EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMA/CHMP/783377/2014
Committee for Medicinal Products for Human Use (CHMP)

Infanrix Hexa

(diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed))

Procedure No. EMEA/H/C/000296/P46/113

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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CHMP Assessment Report for the Post-Authorisation Measure

Infanrix hexa

International non-proprietary name: diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)

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Marketing authorisation holder: GlaxoSmithKline Biologicals

Administrative information

Name of the Rapporteur	**Daniel Brasseur**

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

A phase IV, non-randomised, open-label, multicentre study with two parallel groups to assess the immunogenicity and safety of GlaxoSmithKline (GSK) Biologicals' combined DTPa-HBVIPV/Hib vaccine administered as a three-dose primary vaccination course at 2, 4 and 6 months of age in healthy infants in Canada.

Combination vaccines are appealing due to the need for fewer injections; however, combinations can result in antigenic 'interference' resulting in a lower immune response than achieved by monovalent vaccines and has been noted with Hib combination products, although with unimpaired ability to induce immune memory.

Immune response to vaccines can vary among populations; parameters such as early exposure to pathogen or to cross-reacting pathogens and genetic differences can influence response to vaccines . Trials comparing vaccine efficacy in various ethnic populations have not been conducted in Canada. Studies examining vaccine efficacy and effectiveness in population subgroups are important to informing disease control programs.

Infanrix hexa (DTPa-HBV-IPV/Hib) has extensive immunogenicity and safety data available from non Canadian jurisdictions. Results from previous trials have demonstrated that when administered at 2, 4 and 6 months of age, *Infanrix hexa* is considered equally efficacious as *Pentacel* + HBV vaccines in eliciting immune response to the vaccine antigens. Earlier *Infanrix hexa* studies did not include children of Canadian or Aboriginal origin.

Due to the high rates of Hib disease in Canada, previous data showing antigenic interference with Hib, and the use of this vaccine to provide more easily hep B immunisation, this study focused on evaluating the immune response of the *Infanrix hexa* vaccine with respect to antibody concentrations to the Hib and hepatitis B antigens. **This phase IV trial assessed vaccine safety and immunogenicity in a 'real world' setting, including vaccine administration by community-based providers and co-administration of the other routine vaccinations recommended in the provinces where the study was undertaken.**

1.1. Steps taken for the assessment

Submission date:	05/05/2014
Start of procedure:	19/10/2014
CHMP Rapporteur's preliminary assessment report circulated on:	18/11/2014
CHMP opinion:	18/12/2014

2. Assessment of the post-authorisation measure: Study No.: 103506 (DTPa-HBV-IPV-118 PRI)

The study groups were as follows:

- "Aboriginal infants": infants of the Canadian First Nations, Metis and Inuit people.
- "Other Non-Aboriginal infants": infants exclusive of Aboriginals. This group is referred to as "Non-Aboriginal infants" henceforth.

All subjects were to receive three doses of GSK Biologicals' combined DTPa-HBV-IPV/Hib vaccine administered at 2, 4, and 6 months of age. All subjects were offered two doses of GSK Biologicals' human rotavirus vaccine (HRV) at 2 and 4 months of age and pneumococcal conjugate vaccine, meningococcal serogroup C conjugate vaccine and influenza vaccine according to the recommended provincial infant immunisation schedules.

The primary objective was to assess the immune response to the Hib component of GSK Biologicals' combined DTPa-HBVIPV/Hib preservative-free vaccine in terms of seroprotection rates one month after the three-dose primary vaccination course in "Aboriginal infants" and "Non-Aboriginal infant".

The secondary objectives were 1) to assess the immune response to the Hib component of the combined DTPa-HBV-IPV/Hib vaccine in terms of anti-polyribosyl-ribitol phosphate (PRP) geometric mean concentrations
(GMCs) one month after the three-dose primary vaccination course ; 2) to assess the immune response to the hepatitis B component of the combined DTPa-HBV-IPV/Hib vaccine in terms of seroprotection rates and anti-HBs GMCs one month after the three-dose primary vaccination course ; 3) to assess the safety of the combined DTPa-HBV-IPV/Hib vaccine in terms of medically attended adverse events and serious adverse events (SAEs) during the three-dose primary vaccination course.

MAH's overall conclusion

- One month after the primary vaccination with *Infanrix hexa*, anti-PRP seroprotection levels were seen in 97.9% of subjects in the Aboriginal Infants group and in 99.1% of subjects in the Non-Aboriginal Infants group.
- Anti-PRP GMCs were 6.123µg/ml (95% CI: 4.498-8.334) in the Aboriginal Infants group and 3.510µg/ml (95% CI: 2.745-4.488) in the Non-Aboriginal Infants group.
- One month after the primary vaccination with *Infanrix hexa*, seroprotective anti-HBs antibody concentration ≥10 mIU/mL was observed in 100% of subjects in Aboriginal Infants and Non-Aboriginal Infants and antibody concentration ≥100 mIU/mL was observed in 97.4% and 97.3% of subjects in Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- The anti-HBs GMCs were 1797.9 mIU/mL (95% CI: 1375.1- 2350.7) and 1544.4 mIU/mL (95% CI: 1210.4-1970.5) for Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- No confirmatory analyses were performed on the primary and secondary objectives.
- At least one unsolicited symptom that required medical attention during the 31-day follow-up period after vaccination was reported for 23.2% and 17.0% of subjects in Aboriginal Infants and Non-Aboriginal Infants groups, respectively.
- SAEs were reported for six subjects in the Aboriginal Infants group during the entire study period. One SAE (pyrexia) was assessed by the investigator as causally related to the study vaccine. All the SAEs were recovered/resolved by the end of the study. No fatal SAEs were reported.
- In this study, the study vaccine was generally well tolerated.

The MAH's overall conclusion is endorsed.

3. CHMP overall conclusion

The CHMP is of the opinion that the immunogenicity and safety data of this study are in line with the approved PI in the EU. This Article 46 is fulfilled and no further action required. Therefore no changes to the PI are considered necessary. Based on the review of this Phase IV study, the CHMP considers that the benefit-risk balance for Infanrix-hexa remains unchanged.

☒ PAM fulfilled (all commitments fulfilled) - No further action required

☐ PAM not fulfilled (not all commitments fulfilled) and further action required: