



Australian Government

Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Diphtheria, Tetanus, Pertussis (acellular component), Hepatitis B (rDNA), Poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed)

Proprietary Product Name: Hexaxim

Sponsor: Sanofi Aventis Australia Pty Ltd

January 2015

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory committee on prescription medicines
AE	Adverse event
AESI	Adverse event of special interest
aP	Acellular pertussis
AR	Adverse Reaction
CER	Clinical evaluation report
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
D	Diphtheria
DTPa	Diphtheria, tetanus, pertussis (acellular)
ELS	Extensive limb swelling
EMA	European Medicines Agency
EPI	Expanded Program on Immunisation
EU	European Union
FDA	Food and Drug Administration (USA)
FHA	Filamentous haemagglutinin
GMTs	Geometric mean titers
HBsAg	Hepatitis B surface antigen
HepB	Hepatitis B
HHE	Hypotonic Hyporesponsive Episode
Hib	<i>Haemophilus influenzae</i> type b
ICH	International Conference on Harmonisation of registration requirements for pharmaceuticals for human use
IU	International unit/s
IM	Intramuscular

Abbreviation	Meaning
IPV	Inactivated poliomyelitis virus
ITT	Intention to treat
LCL	Lower confidence limit
MedDRA	Medical Dictionary for Regulatory Activities
mIU	Milli international unit/s
mL	Millilitre/s
MMR	measles, mumps, rubella
NIP	National Immunisation Program
OPV	Oral poliomyelitis vaccine
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PK	Pharmacokinetics
PP	per protocol
PRP-T	[<i>Haemophilus influenzae</i> type b capsular] polyribosyl ribitol phosphate conjugated to tetanus protein
rHBsAg	Recombinant hepatitis B surface antigen
SAP	Statistical analysis plan
SAE	Serious adverse event
TT	tetanus toxoid
V	varicella
WHO	World Health Organization

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	4 September 2014
<i>Active ingredients:</i>	Diphtheria toxoid, <i>Haemophilus</i> type B polysaccharide, hepatitis B surface antigen, pertussis filamentous haemagglutinin, pertussis toxoid, poliovirus, tetanus protein, tetanus toxoid
<i>Product name:</i>	Hexaxim
<i>Sponsor's name and address:</i>	Sanofi Aventis Australia Pty Ltd Talavera Corporate Centre: Building D 12-24 Talavera Rd Macquarie Park NSW 2113
<i>Dose form:</i>	Suspension for injection
<i>Strength:</i>	0.5 mL
<i>Container:</i>	Prefilled syringe
<i>Pack sizes:</i>	10 single dose pre-filled syringes with 1 or 2 separate needles per each syringe; 1 single dose pre-filled syringe with 1 or 2 separate needles
<i>Approved therapeutic use:</i>	<p><i>Hexaxim is indicated for vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b.</i></p> <p><i>Use of this vaccine should be in accordance with the national recommendation as per the current Immunisation Handbook.</i></p>
<i>Route of administration:</i>	Intramuscular injection
<i>Dosage:</i>	<p>The primary vaccination schedule consists of three doses of 0.5 mL to be administered at intervals of at least four weeks, in accordance with the national recommendations as per the current Immunisation Handbook.</p> <p>Hexaxim can also be used for booster vaccination during the second year of life but use of this vaccine as a booster should be in accordance with the national recommendations as per the current Immunisation Handbook.</p>
<i>ARTG number:</i>	215536

Product background

This AusPAR describes the application by Sanofi Aventis Australia Pty Ltd (the sponsor) to register a new combination vaccine containing antigens against 6 organism (a hexavalent vaccine): diphtheria, tetanus, pertussis (acellular), hepatitis B, poliomyelitis and *Haemophilus Influenzae* type B (DTPa-hepB-IPV-Hib vaccine), under the trade name Hexaxim, for the following indication:

primary and booster vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive infections caused by Haemophilus influenzae type b.

The primary vaccination is proposed to be given as 3 doses of 0.5 mL to be administered by intramuscular (IM) injection at intervals of at least four weeks in accordance with official recommendations (Table 1). Booster vaccination is proposed to be given in accordance with official recommendations¹.

