Annex II

Scientific conclusions

Scientific conclusions

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.

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 have been 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, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden as well as in Iceland and Norway. Worldwide they are authorised in over 85 countries. GlaxoSmithKline Biologicals SA group of companies, the marketing authorisation holder (MAH) has performed an analysis of the divergences between the English translations of all national Summary of Product Characteristic (SmPC) of the 26 EU MS 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.

On 21 August 2023, 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) of its Hepatitis A vaccine Havrix and associated names, across the EU MS.

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

Overall summary of the scientific evaluation by the CHMP

Only the major changes are discussed in detail below. However, the harmonised PI is set out in Annex III.

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 MS, with slight differences due to linguistic peculiarities. To support the immunogenicity and efficacy of Havrix against hepatitis A virus (HAV) infection, the MAH provided studies with Havrix Adults and Havrix Junior, as well as studies in which the vaccine has been used as an active control, clinical development program with Havrix as an active control and studies published in the literature.

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

Age groups

Information on age limits of the target population for the two Havrix formulations (Adult and Junior) were not aligned in the national SmPCs. The CHMP considered that the results of studies evaluating the immunisation with Havrix 720 Junior in children in the second year of life demonstrated its suitability for immunisation of children aged 1 year against hepatitis A.

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). Although the immune response in the 16-18 years age group when administered the paediatric dosage was still adequate, these data support the general indication to use preferably Havrix 1440 Adult from the age of 16 years, but still support the possibility to administrate Havrix 720 Junior in adolescents aged 16 to 18 years included.

The CHMP considered the proposed indication acceptable and in line with the European Commission (EC) "Guideline on Summary of Product Characteristics (SmPC)"[1] as well as "Wording of therapeutic indication" (EMA/CHMP/483022/2019), with the addition of separated text for each strength to clarify the age groups in which they can be used, and 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.

Section 4.2 – Posology and method of administration

Posology

Based on the data from the studies discussed in the above section, it was clarified that whilst Havrix 720 Junior is intended to be used in children and adolescents aged 1 to 15 years included, it could also be acceptable to use it in adolescents aged 16 to 18 years included, if necessary. Havrix 1440 Adult is intended to be used in adolescents and adults 16 years of age and above.

Based on data from the studies described in the section above and from a prospective comparative study in adults with a second dose delayed up to 5.5 years, the statement on the time window within which the primary and booster vaccination and regarding a delayed second dose, already included in all MS, but three, was 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[2]. A statement regarding the interchangeability was included in the harmonised SmPC.

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). No dose adjustment is required and a statement on the limited data for the use of Havrix in this population 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, 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

[1] European Commission "Guideline on Summary of Product Characteristics (SmPC)", September 2009
[2] WHO position paper on hepatitis A vaccines, 2022

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 MS 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. 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 the harmonised SmPC. The statements against the administration in the gluteal region or intravascularly, already approved in all the SmPC, were considered appropriate and were kept. Because the subcutaneous or intradermal administration may result in a less optimal anti-HAV responses, a statement against such administration was also already included in most of the MS 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.

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 MS with minor divergencies in wordings (e.g. reference in 10 MS to "residues", or to any "component" or "ingredient"). The statement was kept and aligned to the QRD template and the EC Guideline on SmPC. In addition, the hypersensitivity to formaldehyde was mentioned in the SmPC of 3 MS. The CHMP acknowledged that the EC guideline on Excipients in the labelling and package leaflet of medicinal products for human use (2018)[3] 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 could potentially elicit a more severe reaction. Therefore, the CHMP considered that Havrix should also be contraindicated in case of hypersensitivity to formaldehyde.

Section 4.4 – Special warnings and precautions for use

General recommendations

A warning related to the recommendation to postponed administration of Havrix in individuals suffering from acute severe febrile illness, but not in the presence of a minor infection was included. The CHMP considered that it 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.

Havrix should under no circumstances be administered intravascularly, and a statement in this regards was considered adequately mentioned under 4.2, and was therefore not kept under 4.4 in the harmonised SmPC.

As already included in all MS, 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 worksharing procedure (EMEA/H/C/xxxx/WS/0153) for all injectable GSK vaccines.

[3] Guideline on Excipients in the labelling and package leaflet of medicinal products for human use (2018)

A warning on the uncertainties around efficacy in individuals in the incubation period of a hepatitis A infection was included in all MS 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 insufficient and inconclusive, and as the clinical data did not show complete protection during the incubation period, 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 MS and is generally accepted. The CHMP supported the inclusion of this warning in the harmonised SmPC.

The CHMP considered it is 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 MS, with minor variations. These were aligned to the Annex to the EC guideline on Excipients (2024)[4], expressing also the amounts of phenylalanine in the adults and paediatric formulations separately so that it is clearly visible to healthcare professionals.

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

A statement regarding the expected lack of interference with the immune responses in case of use with other inactivated vaccines and the possibility for concomitant administration with specific vaccines was included in most MS. The CHMP considered these statement justified based on the data and supported its inclusion in the harmonised SmPC.

Statements on the possible concomitant administration of immunoglobulins as seroconversion rates remain unchanged, although antibody titres may be lower, are included in all MS 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". The data was considered insufficient to support this part of the statement on concomitant immunoglobulin administration, therefore it was not kept in the harmonised text.

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

[4] 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

Section 4.6 – Fertility, pregnancy and lactation

The statements on pregnancy and on breast-feeding were included in all MS 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)[5] and to include a cross-reference to section 5.3.

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 MS with minor variation. It was aligned to the QRD template.

Section 4.8 – Undesirable effects

The presentation of the safety profile was not aligned across national SmPCs. In line with the SmPC guideline, the CHMP was of the view that the adverse drug reactions (ADRs) from clinical studies should be presented in a single table. However, the use of footnotes to identify the adverse reactions 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.

A casual relation between the adverse events (AEs) "neuritis, including Guillain-Barre syndrome and transverse myelitis" and Havrix administration was not considered established in line with the last PSUSA (PSUSA/00001596/201901). Therefore, it was not included in the harmonised table.

An update of the terms listed in the post-marketing data section of the harmonised SmPC was not required, however the frequencies calculated were included.

Section 4.9 – Overdose

No significant differences between the national SmPCs were present in this section. 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.

Section 5

The wording for the ATC classification and for the mechanism of action proposed in the harmonised SmPC were already included in most of the SmPCs and was accepted. The wording for the immune response proposed in the harmonised SmPC was included in most of the MS. The MAH included statements related to the immune response generated from clinical studies involving adults and clinical studies involving children 1 to 18 years of age. The CHMP considered the mention that the seroconversion was shorter than the average incubation period of hepatitis A to be arbitrary and not evidence based. Therefore, this was not kept in the harmonised text. 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. The statements on the lack of need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course, already included in all MS but one, were accepted as data showed the ability of the vaccine to stimulate the production of persisting antibodies and showed that a long-lasting immune

[5] Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling (europa.eu)

memory is induced. Results on reproductive toxicity obtained with Twinrix vaccine (GSK's HAV and HBV combination vaccine) were introduced in the harmonised SmPC.

Other sections of the SmPC

In line with the QRD template and the SmPC guideline, the statement "This vaccine should not be mixed with other vaccines" proposed in section 4.5 in the harmonised SmPC, was under section 6.2. Other sections have not been harmonised as it is considered that these should be adapted nationally.

Labelling

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

Package leaflet

The package leaflet 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.

Grounds for the CHMP 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), for which the product information is set out in Annex III.

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.