* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Priorix-Tetra* (refrigerated licensed formulation MMRV$_R$ or frozen formulation MMRV$_F$)<br>• *ProQuad*<br>• *Prevnar* | Children<br>12-14 months | 1783 | 1783 | 1621 | Observer-blind, randomised (2:2:1), controlled, 3 groups<br>• *Havrix* + *MMRV$_R$* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *MMRV$_F$* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *ProQuad* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>**Primary objective:** Non-inferiority of *MMRV$_R$* (OR *MMRV$_F$*) co-administered with *Havrix* and *Prevnar* compared with *ProQuad* co-administered with *Havrix* and *Prevnar* |
| **MMR-157 PRI**<br>[111870]<br>*US, Puerto Rico* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Priorix*<br>• *MMRII*<br>• *Varivax*<br>• *Prevnar* | Children<br>12-15 months | 1220 | 1220 | 1026 | Observer-blind, randomised (1:1:1:1), controlled, 4 groups<br>• *Havrix* + *Priorix* Lot 1 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *Priorix* Lot 2 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *Priorix* Lot 3 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *MMRII* + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>**Primary objective:** Immunogenicity of *Priorix* co-administered with *Varivax*, *Havrix* and *Prevnar* in contrast with *MMRII* co-administered with *Varivax*, *Havrix* and *Prevnar* |

**Table 3 - Overview of the most relevant studies with Havrix Adults vaccine as an active control**

| Study No.<br>*Country(ies)* | Vaccine(s)<br>Dose | Population<br>Age** | Number<br>Enrolled & vaccinated | Number<br>*Havrix**<br>ATP | Design | Objectives |
|---|---|---|---|---|---|---|
| **HAV-189**<br>[208109/189]<br>*Germany* | • *Havrix* 1440 EL.U 0.5 mg Al<br>• *Vaqta* | Adults<br>≥18 years | 240 | 114 | Single-blind, randomised (1:1), 2 groups<br>0, 6 months schedule | **Primary:** Immunogenicity; *post-hoc* post-Dose 1 kinetics evaluation<br>**Secondary:** Safety and reactogenicity |
| **TyphHA-006**<br>[270362/006]<br>*Czech Republic, Germany, Lithuania, Norway, Portugal, Spain* | • *Havrix* 1440 EL.U 0.5 mg Al<br>• *Typherix*<br>• *Hepatyrix*<br>• *Typhim* | Adults<br>18-65 years | 1034 | 700 | Open, randomised (1:1:1:1) 4 groups<br>Co-administration with Typhoid vaccine:<br>• Group 1: *Typhim* at Day 0<br>• Group 2: *Havrix* at 0, 6 months<br>• Group 3: *Hepatyrix* at Day 0, *Havrix* at Month 6<br>• Group 4: *Havrix* + *Typherix* at Day 0, *Havrix* at Month 6 | **Primary:** Non-inferiority of *Hepatyrix* to *Typherix* and *Havrix* given separately, non-inferiority of *Hepatryix* to *Typhim Vi*, and non-inferiority of *Hepatrix* to *Havrix*.<br>**Secondary:** Immunogenicity, safety and reactogenicity |
| **HAB-061**<br>[208127/061]<br>*US* | • *Havrix* 1440 EL.U 0.5 mg Al<br>• *Engerix B*<br>• *Twinrix* | Adults<br>≥19 years | 773 | 271*** | Comparative, open, randomised (1:1), 2 groups; 0, 6 months schedule:<br>• *Havrix* 1440 at 0, 6 months+ *Engerix B* at 0, 1, 6 months<br>• *Twinrix* at 0, 1, 6 months | **Primary:** Non-inferiority of *Twinrix* to *Engerix B* and *Havrix* given separately<br>**Secondary:** Immunogenicity, safety and reactogenicity |
| **HAB-121**<br>[208127/121]<br>*Belgium, Czech Republic, Norway, US* | • *Havrix* 1440 EL.U<br>• *Engerix B*<br>• *Twinrix* Adult | Adults<br>≥18 years | 496 | 212 | Open, controlled, randomised (1:1); 0, 12 months schedule:<br>• *Havrix* 1440 at 0, 12 months + *Engerix B* at 0, 1, 2, 12 months<br>• *Twinrix* at 0, 7, 21-30 days and 12 months | **Primary:** Non-inferiority of Twinrix to *Engerix B* and *Havrix* given separately<br>**Secondary:** Immunogenicity, safety and reactogenicity |