Table 1: Australian National Immunisation Program Schedule for Children ≤ 4 years from 01 July 2013

Age	Vaccine
Birth	<ul style="list-style-type: none"> Hepatitis B (hepB)
2 months	<ul style="list-style-type: none"> Hepatitis B, diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) Pneumococcal conjugate (13 valent pneumococcal conjugate vaccine, 13vPCV) Rotavirus
4 months	<ul style="list-style-type: none"> Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), Haemophilus influenzae type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) Pneumococcal conjugate (13vPCV) Rotavirus
6 months	<ul style="list-style-type: none"> Hepatitis B, diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) Pneumococcal conjugate (13vPCV) Rotavirus*
12 months	<ul style="list-style-type: none"> Haemophilus influenzae type b and Meningococcal C (Hib-MenC) 13 valent pneumococcal conjugate vaccine, 13vPCV
18 months	<ul style="list-style-type: none"> Measles, mumps, rubella and varicella (chicken pox) (MMRV)
4 years	<ul style="list-style-type: none"> Diphtheria, tetanus, acellular pertussis (whooping cough) and inactivated poliomyelitis (polio) (DTPa-IPV) Measles, mumps and rubella (MMR) (to be given only if MMRV vaccine was not given at 18 months)

*Third dose of rotavirus vaccine is dependent on the vaccine brand used.

¹ From The Australian Immunisation Handbook 10th Edition 2013

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 11 September 2014.

At the time the TGA considered this application, a similar application had been approved in the European Union (2013), New Zealand (2014) and 17 additional countries. The vaccine was refused registration in the Russian Federation on the grounds that:

- The diphtheria toxoid content (20 IU) in the vaccine dose for initial inoculation does not comply with conventional standards (30 IU) set by the World Health Organization (WHO) specified by the European Pharmacopoeia (Ph. Eur., 6.0, article 2067)
- The provided hepatitis B and poliomyelitis vaccination scheme does not comply with the Russian Federation National preventive vaccination calendar schedule
- The results of the clinical trials support high reactivity and insufficient efficiency of the medical product Hexaxim for diphtheria and tetanus components

The sponsor advised that in the Russian Federation, a local clinical trial is required and when the Clinical Trial Application (CTA) and Licence Application (LA) for Hexaxim were submitted together in 2012, the CTA was refused for the reasons provided above, not the LA. However, as licensure cannot be granted without a local clinical trial, Sanofi Pasteur re-submitted the CTA in 2013, and it was refused again for a different reason which is any clinical trials in Russia Federation should be performed in adults before performing in children.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

One dose (0.5 mL) of Hexaxim vaccine contains the following:

- ≥ 20 IU diphtheria toxoid
- ≥ 30 IU tetanus toxoid
- *Bordetella pertussis* antigens
 - 25 μ g pertussis toxoid
 - 25 μ g pertussis filamentous haemagglutinin (PFH)
- 10 μ g hepatitis B surface antigen (HBsAg)
- Poliovirus (inactivated)
 - 40 D antigen Units Type 1 (Mahoney)
 - 8 D antigen Units Type 2 (MEF-1)
 - 32 D antigen Units Type 3 (Saukett)
- 12 μ g *Haemophilus* type B polysaccharide
 - conjugated to tetanus protein (22–36 μ g)

Drug substance (active ingredient)

There are six active ingredients, each comprised of one or more antigens, in Hexaxim (see above). Most of the antigens have been chemically modified in some way; detoxified or conjugated to other molecules, so the structural properties of these ingredients are not pharmacologically significant. To the extent that structure is of immunological significance, it is discussed under *Physical and chemical properties* below.

Information was provided on the manufacturing processes for the following drug substances:

Diphtheria and tetanus toxoid

Purified diphtheria toxoid (PDT) and purified tetanus toxoid (PTT) are detoxified proteins obtained from *Corynebacterium diphtheria* and *Clostridium tetani* respectively. The fermentation of appropriate bacterial strains produces the toxins which are harvested and then detoxified. The resulting crude diphtheria or tetanus toxoid (CDT or CTT) is further purified, leading to the PDT or PTT.

Pertussis

The drug substance is composed of two antigenic proteins, the adsorbed purified pertussis toxoid (PTxd) and the adsorbed, purified FHA. These proteins are obtained from *Bordetella pertussis*. Both pertussis antigen intermediates (native purified FHA and native purified pertussis toxoid) are obtained from the same fermentation process and are separately processed. Native purified toxin is then detoxified. Purified FHA, devoid of toxic activities, is used in its native form. Both antigens (PDT in solution and purified FHA in solution) are then adsorbed separately onto aluminium hydroxide.

Hepatitis B

The HBsAg is produced by recombinant deoxyribonucleic acid (rDNA) technology. The main stages of the production process of HBsAg are cell culture and harvest, purification and maturation.

Inactivated poliomyelitis virus (IPV, trivalent, inactivated)

The poliomyelitis virus comprises three types (1, 2 and 3), each monovalent is manufactured separately. The virus replicates and is then harvested in a single harvest by decanting the supernatant from the bioreactor. After settling, the harvest is clarified, concentrated and purified. The resultant volume of concentrated purified viral suspension undergoes inactivation. The viral inactivation takes place in two stages; the inactivation stage is confirmed by control test results. The monovalent batch can be prepared from one to three lots of concentrated purified viral suspension of the same type. Concentrated purified viral suspension lots are pooled to have a minimal volume needed for the inactivation step.

To produce the concentrated trivalent drug substance, quantities of each of the three monovalents are blended in proportions calculated to obtain the required antigen content.

Haemophilus influenzae type b capsular polyribosyl ribitol phosphate conjugated to tetanus protein (PRP-T)

The production of the concentrated bulk of *Haemophilus* polysaccharide conjugated to tetanus protein (PRP-T) is divided into three main production steps:

- Production of the *Haemophilus* type b polysaccharide,

- Production of the tetanus protein and
- Conjugation of the *Haemophilus* type b polysaccharide with the concentrated tetanus protein.

The polysaccharide is extracted by precipitation from a culture of *Haemophilus influenzae* type b, purified and transformed into an activated polysaccharide (PRP-AH).

The tetanus protein is prepared by cell fermentation of *Clostridium tetani* followed by cell lysis, purification and inactivation of the toxin. The tetanus protein is concentrated in order to be conjugated. A point of note is that, although the tetanus protein derives from a fermentation of the same strain of *C. tetani* as that from which the tetanus toxoid (TT) is produced and although both proteins are the products of detoxification of tetanus toxin, the manufacturing processes differ. In the TT process, crude toxin is detoxified and the crude toxoid is then purified. In the tetanus protein process, the TT is purified and then detoxified.

The covalent binding of the activated polysaccharide to the concentrated tetanus protein is performed. The conjugate product is purified. Finally, the *Haemophilus* polysaccharide conjugate concentrated product is diluted and constitutes the drug substance.

All drug substance manufacturing processes are considered to be satisfactorily controlled by the various in-process controls, release and shelf-life specifications.

Cell banking processes for all the drug substances (bacterial and viral sources and substrates) are satisfactory.

All viral/prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

Diphtheria and tetanus

Purified diphtheria toxoid and PTT are manufactured by long established procedures that produce highly immunogenic antigens that have been used in a large number of effective vaccines.

The bulk purified toxoids comply with the European Pharmacopoeia (Ph. Eur) requirements for antigenic purity and absence of toxin and irreversibility of toxoid.

Levels of free formaldehyde (a potential product-related impurity) are monitored.

Pertussis

The two components acellular pertussis drug substance complies with Ph. Eur monograph Number 1356, Pertussis vaccine (acellular, component, adsorbed). Both the PTxd and the adsorbed, purified FHA are tested to be free of toxic activity and any residual process related impurities before adsorption to aluminium hydroxide.

Hepatitis B surface antigen

The HBsAg complies with the bulk HBsAg part of the Ph. Eur. monograph 1056 *Hepatitis B vaccine (rDNA)*, and with the World Health Organization (WHO) recommendations to assure the quality, safety and efficacy of recombinant hepatitis B vaccines, adopted by the Expert Committee on Biological Standardisation (ECBS) in October 2010 (revised Technical Report Series (TRS) 786).

HBsAg is the product of expression of a viral DNA sequence inserted into the DNA of the yeast *Hansenula polymorpha* by a plasmid vector. Only the gene coding for the major surface antigen of the hepatitis B virus is inserted in the DNA of the yeast.

The antigen exists as a particle composed of proteins and lipids (60% protein, 40% lipid by weight). The protein component is the hepatitis B virus small surface protein (S

protein) which is a membrane protein of around 25 kDa. The lipid component consists of yeast lipids, mainly phospholipids.

It is highly likely that the lipid organisation and composition affects the exposure of S protein epitopes at the particle surface, and thus the immunogenicity. The conformation of S protein molecules in this particle is such that multiple conformational epitopes, mainly dependent on disulphide bonds, are present at the lipid layer surface. The antigenic and immunological properties of the particle depend on the satisfactory formation of these disulphide bonds. These epitopes induce a protective antibody response against the hepatitis B virus in animals and in man. The antigenicity is demonstrated through the interaction with different monoclonal antibodies recognising the disulphide bond dependent epitopes.

Removal of the impurities coming from the HBsAg manufacturing process or from the raw materials has been validated.

Inactivated poliomyelitis vaccine (trivalent, inactivated)

Poliovirus vaccine consists of an aqueous suspension of inactivated types 1, 2 and 3 polioviruses, all produced in vero cells. An optimum combination of the three poliovirus serotypes is necessary to achieve a clinically protective immune response.

Impurities from the cell culture and inactivation steps of the manufacturing process are controlled to acceptable levels.

Haemophilus influenzae type b capsular polyribosyl ribitol phosphate conjugated to tetanus protein

The PRP-T is a conjugate of the polysaccharide polyribosyl ribitol phosphate, prepared from the *Haemophilus influenzae* type b strain 1482, covalently bound to a carrier protein, detoxified tetanus toxin, prepared from *C. tetani*. The *Haemophilus* type b polysaccharide and the tetanus protein are produced, extracted and purified separately, and covalently bonded during last step of the manufacturing process.

The polysaccharide or polyribosyl ribitol phosphate, the main component of the outer capsule of *Haemophilus influenzae* type b, is a linear copolymer.

Because of the importance of the polysaccharide conjugation rate in the immunogenicity of the drug substance (conjugate antigen), particular attention has been paid to characterisation of the conjugation level. Several parameters are analysed on PRP-T and assayed as drug substance release tests:

- The content of free carrier protein;
- The content of free polysaccharide;
- The polysaccharide to protein ratio;
- The molecular size distribution.

Irreversibility of detoxified tetanus protein and removal of reagents involved in the conjugation reaction are routinely tested.

PRP-T is able to elicit a T-cell-dependent humoral immune response and anti-polysaccharide immunoglobulin G (IgG) is correlated with vaccine efficacy.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of all the drug substances, and their intermediates, are consistent with relevant Pharmacopoeial monographs and other standards.

Appropriate validation data have been submitted in support of the test procedures.

Stability

Appropriate storage conditions and shelf lives, supported by real time stability data, have been established for all the drug substances.

Drug product

Hexaxim is a preservative free liquid formulation (suspension for injection) for IM administration.

All the antigens in Hexaxim have been extensively investigated in clinical trials and with the exception of the HBsAg, all the antigens have accumulated substantial post-market experience as part of various licensed vaccines produced by Sanofi Pasteur. The quantities of diphtheria toxoid, tetanus toxoid, poliomyelitis antigens, and pertussis antigens contained in Hexaxim are identical to those contained in Pentavac/Pentaxim, a vaccine that the company claims has a proven efficacy and safety record over more than 20 years of clinical development and post-marketing experience. Pentavac/Pentaxim is not licenced in Australia.

Compatibility of the combination of antigens has been demonstrated. Formulation process development for Hexaxim was conducted over a six year period and resulted in an optimised process for which the stability, safety and clinical efficacy have been demonstrated.

Manufacture

The drug product manufacturing process consists of three stages:

- Manufacture of final bulk product (FBP);
- Filling of FBP into single dose syringes;
- Secondary packaging of filled FBP.

The FBP is formulated by sequential addition and mixing of drug substances and excipients in a defined order to achieve a homogeneous blend. Sterility is maintained by validated aseptic addition of aluminium hydroxide and the adsorbed pertussis antigens while other ingredients are sterile filtered. The dossier contains a detailed flow-chart of the process identifying process controls. The volume of active components to be used according to the composition depends on the initial concentration of each batch of active component.

