19 September 2013
EMA/355024/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

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)

Procedure No. EMEA/H/C/000296/P46/106.2

Note

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

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Infanrix Hexa
INN (or common name) of the active substance(s):	Diphtheria toxoid, adsorbed/ Tetanus toxoid, adsorbed/ Pertussis toxoid, adsorbed/ Filamentous haemagglutinin, adsorbed/ Pertactin, adsorbed/ Recombinant Hepatitis B surface Antigen (S protein), adsorbed/ Inactivated type 1 Poliovirus/ Inactivated type 2 Poliovirus/ Inactivated type 3 Poliovirus/ Conjugate of Haemophilus influenzae type b capsular polysaccharide and Tetanus toxoid, adsorbed
MAH:	GSK Biologicals (GlaxoSmithKline Biologicals) S.A.-N.V.(Belgium)
Currently approved Indication(s)	Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b.
Pharmaco-therapeutic group (ATC Code):	J07CA09 - Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B
Pharmaceutical form(s) and strength(s):	Powder and suspension for suspension for injection in a pre-filled syringe After reconstitution, 1 dose (0.5 ml) contains: Diphtheria toxoid not less than 30 International Units (IU) Tetanus toxoid not less than 40 International Units (IU) Bordetella pertussis antigens Pertussis toxoid ** 25 micrograms Filamentous Haemagglutinin ** 25 micrograms Pertactin ** 8 micrograms Hepatitis B surface antigen ** 10 micrograms Poliovirus (inactivated) type 1 (Mahoney strain) ** 40 D-antigen unit type 2 (MEF-1 strain) ** 8 D-antigen unit type 3 (Saukett strain) ** 32 D-antigen unit Haemophilus influenzae type b polysaccharide (10 micrograms) (polyribosylribitol phosphate) conjugated to tetanus toxoid as carrier protein approximately 25 micrograms

1. Executive Summary

This document contains the assessment of the responses to the second RSI (see also P46/106 and P46/106.1).

No SmPC and PL changes are proposed.

2. Rapporteur's Overall Conclusion and recommendation

The MAH submitted the results of a double-blind, randomised, multicentre study to assess safety and immunogenicity of 2 new formulations of the MAH's DTPa-HBV-IPV/Hib vaccine compared to the licensed Infanrix Hexa vaccine when co-administered with Prevenar 13 to healthy infants as a primary vaccination course at 2, 3 and 4 months of age.

The primary objective, i.e. non-inferiority of the immunogenicity of at least one of the novel DTPa-HBV-IPV/Hib vaccine formulations compared to the licensed Infanrix Hexa vaccine, was not met according to the criteria set for non-inferiority, as the immune response to the pertactin component of both novel formulations was not non-inferior to Infanrix Hexa. No divergent safety signals were detected in the comparison of the new formulation with the licensed Infanrix Hexa.

The MAH should continue to investigate in pertussis vaccines that offer prolonged protection compared to the currently authorised vaccines in view of the resurgence of pertussis in fully vaccinated individuals which appears to be at least partly due to waning vaccine-induced immunity (Cherry, 2012).

The second request for supplementary information has been addressed by the MAH.

No further action required.

3. MAH's responses to the second RSI

Question No. 1 - Regulatory

It is noted that the Company has put on hold any further clinical development. Preclinical investigations are currently ongoing to try to identify the root cause for these observed differences. A comprehensive data pack will be available in 1H2013 to allow planning for the next steps. The MAH's results are awaited for further evaluation. The MAH should provide update on the posed question by the end of 1st half of 2013.

The Company conducted a phase I/II, double-blind, randomized, multicentre study to evaluate the safety and immunogenicity of new formulations of the Company's DTPa- HBV-IPV/Hib vaccine when administered to healthy infants as a primary vaccination course at 2, 3 and 4 months of age (Study 113948, DTPA-HBV-IPV-124 PRI). The study failed to meet its primary inferential non-inferiority criteria due to lower anti-PRN antibody concentration with both new formulations: the upper limits of the 97.5% CI on the GMC ratio for anti-PRN was 1.54 (Control group divided by Form A group) and 1.84 (Control group divided by Form B group), and exceeded the pre-defined non-inferiority margin of 1.5. A trend to higher reactogenicity was observed for solicited symptoms and grade 3 solicited symptoms, in particular with regard to pain and fever ($p<0.001$): the observed incidence of solicited adverse events tended to be higher in the investigational groups than in the Control group. Overall

solicited incidence of fever >38 °C per subject was higher in Form A (33.8%) and Form B (30.8) compared to the control group (18.1%).

Based on the clinical study results, the Company has decided to stop the clinical evaluation of the candidate formulations evaluated in this clinical study.

Please note that a preclinical investigation has been performed to identify the root cause for the reactogenicity signal observed in the clinical study. Two *in vivo* models were evaluated but were not successful in reproducing the clinical observation: a pyrogenicity model based on high frequency temperature monitoring of rabbits immunized with vaccines under study (abdominal insert), and a reactogenicity study in rabbits based on local pain assessment using a P.A.M. (Pressure Application Measurement) device. An *in vitro* model was developed to pre-clinically evaluate the reactogenicity of candidate vaccine formulations (innate pro-pyretic mediators secretion profile after a short stimulation of adult whole blood cells). Although this new preclinical model is not validated and the use of adult blood cells may be questionable to assess reactogenicity of a paediatric vaccine, clear differences between the candidate vaccine and the commercial *Infanrix hexa* comparator were observed: a six-hour stimulation of whole blood by both candidate vaccines results in a statistically significantly increased secretion of five cytokines (IL-1b, IL-6, TNFa, IL-1a,IL-8) when compared to stimulation by commercial Infanrix Hexa. Preclinical evaluation has been stopped since the clinical evaluation of the candidate formulation has been stopped.

The Company believes the additional information provided herewith adequately addresses the request for supplementary information expressed in the Assessment Report of EMEA-H-C-296-P46 106.

Rapporteur's comment:

Issue resolved.