**Table 4 - Overview of the most relevant studies with Havrix Junior vaccine as an active control**

| Study No.<br>*Country(ies)* | Vaccine(s)<br>Dose | Population<br>Age** | Number<br>Enrolled & vaccinated | Number<br>*Havrix**<br>ATP | Design | Objectives |
|---|---|---|---|---|---|---|
| **HAV-210**<br>[208109/210]<br>*US, Australia* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Infanrix*<br>• *OmniHIB* | Children<br>11-25 months | 1084 | 881 | Open, comparative, multicentre, 5 groups<br>• 11-13 months: *Havrix* at 0, 6 months<br>• 15-18 months: *Havrix* at 0, 6 months<br>• 15-18 months: *Havrix* + *Infanrix* + *OmniHIB* at Day 0 and *Havrix* at Month 6<br>• 15-18 months: *Infanrix* + *OmniHIB* at Day 0 and *Havrix* at Months 1 and 7<br>• 23-25 months: *Havrix* at 0. 6 months | **Primary:** Non-inferiority of *Havrix* in children 11-13 months and 15-18 months to *Havrix* in children 23-25 months<br>**Secondary:** Immunogenicity, safety and reactogenicity |
| **HAV-231**<br>[208109/231]<br>*US* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *MMRII*<br>• *Varivax* | Children<br>12-13 months | 1241 | 854 | Open, randomised (1:1:1), controlled, 3 groups<br>• *Havrix* at Day 0 and Month 6-9<br>• *Havrix* + *MMRII* + *Varivax* at Day 0 and *Havrix* at Month 6-9<br>• *MMRII* +*Varivax* at Day 0, *Havrix* at Day 42 and *Havrix* at Month 7.5-10.5 | **Co-primary objective:** Non-inferiority of *Havrix* co-administered with *MMRII* and *Varivax*, compared to *Havrix* given alone; non-inferiority of *MMRII* and *Varivax*, co-administered with *Havrix* compared to *MMRII* and *Varivax* given alone<br>**Secondary:** Immunogenicity, safety and reactogenicity |
| **MMRV-054 PRI**<br>[110058]<br>*US* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Priorix-Tetra* (refrigerated licensed formulation $MMRV_R$ or frozen formulation $MMRV_F$)<br>• *ProQuad*<br>• *Prevnar* | Children<br>12-14 months | 1783 | 1621 | Observer-blind, randomised (2:2:1), controlled, 3 groups<br>• *Havrix* + $MMRV_R$ + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + $MMRV_F$ + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *ProQuad* + *Prevnar* at Day 0 and *Havrix* at Month 6 | **Primary objective:** Non-inferiority of $MMRV_R$ (OR $MMRV_F$) co-administered with *Havrix* and *Prevnar* compared to co-administered with *Havrix* and *Prevnar*<br>**Secondary:** Immunogenicity, safety and reactogenicity |
| **MMR-157 PRI**<br>[111870]<br>*US, Puerto Rico* | • *Havrix* 720 EL.U 0.25 mg Al<br>• *Priorix*<br>• *MMRII*<br>• *Varivax*<br>• *Prevnar* | Children<br>12-15 months | 1220 | 1026 | Observer-blind, randomised (1:1:1:1), controlled, 4 groups<br>• *Havrix* + *Priorix* Lot 1 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *Priorix* Lot 2 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *Priorix* Lot 3 + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6<br>• *Havrix* + *MMRII* + *Varivax* + *Prevnar* at Day 0 and *Havrix* at Month 6 | **Primary objective:** Immunogenicity of *Priorix* co-administered with *Varivax*, *Havrix* and *Prevnar* in contrast with *MMRII* co-administered with *Varivax*, *Havrix* and *Prevnar*.<br>**Secondary:** Immunogenicity, safety and reactogenicity |

Al: aluminium; ATP: according-to-protocol; EL.U: enzyme-linked immunosorbent assay (ELISA) units; HAV: hepatitis A virus; US: United States.
* Number of subjects who received the approved formulation of *Havrix* for the population studied i.e., *Havrix* 720 EL.U 0.25 mg Al.
** Age range of subjects according to the inclusion criteria.

**Table 5 - Most relevant studies published in the literature supportive of the hepatitis A vaccine efficacy**

| Reference | Population/Study design | Treatment | Efficacy outcome | Main efficacy results |
|---|---|---|---|---|
| Belmaker et al., 2007 | According to the records at Maternal and Child Health clinics of the birth cohort of 2000, 86.4% kids received 1 dose and 77.3% received 2 doses by age 3 years | hepatitis A vaccine Havrix, doses are not specified, but probably Paediatric | The number of exposed contacts for whom postexposure prophylaxis was administered was retrieved from records of epidemiologic investigations. Rates of immunization coverage were extracted from records of Maternal and Child Health Clinics. | Three hundred nineteen cases of hepatitis A illness during the years 1993 through 2005 were associated with 113 outbreaks in day-care and school settings of which 92% occurred before the institution of universal toddler immunization. Since 2000, no hepatitis A infection outbreaks have been reported in any day-care and school settings in the region |
| Bienzle et al., 1996 | A total of 2036 volunteers (1057 travellers, 973 non- travellers, 6 subjects with no data) participated in the study. An open prospective clinical trial with two vaccination schedules. | The SmithKline Beecham formaldehyde-inactivated hepatitis A vaccine, strain HAV-175, was used. All vaccinees were to be given a booster of hepatitis A vaccine 6—12 months after the primary course (Havrix 720 El.U) | to compare the immunogenicity [seroconversion rates and mean antibody titres (GMTs)] of an schedule to that of the standard schedule. as measured 2 weeks after of the second vaccine dose; and to evaluate the influence of the simultaneous administration of other vaccines on the immunogenicity and reactogenicity of the hepatitis A vaccine | the seroconversion rates of groups I and II were not significantly different (97.8 and 96.0%, respectively). The GMTs also similar (581 and 500 mIU respectively). |
| De Silvestri et al.,2006 | 269 mother-baby couples; anti-HAV IgM was not detected in any of the samples, while anti-HAV IgG was positive in 69 samples | Anti-HAV vaccination (commercial HAVRIX Pediatrics (commercial HAVRIX Pediatrics (GSK Biologicals) with a two-dose schedule was offered to babies seronegative at birth who did not present HAV-RNA shedding in their stool samples. Antibody level was evaluated 1 month after the first dose, and 1 month and 12 months after the second dose. | the safety and immunogenicity of anti-HAV-inactivated vaccine administered during the first year of life to anti-HAV seronegative babies; HAV IgG detection GMT | After the first dose of vaccine (5 months of life), 36/82 (43.9%) developed a protective antibody level>20 mIU/ml: GMT was 17.5 (median 18.65, 25th percentile 12.4 and 75th percentile 26.4) mIU/ ml. Among the 46 who did not develop a protective titre, 12 had antibody level<10 mIU/ml. After the second dose (11 months of life), all babies achieved a protective titre (> 20 mUI/ml) and GMT was 877.6 (median 859, 25th percentile 574 and 75th percentile 1528) mIU/ml. |

Further, data from two studies published in the literature (Dagan, 2005[2]; Hanna, 2004[3]) show a decrease in the number of hepatitis A cases after the implementation of a hepatitis A vaccination programme. For example, after implementation of the hepatitis A vaccination programme in north Queensland for indigenous children, the average annual notification rates were 4 and 2.5 cases per

[2] Dagan R. et al. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA. 2005;294(2):202-10
[3] Hanna J, Hills S and Humphreys J., Impact of hepatitis A vaccination of Indigenous children on notifications of hepatitis A in north Queensland, MJA 2004; 181: 482-485

100,000 persons in Indigenous and non-Indigenous people, respectively, in the period 2000–2003, and 3.5 per 100,000 for Indigenous children aged under 5 years.

The CHMP considered that the submitted data from clinical trials and the literature supported the immunogenicity and efficacy of anti-HAV vaccine to prevent HAV-infections and endorsed the proposed harmonised text.

Age groups

Information on age limits for the target population for the two Havrix formulations (Adult and Junior) were not aligned in the national SmPCs. The MAH proposed to include a lower age limit of 1 year, as currently approved in 10 MSs (no age limit is specified in section 4.1 of the remaining 16 MSs). To support the indication from 1 year of age, the MAH provided data from 12 studies in paediatric population aged between 11 months to 18 years (Table 2).

Focusing on defining the appropriate minimal age for Havrix, the results of studies HAV-204 and HAV-210 are most relevant. In study HAV-204 (Table 6), which included children aged 12 to 23 months, a seropositivity of 100% was measured after 7 months.

**Table 6 – Key results from Study HAV-204**

| Timing | N | Seropositivity (≥33 mIU/mL) | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|
| | | n | % | 95% CI | | mIU/mL | 95% CI | |
| | | | | LL | UL | | LL | UL |
| PI(M1) | 116 | 115 | 99.1 | 95.3 | 100 | 161.7 | 137.3 | 190.4 |
| PI(M6) | 114 | 105 | 92.1 | 85.5 | 96.3 | 112.9 | 98.2 | 129.7 |
| PII(M7) | 115 | 115 | 100 | 96.8 | 100 | 2939.0 | 2479.4 | 3483.7 |

95% CI: 95% confidence interval; ATP: according-to-protocol; GMC: geometric mean concentration; LL: lower limit; M: Month; N: number of subjects tested; n/%: number/percentage of subjects who were seropositive for anti-HAV antibodies; UL: upper limit.
GMCs calculated on seropositive subjects; PI(M1): Blood sampling post-Dose 1 Month 1, etc.

Study HAV-210 evaluated the immunisation with Havrix Junior in children in the second year of life at 2 ages (11-13 months or 15-18 months), compared to children of 23-25 months of age. In the 15 to 18-month-old group, Havrix was given either alone or in co-administration with DTPa (Infanrix) and Hib (OmniHIB) vaccines that are recommended in the second year of life. Children with either positive or negative anti-HAV concentrations at baseline were eligible for entry into the study. The objectives of the study were to demonstrate equivalence of the response to Havrix in children less than 23 months old to the response in children of 23-25 months old and to demonstrate non-inferiority in case of co-administration of Havrix with other vaccines at that age. The CHMP considered that the results of this study showed that immune response to Havrix 720 Junior in 11 to 13-month-old and 15 to 18-month-old children is equivalent to the response in 23 to 25-month-old children at Month 2, after the primary vaccine dose, and at Month 7, after the second dose of vaccine (Table 7).

**Table 7 – Key results from study HAV-210 on seropositivity with Havrix 720 Junior at month 2 and month 7 in children of different age groups**

| Group | Age (months) | N | Month 2 (after 1-st dose) | | Month 7 (after 2-nd dose) | |
|---|---|---|---|---|---|---|
| | | | n / % | GMC (mIU/ml) | n / % | GMC (mIU/ml) |
| **1** | 11-13 | 204 | 178 (88.6%) | 46.1 | 204 (100 %) | 1486.5 |
| **2** | 15-18 | 196 | 171 (89%) | 57.4 | 196 (100%) | 1619.8 |
| **3** | 15-18 | 129 | 108 (84.4%) | 40.7 | 129 (100%) | 1508.8 |
| **4** | 15-18 | 113 | 0 (0%) | 7.5 | 113 (100%) | 1474.6 |
| **5** | 23-25 | 203 | 193 (96%) | 83 | 203 (100%) | 1852.6 |

Based on the data provided, the CHMP concluded that the benefit-risk balance of Havrix 720 Junior for active immunisation against HAV infection in children from 1 year of age is positive.