Hexaxim vaccine is filled in syringes without attached needle.

Validation of critical manufacturing steps of Hexaxim vaccine drug product has been demonstrated. The FBP batches and the final product batches were shown to be consistently manufactured with the required quality attributes. Sterility aspects of formulation and filling have been for the most part satisfactorily evaluated with some outstanding issues that should be resolved; see *Summary of evaluation and issues of importance* below.

Specifications

Information was provided on the proposed specifications, which control identity, potency, purity and other physical, chemical and microbiological properties relevant to the clinical use of the vaccine. Appropriate validation of test methods relating to the specifications was conducted.

Between them, the FBP and the filled product specifications comply, for the most part, with the requirements of Ph. Eur. monograph 2067 *Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed)*. The most notable exception is the FBP specification for diphtheria potency (activity ≥ 30 IU/dose; lower confidence limit (LCL, $p = 0.95$) of estimated potency ≥ 20 IU/dose). The monograph (2067) requires that the LCL ($p = 0.95$) is ≥ 30 IU/dose.

This is addressed under *Summary of evaluation and issues of importance* below.

Stability

Stability data have been generated under real time conditions to characterise the stability profile of the product. The proposed final product shelf life is 36 months at 2 to 8°C and this is, for the most part, supported by the data that demonstrate compliance of lots of product with the stability acceptance criteria throughout the storage period.

The stability of the PRP-T conjugates requires some discussion. The stability data demonstrate that significant depolymerisation of PRP occurs through the recommended final product shelf life of 36 months at 2-8°C and this has been recognised by the proposed end of shelf life specification of: depolymerised PRP < 50%. The company claims that this “end of shelf life” specification proposed for the concentration of depolymerised PRP ($\leq 50\%$) was set up by “modelization” and clinically validated through the A3L17 Study. However, this limit was set by analysis of real time stability data on final lots derived from bulk product showing depolymerised PRP levels < 10% at release. So, the depolymerisation profile of batches with at-release depolymerised PRP levels between 10% and 20 % (the release specification) remains un-elucidated.

It is recommended that, should approval be granted, a condition should be applied that the company should make a commitment to monitor depolymerised PRP levels in final lots derived from bulk product showing depolymerised PRP levels close to 20% at release by enrolling such lots in ongoing 36 month stability studies. This issue is raised under *Summary of evaluation and issues of importance*, below.

Biopharmaceutics

Biopharmaceutical data are not required for this product because it is a vaccine.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, Pharmacopoeial standards and relevant technical guidelines adopted by the TGA. Evaluations included the following:

- Primary evaluation;
- Viral/prion safety;
- Sterility;
- Containers and closures;
- Endotoxin safety.

The following aspects of this application were drawn to the Delegate’s attention:

Product labelling

It is the intention of the company to apply for exemption from the requirement of the labelling to comply with a number of clauses of Therapeutic Goods Order 69 (TGO 69) under Section 14. The exemptions would apply to both the carton and final container labels and are justified by the lack of available space to include all the information required by TGO 69. The evaluator will recommend approval of such an application by the sponsor.

Final product diphtheria potency specification

According to the composition details and the product labelling, each 0.5 mL dose of Hexaxim contains ≥ 20 IU diphtheria toxoid. Other combination diphtheria-containing paediatric vaccines (for example, Infanrix Hexa, Pediaxel) contain ≥ 30 IU diphtheria toxoid or equivalent.

Ph. Eur. Monograph 2067, *Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed)* requires that the minimum potency for diphtheria stated on the label is 30 IU per single human dose unless otherwise justified and authorised. It also requires that the LCL ($p = 0.95$) of the estimated potency determined in the test is not less than the minimum potency stated on the label. Essentially, this means that the specification for diphtheria potency in the formulated vaccine, unless otherwise justified and authorised, must be LCL ≥ 30 IU/dose.

