NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 30 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 30 of Directive 2001/83/EC to the CHMP made by Marketing Authorisation Holder (MAH):
GlaxoSmithKline Biologicals SA

THIS NOTIFICATION IS TO BE COPIED BY THE REFERRING PARTY TO APPLICANT/ MARKETING AUTHORISATION HOLDER AND ALL CHMP MEMBERS

Product Name	HAVRIX and associated names *See Annex I*
Active substance(s)	Hepatitis A virus (inactivated, adsorbed)
Pharmaceutical form(s)	Suspension for injection
Strength(s)	HAVRIX 1440 Adult: 1 dose (1 ml) contains: 1440 ELISA units (EL.U) of inactivated hepatitis A viral antigen adsorbed onto 0.5 mg of aluminium as aluminium hydroxide HAVRIX 720 Junior: 1 dose (0.5 ml) contains: 720 ELISA units (EL.U) of inactivated hepatitis A viral antigen adsorbed onto 0.25 mg of aluminium as aluminium hydroxide
Route(s) of administration	Intramuscular use See Annex I
Presentations	Suspension for injection in pre-filled syringe (PFS) Suspension for injection in vial
Applicant(s)/Marketing Authorisation Holder(s)	See Annex I

For its Hepatitis A vaccine, *Havrix* (HAVRIX 1440 Adult and HAVRIX 720 JUNIOR and associated names), GlaxoSmithKline Biologicals intends to initiate a referral procedure under Article 30(1) of Directive 2001/83/EC to harmonise the SmPCs across 26 EU countries, as well as Iceland and Norway (see Annex I) where the vaccine is currently authorised via purely national procedures.

The Company has performed an analysis of the divergencies between the English translations of the national SmPCs for *Havrix* 1440 Adult and *Havrix* 720 Junior from the EU Member States, Iceland and Norway where *Havrix* is authorised. Divergencies were identified with respect to the below sections and proposes to harmonise these sections across EU countries:
4.1 Therapeutic indications
4.2 Posology and method of administration
4.3 Contraindications
4.4 Special warnings and precautions for use
4.5 Interaction with other medicinal products and other forms of interaction
4.6 Fertility, pregnancy and lactation
4.7 Effects on ability to drive and use machines
4.8 Undesirable effects
4.9 Overdose
5.1 Pharmacodynamic properties
5.2 Pharmacokinetics properties
5.3 Preclinical safety data

The following examples constitute a non-exhaustive list.

- Section 4.1 Therapeutic indications

The Company proposes to include a lower age limit of 1 year, as currently approved in 10 countries (AT, CY, DE, FR, IE, IS, MT, NL, NO, PT). No limit of age is specified in Section 4.1 of the remaining 18 countries.

- Section 4.2 Posology

The Company also proposes to include the appropriate age categories in Section 4.2 Posology (*Havrix 720 Junior - children and adolescents from 1 year up to and including 15 years of age; adolescents up to and including 18 years of age / Havrix 1440 Adult - adolescents and adults 16 years of age and above*), as currently approved in 24 countries (all but DE, EL, ES, PL) for the age groups 1-15 years and 16 years and older, with local divergencies. In one country (NL), no lower age limit is specified ("*children and adolescents up to and including 15 years of age*"). In two countries (DE, FR), *Havrix* 1440 Adult is indicated in individuals over 15 years of age and *Havrix* 720 Junior from 1 year of age up to 15 years of age (FR) or up to and including 14 years of age (DE). In the other SmPCs (EL, ES, PL), the primary dosage for *Havrix* 720 Junior is recommended for a population from 1 year of age up to and including 18 years of age and for *Havrix* 1440 Adult is recommended for subjects 19 years of age and above. The use of *Havrix* 720 Junior in adolescents up to and including 18 years of age is present in 10 countries (AT, BG, CZ, EE, HU, LV, PT, RO, SK, SI).

- Section 4.4 Special warnings and precautions for use:

The Company proposes to add in section 4.4 of the proposed harmonized SmPC, in line with the SmCP guideline (2009), a warning statement on acute febrile illness as currently approved in Section 4.4 in 18 countries (BE, BG, CZ, DK, EE, EL, ES, HU, IT, LV, LT, LU, PL, PT, RO, SI, SE, SK). In the other 10 countries (AT, CY, DE, IE, FI, FR, DE, IS,

MT, NL, NO) "*acute (severe) febrile illness*" is listed as a contraindication in Section 4.3, where it is further specified in 6 countries (AT, DE, IS, FI, NL, NO) that a mild infection is not a contraindication for the vaccination. The Company considers that this statement is a risk that leads to a precaution for use, and not a strict contraindication to vaccination.

- Section 4.8 Undesirable effects

The presentation of the safety profile is not aligned across national SmPCs in countries where *Havrix* is authorised. In the proposed harmonised SmPC, the Company proposes to present the adverse reactions in two separate tables, according to the vaccine strength they were reported for and the population they were reported in, as currently approved in BE and LU. In addition, in these two countries, the adverse reaction "neuritis, including Guillain-Barre syndrome and transverse myelitis" is present with the frequency "very rare" under the system organ class "nervous system disorders". The Company is not intending to include these events in the proposed harmonised SmPC, because not in line with the Reference Safety Information (RSI) and the most recent PSUR approved by the PRAC on 5 September 2019.

Additional divergencies across pre-clinical and clinical sections of the national SmPCs exist and are not detailed in this notification form. All divergencies are presented and discussed in the supporting document provided in the referral application, in addition to the presentation of the data in Module 2 and Module 5.

Due to national decisions taken by Member States over time leading to divergencies in the Product Information of the above-mentioned product, GlaxoSmithKline Biologicals notifies the Agency of an official referral under Article 30 of Directive 2001/83/EC in order to resolve these divergencies and thus to harmonise its divergent SmPCs across the EU Member States, Iceland and Norway where the product is authorised.

Signed 

Date: 1/08/2023