The preferred use of Havrix 1440 Adult in adolescents as of the age of 16 years is supported by a pooled analysis showing the immunogenicity data with Havrix 720 Junior stratified by age (1-6 years, 7-9 years, 10-12 years, 13-15 years and 16-18 years). In this analysis, a lower persistence before booster and a trend for a lower anti-HAV antibody GMC (geometric mean concentration) post-booster were observed in the 16-18 years age group compared with the younger age groups. Although the immune response in the 16-18 years age group when given the paediatric dosage was still adequate, these data support the general indication to preferably use Havrix 1440 Adult from the age of 16 years, but still support the possibility of using Havrix 720 Junior in adolescents aged 16 to 18 years included.

Finally, the CHMP considered the characterisation of the population as "*at risk of exposure to HAV*" uninformative for prescribers. In the clinical studies, there were no inclusion criteria relating to subjects at risk. Hepatitis A virus is transmitted through the faecal-oral route and HAV disease pattern occurs in different ways according to endemicity of disease as well as the subject's risk behaviour and age, making at-risk subjects a highly heterogeneous population. Therefore, this mention should be removed from the indication.

The CHMP considered the proposed indication acceptable and in line with the European Commission (EC) "Guideline on Summary of Product Characteristics (SmPC)"[4] as well as "Wording of therapeutic indication" (EMA/CHMP/483022/2019), with the addition of separate text for each strength to clarify the age groups in which they can be used, the removal of the additional mention on patients at risk of exposure, and the usual mention that the use should be in accordance with official recommendations.

The statement to prevent off-label use "*Havrix will not prevent hepatitis infection caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver*" was approved in all SmPCs but included in different sections. The CHMP concluded that the appropriate section for this statement was section 4.4 – Special warnings and precautions of use.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.2 – Posology and method of administration**

Posology

In most MS, the posology of Havrix 720 Junior was given for children and adolescents from 1 year up to and including 15 years of age; as well as for adolescents up to and including 18 years of age, while the posology of Havrix 1440 Adult was given for adolescents and adults 16 years of age and above. Some variability existed in the lower age and regarding the cut-off between the two formulations. Based on the data from the studies discussed in the above section, it was clarified that while Havrix 720 Junior is intended to be used in children and adolescents aged from 1 through to 15 years inclusive, it could also be acceptable to use it in adolescents aged 16 to 18 years inclusive, if necessary. Havrix 1440 Adult is intended to be used in adolescents and adults 16 years of age and above.

The wording on the time window within which the primary and booster vaccination should be administered is supported by immunogenicity data from the studies described in the section above. This wording was approved in all the MSs, but one, and has been kept. These data were generated in adults (from 18 to 50 years old) and adolescents from 16 years old with the adult dosage and in

[4] European Commission "Guideline on Summary of Product Characteristics (SmPC)", September 2009

children 1 to 18 years old with the paediatric dosage. Furthermore, a prospective comparative study in adults with a second dose delayed up to 5.5 years showed that similar protection is reached when the booster dose is given up to 5 years after the first dose (Landry, 2001[5]). The statement regarding a delayed second dose was already included in all MS, but three, and is kept.

The interchangeability of Havrix with other inactivated hepatitis A vaccines is part of the WHO (World Health Organisation) position on hepatitis A vaccines, 2022[6]. A statement regarding the interchangeability was included in the harmonised SmPC.

Limited data regarding the immunogenicity of the vaccine in adults older than 65 years of age are available. The acceptability of the posology in the elderly population is based on data available globally with hepatitis A vaccines (WHO position paper on hepatitis A vaccines, 2022). Therefore, no dose adjustment is required and a statement on the limited data for the use of Havrix in elderly individuals was included.

With regards to the paediatric population, the CHMP approved the statement that the safety and efficacy of Havrix 720 Junior in children less than 1 year of age have not been established, but in line with the QRD template[7], requested to include a cross reference to section 5.1 where the currently available data are described whilst no recommendation on a posology can be made.

Methods of administration

The antero-lateral part of the thigh in young children and the deltoid region in adults, adolescents and children were the administration sites included in all MSs for Havrix. However, in the harmonised SmPC, the CHMP requested separate text for each vaccine dose. In young children, the administration site depends on physical development, therefore the CHMP considered the additional text proposed in this regard to be acceptable. In addition, the statement "*With any administration site, firm pressure should be applied to the injection site (without rubbing) for at least two minutes post injection*" was included in 9 MSs and the CHMP considered it appropriate for inclusion in the harmonised SmPC. The statements against the administration in the gluteal region or intravascularly, already approved in all SmPCs, were considered appropriate and were kept. Because subcutaneous or intradermal administration may result in a less optimal anti-HAV response, a statement against such administration was also already included in most of the MSs and was kept. However, it is good medical practice to consider such administration in individuals with thrombocytopenia or a bleeding disorder. The CHMP considered a statement to this regard should be included in section 4.4.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.3 – Contraindications**

The standard contraindication in case of hypersensitivity to the active substance or any of the excipients or, in this case, to neomycin was already included in the SmPC of all MSs with minor divergencies in wordings (e.g., reference in 10 MSs to "residues", or to any "component" or "ingredient"). The statement was kept and aligned with the QRD template and the EC Guideline on SmPC. In addition, hypersensitivity to formaldehyde was mentioned in the SmPC of 3 MSs. The CHMP acknowledged that the EC guideline on Excipients in the labelling and package leaflet of medicinal products for human use (2018)[8] only mandates the listing of this excipients for formulations intended for topical and oral use. However, CHMP was of the view that a potential reaction in subjects with previous hypersensitivity to formaldehyde after parenteral administration cannot be excluded as it

[5] Landry P, Tremblay S, Darioli R, et al. Inactivated hepatitis A vaccine booster given ≥24 months after the primary dose. Vaccine. 2001;19(4-5):399-402
[6] WHO position paper on hepatitis A vaccines, 2022
[7] QRD product-information annotated template (English) version 10.4 (europa.eu)
[8] Guideline on Excipients in the labelling and package leaflet of medicinal products for human use (2018),

could potentially elicit a more severe reaction. Therefore, the CHMP considered that Havrix should also be contraindicated in case of hypersensitivity to formaldehyde.

Further, a contraindication in case of hypersensitivity after previous administration of Havrix was also included in all MSs with minor divergences in wordings. The CHMP was of the view that this was already covered in the general contraindication to the active substance, which relates to all hepatitis A vaccines, and did not warrant a separate contraindication.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.4 – Special warnings and precautions for use**

Traceability

A statement on traceability of biological medicinal products was included in 7 SmPCs. To be aligned with the QRD template, this statement was added to the harmonised SmPC.

General recommendations

A warning related to the recommendation to postpone administration of Havrix in individuals suffering from acute severe febrile illness, but not in the presence of a minor infection was included in the majority of MSs. Further, acute (severe) febrile illness was listed as a contraindication in 10 MSs. However, the CHMP considered that the warning informs healthcare professionals to evaluate, depending on the symptoms of the patient, whether the vaccination should be postponed or not. Therefore, in accordance with the EC Guideline on SmPC, this did not warrant a contraindication, but should rather be reflected under special warnings and precautions for use.

The MAH proposed to include a warning that Havrix should under no circumstances be administered intravascularly, which was present in 2 MSs. This was considered adequately mentioned under 4.2 and was therefore not kept under 4.4 in the harmonised SmPC.

As already included in all MSs, the precaution related to the need for appropriate medical treatment and supervision to be readily available in case of a rare anaphylactic event following the administration of the vaccine was retained, with the addition of a minimum observation period after vaccination of at least 15 min.

A warning for syncope was included in all MS with some small divergences on the exact wording used. The wording was aligned to the conclusion from CHMP on 26 October 2012 in relation to a work-sharing procedure (EMEA/H/C/xxxx/WS/0153) for all injectable GSK vaccines.

As described above under section 4.1, the CHMP concluded that the statement to prevent off-label use for other types of hepatitis should be included under section 4.4.

A warning on the uncertainties around efficacy in individuals in the incubation period of a hepatitis A infection was included in all MSs but one. The MAH did not specify the length of the incubation period of HAV infection as it is not clearly defined. The CHMP considered the clinical evidence supporting the use of Havrix for effective post-exposure prophylaxis in all age groups to be insufficient and inconclusive, and as the clinical data did not show complete protection during the incubation period (particularly for people older than 30 years), the warning was considered appropriate.

A warning related to the fact that a protective immune response may not be elicited in all vaccinees, as with any vaccine, was included in two MSs and is generally accepted. As such the CHMP supported the inclusion of this warning in the harmonised SmPC.

The CHMP considered it good medical practice to consider subcutaneous administration to individuals with thrombocytopenia or a bleeding disorder. A statement to this effect was included in the majority

of the SmPC with minor divergencies. Submitted publications showed that over 95% of the patients who received the vaccine subcutaneously developed a high anti-HAV antibodies titre, although it was lower than those who received the intramuscular (IM) vaccine. The CHMP was of the view that this information together with possible exceptional administration of Havrix in individuals with thrombocytopenia or a bleeding disorder should be reflected in this section.

Wording was also included in some MS specifying that Havrix can be given to HIV-infected persons or that seropositivity against hepatitis A is not a contraindication. In line with the recommendations from the EC Guideline on SmPC such statement not constituting a warning or specific precaution for use are normally not included in the SmPC, and as such were not included in the harmonised text.

Excipients

Statements on the amounts of phenylalanine per dose, related risk for individuals with phenylketonuria (PKU), and on the amounts of sodium and potassium per dose (essentially "sodium-free" and "potassium-free") were included in most MSs, with minor variations. These were aligned to the Annex to the EC guideline on Excipients (2024)[9], to also express the amounts of phenylalanine in the adults and paediatric formulations separately so that they are clearly visible to healthcare professionals.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.5 – Interaction with other medicinal products and other forms of interaction**

Concomitant use with other inactivated vaccines

A statement regarding the expected lack of interference with the immune responses in case of use with other inactivated vaccines was included in all MSs but two. The CHMP considered this supported by the results of the studies provided and agreed on the inclusion of this statement in the harmonised SmPC.

Concomitant administration with specific vaccines

A statement regarding the possibility for concomitant administration with any of the following vaccines: typhoid, yellow fever, cholera (injectable), tetanus or with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella was included in most MSs. The clinical studies have shown that Havrix can be safely and effectively co-administered with other vaccines that may be recommended at the same time, such as DTPa and Hib vaccines and monovalent and combination vaccines comprised of measles, mumps, rubella and varicella in children (Table 4), and typhoid, yellow fever and HBV vaccines or other travellers' vaccines in adults (Table 5). The response to Havrix when co-administered with these vaccines was similar to the response observed when Havrix was administered alone (Table 8).