The company has proposed the following specification for diphtheria potency: Activity ≥ 30 IU/dose with a LCL of the estimated potency ≥ 20 IU/dose. The proposed labelling states that one dose of vaccine contains ≥ 20 IU of diphtheria toxoid. Justification of this specification is based on the argument that clinical batches of vaccine that, when tested in the diphtheria potency test, resulted in LCL estimation between 20 and 30 IU/dose were efficacious in clinical studies and were not demonstrated to be inferior to batches for which LCL above 30 IU/dose were measured with respect to the observed percentage of subjects attaining the established seroprotection rate of major clinical relevance (≥ 0.01 IU/mL). The clinical studies were A3L10; A3L11; A3L12; A3L15p; A3L17; A3L24.

Because of the element of this justification for the proposed diphtheria potency specification that is based on performance of various vaccine batches in clinical studies, acceptance of the specification (and corresponding labelling of diphtheria potency) is referred to the clinical Delegate for consideration.

Stability of PRP-T conjugates

The stability data demonstrate that significant depolymerisation of PRP occurs through the recommended final product shelf life of 36 months at 2-8°C and this has been recognised by the proposed end of shelf life specification of depolymerised PRP $< 50\%$. The company claims that this “end of shelf life” specification proposed for the concentration of $\leq 50\%$ was set up by “modelization” and clinically validated through A3L17 Study. However, this limit was set by analysis of real time stability data on final lots derived from bulk product showing depolymerised PRP levels $< 10\%$ at release. So, the depolymerisation profile of batches with at-release depolymerised PRP levels between 10% and 20 % (the release specification) remains un-elucidated.

It is recommended that, should approval be granted, a condition should be applied that the company should make a commitment to monitor depolymerised PRP levels in final lots derived from bulk product showing depolymerised PRP levels close to 20% at release by enrolling such lots in ongoing 36 month stability studies.

Conclusions and recommendations

Subject to appropriate clinical comment on matters identified above and satisfactory resolution of sterility issues, the Module 3 evaluator(s) recommend that the application to register Hexaxim diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) [DTPa-hepB-IPV-Hib] suspension for injection syringe should be approved with conditions detailed below.

- The company should make a commitment to monitor depolymerised PRP levels in final lots derived from bulk product showing depolymerised PRP levels close to 20% at release by enrolling such lots in ongoing 36 month stability studies.
- Standard Lot Release and CPD requirements should also be applied.

III. Nonclinical findings

Introduction

The nonclinical (Module 4_ dossier was designed to assess the potential effects of the addition of the HBsAg to Pentavac (DTPa-IPV-Hib vaccine registered in Europe). While Pentavac is not registered in Australia, the submitted Module 4 dossier is considered acceptable given that the individual components of Hexaxim are contained in vaccines that have previously been evaluated by the TGA. However, there are a number of things to note:

- The HBsAg is produced in a novel yeast cell line. The submitted studies are considered adequate for assessing the potential toxicity associated with this component.
- The Hexaxim vaccine formulation contains only two acellular pertussis antigens (toxoid and FHA). All pertussis vaccine products on the ARTG are three or four component acellular pertussis vaccines. There is no two component acellular pertussis vaccines registered in Australia. This is unlikely to impact the safety assessment but may have some impact on efficacy (see below).

The quality of the submitted nonclinical studies was generally satisfactory, with relevant studies conducted according to good laboratory practice (GLP) principles. Study designs were consistent with relevant guideline requirements (CPMP/SWP/465/95²) and investigated parameters that adequately characterised potential toxicities which might be anticipated with the proposed product. All the toxicity studies used the clinical dose and treatment schedules used were similar to or greater than the proposed clinical dosing schedule (nonclinical: 4 or 5 fortnightly injections compared with clinical: 3 doses given at 4 week intervals).

Pharmacology

Primary pharmacology

The sponsor did not provide studies in Module 4 that specifically set out to confirm the immunogenic potential of each antigen of Hexaxim; presumably on the assumption that since they are in the Pentavac formulation (registered in Europe) their efficacies/antigenicities are already well known. Notwithstanding the fact that Pentavac is not available in Australia, the product does however contain the same antigens (DT, TT,

² CPMP/SWP/465/95 Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines; Annex 1 – WHO guidelines on nonclinical evaluation of vaccines.

PT, FHA and IPV Types I-III) as two registered vaccine products (Adacel and Quadracel), so the lack of antigenicity studies for these components is not considered a major deficiency.

In the primary pharmacology study antibody titres against the novel antigen, HBsAg, as well as the *Haemophilus influenzae* type b antigen conjugated to tetanus toxoid, PRP-T, were measured over an extended period in mice. Antibody titre levels confirmed that both antigens could ably evoke antigenic responses either when administered singularly, in combination with aluminium hydroxide adjuvant, concurrently or as part of the hexavalent vaccine formulation (initial formulation of Hexaxim). There was no evidence of interference between the two antigens and peak antibody production was at the week 6 and week 8 sampling time points, before plateauing by weeks 12 and 16. The study did not monitor the interactions of other antigens by HBsAg; however, interference is not anticipated since the registered Infanrix Hexa also contains the same group of antigens including HBsAg (albeit, from a different source). In addition, although not specifically measured for each of the six antigens, antibody titres against HBsAg, DT and TT were also recorded in rabbits in the repeat dose toxicity studies, presumably as a marker of effective dosing for these studies.

For the other antigens, the sponsor referred to a number of in vivo release tests (which were not included in Module 4) on the potency/immunogenicity of each drug substance (antigen) of Hexaxim, presumably as indirect demonstration of likely efficacy of the finished product formulation. While tests were designed to confirm the ability of antigens to evoke the desired immune response in a test systems, the approaches used (adopted according to Ph. Eur. standards) raised some concerns. Firstly, the route of administration of some tests did not correspond to the proposed clinical route (that is, subcutaneous and intraperitoneal injection were used instead of IM injection), creating uncertainty on how accurately the immune responses align with the clinical response. The WHO guidance document advocates using the same route of administration for the nonclinical studies as the clinical route and states that other routes should be considered if notable toxicities have been reported, which does not apply in this situation.

Notably, tests on pertussis immunogenicity raised uncertainty about the effectiveness of Hexaxim against pertussis infection. Mice given an intranasal *Bordetella pertussis* challenge were immunised 36 days prior with either one of three batches of Hexaxim, the reference vaccine Tetravac, which like Hexaxim is also a two component pertussis antigen, or the internal control DTcoq (Diphtheria, Tetanus, Whole-Cell Pertussis vaccine), which is a whole cell component pertussis vaccine. Bacterial counts were measured on days 5, 8 and 12 post-challenge and according to the sponsor's *Pharmacology Written Summary* colony counts were substantially lower from day 5 onwards for the DTcoq group compared to all other groups, which were unchanged on day 5. By day 12 all vaccinated groups had similarly reduced colony counts. However, the early onset of protection in the DTcoq group suggests that the whole cell pertussis component is better able to protect against pertussis than either Hexaxim or Tetravac.

Hexaxim, unlike other registered pertussis vaccine products does not contain pertactin in its formulation; whether this difference is an important determinant of immunogenicity is uncertain but the lack of a pertactin component does not appear to confer as rapid an onset of protection in Hexaxim vaccinated mice cf. to those immunised with DTcoq. Protective efficacy was not demonstrated for other antigens either; although (with the exception of HBsAg) all other antigens are included in other registered vaccines and their protective efficacy profiles are well established.

None of the studies compared the overall efficacies of Hexaxim and its registered counterpart, Infanrix Hexa, to demonstrate that the proposed product is a viable and comparable alternative hexavalent vaccine to the existing registered option. Nonclinical demonstration of equivalent immunogenicity would have been helpful in establishing

comparable activities of the two vaccines, in view of the differences in pertussis antigen composition; although clinical demonstration of equivalent immunogenicity may be more pertinent and useful.

Safety pharmacology

The sponsor did not provide any safety pharmacology studies, citing the lack of any cardiotoxic, respiratory and neurotoxic risks identified during nonclinical testing and development. The European Medicines Agency (EMA) guideline (CPMP/SWP/465/95) recommends considering such studies for any newly developed vaccines. Since the antigen composition of Hexaxim is similar to already registered products, there is no reason to anticipate unusual toxicities with any of these components. The repeat dose toxicity studies also did not reveal any adverse clinical signs unrelated to the intended pharmacological/immunological effect of the vaccine. None of the submitted studies measured body temperatures after administration of the proposed product.

Pharmacokinetics

No pharmacokinetic (PK) studies were conducted with Hexaxim, which is acceptable according to the EMA guideline for preclinical testing of vaccines (CPMP/SWP/465/95).