[9] Annex to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal products for human use", EMA/CHMP/302620/2017 Rev. 4, 17 April 2024

**Table 8 - Anti-HAV seropositivity for Havrix administered alone and co-administered with other vaccines**

| Study | Group | Timing | N | Seropositivity (≥15 mIU/mL) | | | | GMC | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n | % | 95% CI | | mIU/mL | 95% CI | |
| | | | | | | LL | UL | | LL | UL |
| TypHA-006 | *Havrix* + *Typherix* | PI(D14) | 232 | 211 | 90.9 | 86.5 | 94.3 | 190.1 | 166.0 | 217.8 |
| | | PI(M1) | 233 | 230 | 98.7 | 96.3 | 99.7 | 389.7 | 344.9 | 440.3 |
| | | PI(M6) | 231 | 225 | 97.4 | 94.4 | 99.0 | 130.7 | 113.9 | 149.9 |
| | | PII(M7) | 226 | 226 | 100 | 98.4 | 100 | 2615.1 | 2281.8 | 2997.2 |
| | *Havrix* | PI(D14) | 230 | 213 | 92.6 | 88.4 | 95.6 | 179.8 | 156.4 | 206.6 |
| | | PI(M1) | 231 | 230 | 99.6 | 97.6 | 100 | 373.4 | 329.8 | 422.8 |
| | | PI(M6) | 228 | 220 | 96.5 | 93.2 | 98.5 | 135.5 | 117.9 | 155.8 |
| | | PII(M7) | 223 | 223 | 100 | 98.4 | 100 | 2417.1 | 2103.2 | 2777.9 |
| | *Hepatyrix d0* + *Havrix at m6* | PI(D14) | 235 | 219 | 93.2 | 89.2 | 96.1 | 157.6 | 137.6 | 180.4 |
| | | PI(M1) | 235 | 232 | 98.7 | 96.3 | 99.7 | 360.0 | 314.2 | 412.6 |
| | | PI(M6) | 235 | 224 | 95.3 | 91.8 | 97.6 | 126.6 | 110.1 | 145.6 |
| | | PII(M7) | 228 | 228 | 100 | 98.4 | 100 | 2091.2 | 1825.3 | 2395.8 |

95% CI: 95% confidence interval; ATP: according-to-protocol; D: Day; GMC: geometric mean concentration; LL: lower limit; M: Month; N: number of subjects tested; n/%: number/percentage of subjects who were seropositive for anti-HAV antibodies; UL: upper limit.
GMCs calculated on seropositive subjects; PI(D14), etc.: Blood sampling post-Dose 1 Day 14, etc.

The CHMP considered this statement justified based on the data and supported its inclusion in the harmonised SmPC.

Concomitant administration of immunoglobulins

Statements on the possible concomitant administration of immunoglobulins as seroconversion rates remain unchanged, although antibody titres may be lower, are included in all MSs but one. This was considered supported and kept in the harmonised text. In one MS, the statement is preceded with "If immediate protection against hepatitis A is wanted, concomitant administration with gamma globulin may be considered when the first dose of the vaccine is given". Based on results from study HAV-047, a randomised controlled study with 3 groups receiving either the vaccine or immunoglobulins alone or vaccine and immunoglobulins, no significant difference in anti-HAV seropositivity between the administration of the vaccine alone or co-administered with immunoglobulins was demonstrated (Table 9). Therefore, the data were considered insufficient to support this part of the statement on concomitant immunoglobulin administration and it was not kept in the harmonised text.

**Table 9 - Comparison of anti-HAV seropositivity rates when Havrix is administered alone or co-administered with immunoglobulins**

| Group | Pre | PI(D5) | PI(M1) | PII(M2) | PII(M6) | PIII(M7) |
|---|---|---|---|---|---|---|
| *Havrix* (N=49) | 0 | 0 | 95.9 | 100 | 97.9 | 100 |
| Immunoglobulins (N=49) | 0 | 100 | 100 | 87.5 | 0 | 0 |
| *Havrix* + immunoglobulins (N=48) | 0 | 100 | 100 | 100 | 95.7 | 97.7 |

ATP: according-to-protocol; D: Day; M: Month; N: number of subjects tested.
Pre: before vaccination; PI(D5), PI(M1), etc.: post-vaccination I blood sample at Day 5, at Month 1, etc.
Data source: Module 5.3.5.1, HAV-047-208109 (HAV) 062 Annex Report 1 5 February 1992, Table 4A.

Separate injection sites for concomitant administration of injectable vaccines or of immunoglobulins

A statement on the need to use different syringes and needles when considering concomitant administration of injectable vaccines or of immunoglobulins, which must also be done at different injection sites, was included in most of the MSs and is considered common practice. Therefore, it was considered appropriate to retain it in the harmonised text.

Further the statement "This vaccine should not be mixed with other vaccines" present in one MS should rather be reflected under section 6.2 in line with the QRD template and the SmPC guidelines.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.6 – Fertility, pregnancy and lactation**

The statements on pregnancy and on breast-feeding were included in all MSs with minor divergences. However, the CHMP considered that the information on pregnancy and lactation should be further substantiated to reflect the available clinical and non-clinical data. Therefore, the MAH was requested to align the wording with the guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005)[10] and to include a cross-reference to section 5.3.

*Pregnancy*

The MAH did not perform clinical studies to evaluate Havrix in pregnant women. However, the MAH used the results of studies of the risk of miscarriage after human papillomavirus (HPV) vaccination with Cervarix, in which women of reproductive age were mostly enrolled and Havrix was used as an active control (Wacholder, 2010)[11]. In addition, the review of the GSK worldwide safety database for AEs following vaccination of pregnant women with Havrix did not show any concerning pattern of adverse pregnancy outcomes following exposure to Havrix during pregnancy.

*Breast-feeding*

In accordance with the statements listed in the Appendix of the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005) it was specified in the harmonised SmPC that it is unknown whether Havrix is excreted in human milk. The sentence "Although the risk can be considered as negligible, Havrix should be used during lactation only when clearly needed" already approved in all MS was kept.

*Fertility*

A statement on fertility was included in only 6 SmPCs. Although there are no data on human fertility for Havrix, a statement was added in the harmonised SmPC in accordance with requirements set out in the SmPC guideline.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.7 – Effects on ability to drive and use machines**

The lack of or negligible influence of Havrix on the ability to drive and use machines was included in all MSs with minor variation. It was aligned to the QRD template.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.8 – Undesirable effects**

The presentation of the safety profile was not aligned across national SmPCs. In the SmPC of all MSs but two, the adverse reactions reported with Havrix 1440 Adult and with Havrix 720 Junior were presented in a single list. In the CHMP view, the use of different vaccine strengths per different age population but in the same therapeutic indication is not considered a different use of the product. Further, data submitted to determine adverse drug reactions (ADRs) incidences are derived from a

[10] Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (europa.eu)
[11] Wacholder S, Chen BE, Wilcox A et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ 2010;340:c712 doi:10.1136/bmj.c712

pooled analysis of studies with Havrix that included subjects of all ages. In addition, where ADRs are presented in two separate tables, these refer to the Junior and Adult dose posology and not to age group. Finally, the CHMP considered that no safety concerns are foreseen with the use of a single table since the Havrix safety profile is well established, and the group of 16-18-year-olds can use both strengths. Therefore, in line with the SmPC guideline, and considering that a combined SmPC is proposed, the ADRs from clinical studies should be presented in a single table. However, the use of footnotes to identify ADRs reported only with one formulation or with a difference in frequency in each formulation was considered acceptable.

MedDRA system organ classification was used, and frequencies recalculated based on the data from 26 studies, including studies with Havrix 720 and with Havrix 1440.

The MAH reviewed all the cases reported spontaneously in their safety database since first marketing of the Havrix vaccine (January 1992) up to the data lock point (19 September 2006). Patient exposure during this period was estimated to be between 60 and 120 million subjects. Since then, no significant changes to the safety profile were identified based on post-marketing data from spontaneous reporting. No new type of ADR was reported, and the frequency of reporting has not increased, and therefore, an update of terms listed in the post-marketing data section of the harmonised SmPC was not required, however the frequencies calculated were included. Further the AEs "neuritis, including Guillain-Barre syndrome and transverse myelitis", reported spontaneously post-marketing, were listed in two MSs with the frequency "very rare". However, a casual relation with Havrix was not considered established in line with the last PSUSA (PSUSA/00001596/201901). Therefore, it was not included in the harmonised table.

The statement on reporting of suspected adverse reactions was aligned to the QRD template and the link to the Appendix V of the QRD template was included.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 4.9 – Overdose**

No significant differences between the national SmPCs were present in this section. The MAH's proposal to include the fact that cases of overdose have been reported during post-marketing surveillance and that adverse events reported following overdosage were similar to those reported with normal vaccine administration was considered acceptable for inclusion in the harmonised SmPC.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 5.1 – Pharmacodynamic properties**

The wording for the ATC classification and for the mechanism of action proposed in the harmonised SmPC was already included in most of the SmPCs and was accepted.

Pharmacodynamic effects

Immune response

The wording for the immune response proposed in the harmonised SmPC was included in most of the MSs. The MAH included statements relating to the immune response generated from clinical studies involving adults and clinical studies involving children 1 to 18 years of age, including the mention that seroconversion was shorter than the average incubation period of hepatitis A (4 weeks). The CHMP considered the latter mention to be arbitrary and not evidence based. Therefore, this was not kept in the harmonised text. Moreover, it was further specified whether the results reported for children 1-18 and 16-18 years of age were obtained after the primary or booster dose, and the term "primary dose" was used in the description of the study results rather than "first" or "single".

Although limited data was available, the CHMP considered that relevant available information in children less than 1 year of age should be reported.

It is known that chronic liver diseases (CLD) patients are at risk of hepatitis A, therefore the CHMP requested to include the results of clinical trials and scientific publications demonstrating the efficacy (immunogenicity) of the vaccine in this specific group.

Persistence of the immune response

The wording on the booster vaccination and the wording on long-term persistence of the immune response following two doses of Havrix given 6 to 12 months apart were already included in all the MSs and were considered acceptable.

The proposals from the MAH on the lack of a need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course, already included in the SmPC of all MSs but one, were accepted. Data showed the ability of the vaccine to stimulate the production of persisting antibodies and showed that a long-lasting immune memory is induced (Table 10). The statement on the long-term protection in children present in one MS was also considered supported by studies published in the literature (Dagan, 2005; Hanna, 2004), and was accepted.

**Table 10 - Overview of clinical studies investigating long-term immunogenicity of Havrix in adults**

| Study No.<br>*Country* | Vaccine(s)<br>(Dose) | Population<br>Age** | Follow-up<br>duration | Enrolled | *Havrix*<br>ATP | Design | Objectives |
|---|---|---|---|---|---|---|---|
| **HAV-112 Ext M198**<br>[110677]<br>**HAV-112 Ext M 210**<br>[110678]<br>*Belgium* | *Havrix* 1440 EL.U 0.5 mg Al | Adults<br>18-40 years | 17.5 years | 124 | 91 | 17.5-year immunogenicity follow-up after vaccination at 0 and 12 months in study HAV-112 | **Primary:** Immunological persistence |
| **HAV-123 Ext Y16**<br>[111028]<br>**HAV-123 Ext Y17**<br>[111029]<br>*Belgium* | *Havrix* 1440 EL.U 0.5 mg Al | Adults<br>18-40 years | 17 years | 63 | 45 | 17-year immunogenicity follow-up after vaccination at 0 and 6 months in study HAV-123 | **Primary:** Immunological persistence |
| **HAV-228**<br>[208109/228]<br>*Belgium* | *Havrix* 720 EL.U 0.5 mg Al | Adults<br>18-35 years | 12 years | 31 | 28 | 12-year immunogenicity follow-up after vaccination at 0, 1 and 6 months in study HAV-058 | **Primary:** Immune response to challenge immunisation<br>**Secondary**: Immunological persistence, safety and reactogenicity |
| **TOTAL** | | | | **218** | **164** | | |

Efficacy of Havrix for outbreak control and impact of mass vaccination on disease incidence

The MAH proposed to include in the harmonised SmPC a statement on the efficacy of Havrix for outbreak control and a statement on the impact of mass vaccination on disease incidence. The CHMP was of the view that according to the EC guideline on SmPC, results presented in section 5.1 should be limited to the most clinically relevant and statistically compelling findings in term of robustness. Therefore, the CHMP considered these statements out of the scope of the SmPC and requested their deletion.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 5.2 – Pharmacokinetic properties**

The fact that evaluation of pharmacokinetic properties is not required for vaccines was already mentioned in 11 MSs, with slightly different wording in the remaining MSs. This was considered acceptable in line with relevant guidelines. The CHMP endorsed this sentence.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Section 5.3 – Preclinical safety data**

The MAH submitted nonclinical data generated for the first registered HAV vaccine. As the antigen used in all HAV vaccines is the same, no novel excipients are used in the HAV vaccine formulations and the qualitative composition of the current HAV vaccine is the same as the initial HAV vaccine, with the exception of 2-phenoxyethanol which was initially used as a preservative but was removed from the Havrix vaccine formulation, the CHMP considered these data applicable for the current HAV vaccine formulations and requested to update the wording according to the QRD template. Further the relevant results on reproductive toxicity obtained with Twinrix vaccine (GSK's HAV and HBV combination vaccine) were introduced, indicating the corresponding dose of HAB in 200 µl injection of Twinrix vaccine and that rats were administered Twinrix intramuscularly. The CHMP endorsed the harmonised wording.

The final agreed wording for this section of the SmPC can be found in Annex III of the CHMP opinion.

**Other sections of the SmPC**

Sections 1 (name of the medicinal product), 2 (qualitative and quantitative composition), 3 (pharmaceutical form), 6 (pharmaceutical particulars), 7 (marketing authorisation holder), 8 (marketing authorisation number(s)), 9 (date of first authorisation/renewal of the authorisation) and 10 (date of revision of the text) have not been harmonised as it is considered that these should be adapted nationally, until their revision with the harmonisation of Module 3 after the finalisation of the article 30 referral procedure. However as mentioned in the section on 4.5 above, the fact that this vaccine should not be mixed with other vaccines, was reflected under 6.2.

### 2.2.2. Labelling

Changes introduced in the SmPC were consistently reflected in the labelling, however most sections were left to be completed nationally.

### 2.2.3. Package Leaflet

The package leaflet (PL) was amended in accordance with the changes made to the SmPC, adapting the language and taking into consideration the relevance of the information for patients. The MAH submitted a bridging study of the user readability testing providing a critical analysis of the similarity of the Ambirix 'parent' PL, and Havrix Adult and Havrix Junior 'daughter' PLs in terms of overall format and content. The CHMP considered it acceptable.

## *2.3. Risk Management Plan*

The CHMP did not require the MAH to submit a risk management plan.

# 3. Recommendation

Based on the review of all available data the CHMP recommended the revision and harmonisation of the product information for Havrix and associated names. The final agreed wording of the product information can be found in Annex III of the CHMP opinion.

# 4. Grounds for Opinion

Whereas,

- The committee considered the referral under Article 30 of Directive 2001/83/EC.
- The committee considered the identified divergences for Havrix and associated names, for the indication, posology and method of administration, special warnings and precautions for use and undesirable effects, as well as the remaining sections of the product information.
- The committee reviewed the totality of the data submitted by the MAH in support of the proposed harmonisation of the product information, including MAH-sponsored clinical trials, scientific literature, as well as consensus guidelines.
- The committee agreed on a harmonised product information for Havrix and associated names.

Therefore, CHMP recommended the variation to the terms of the marketing authorisations for Havrix and associated names (see Annex I of the CHMP opinion), for which the product information is set out in Annex III of the CHMP opinion.

The CHMP as a consequence, concluded that the benefit-risk balance of Havrix and associated names remains favourable, subject to the agreed changes to the product information.