Toxicology

Toxicity testing of the vaccine entailed two repeat-dose toxicity studies and one dedicated local tolerance study in rabbits. All studies were conducted according to GLP and were generally consistent with guideline requirements regarding study design, group sizes, dosing schedules and monitored parameters³. The studies used the same dose as that proposed for clinical use (0.5 mL) at a dosage regimen in excess of the proposed vaccination schedule (5 doses given once every 2 weeks compared with the proposed clinical vaccination schedule of 3 doses given once every 4 weeks). The WHO guideline recommends that vaccine doses used in nonclinical tests should exceed the proposed clinical dose on a mg/kg basis (or in this case a mL/kg basis), at dose levels that evoke a meaningful pharmacological effect (that is, an immune response). Since all animal studies used the clinical dose and the body weight of test animals (rabbits about 2.5–3.5 kg) is similar to neonate body weight range, the vaccine doses used were not sufficiently high enough to meet WHO recommendations; although the slightly more frequent dosing regimen might control for this to an extent. All submitted nonclinical studies used the clinical route (IM injection).

Repeat dose toxicity

Two repeat dose studies were conducted in rabbits in which an initial vaccine formulation was tested in one, while in the other an optimised formulation intended for clinical use was used. Positive serology in the treated groups confirmed that dosing schedules were effective at bringing on immune responses, although this was only reported for up to three of the antigens of the vaccine (diphtheria, hepatitis B and tetanus toxoid). All treatment related changes were associated with immune responses to the vaccine. Changes to haematological and serum chemistry parameters were anticipated effects of an immune reaction to the vaccine and included increases in lymphocyte counts (eosinophils, neutrophils and basophils) and globulin levels. In the second rabbit study lymphocyte infiltration also brought about increases to both absolute and relative weights of inguinal and popliteal lymph nodes, which also corresponded to histological changes in these

³ CPMP/SWP/465/95 Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines; Annex 1 – WHO guidelines on nonclinical evaluation of vaccines.

tissues, as well as the spleen (minimal to slight development of germinal centres and paracortex). The remainder of histological observations were changes associated with injection site reactions such as local inflammation and haemorrhaging, chronic inflammation, reddening of the injection site and oedema. Overall, toxicities were minimal and any adverse findings were related to the intended pharmacological effect (that is, provoking an immune response).

Other toxicity studies

The sponsor did not submit studies on genotoxicity, carcinogenicity or reproductive toxicity for Hexaxim, which is acceptable based on CPMP/SWP/465/95 Guideline recommendations and taking into account the target patient group.

Pregnancy classification

The sponsor did not propose a pregnancy category, presumably since the potential for exposure during pregnancy does not apply to the intended patient population (infants and toddlers). The sponsor did not conduct reproductive toxicity studies as they are not a requirement according to EMA guidelines on preclinical testing of vaccines (CPMP/SWP/465/95). Other paediatric vaccine formulations approved in Australia, including Infanrix Hexa, have a pregnancy category of B2⁴ and for this reason this category is also appropriate for Hexaxim since there are no adequate animal studies that have assessed its effects on embryofetal development.

Local tolerance

Local tolerance assessments were incorporated in the two rabbit repeat dose toxicity studies, as well as in a dedicated tolerance study. All studies used the clinical dose (0.5 mL) with two studies using batches of the final clinical formulation. The local tolerance study tested three different batches of Hexaxim as a follow up of observations from a release test in which ulceration was noted in guinea pigs given Hexaxim by the subcutaneous route. Details on these earlier findings were limited to brief descriptions in the sponsor's *Toxicology Written Summary*, in which the sponsor outlined a rationale for the rabbit local tolerance study design (that is, to conduct a full local tolerance evaluation in a highly responsive species, the rabbit). In the two studies that used the clinical formulation, local injection site reactions were a common observation, with evidence of inflammatory cell infiltrate, presence of macrophages and local haemorrhaging being a persistent feature for all tested batches. In both studies the recovery animals showed some reversal of effects but lingering signs of injection site reactions were still seen at 70 days post-injection (inflammatory cell infiltrate and foam cell aggregate). The sponsor attributed the persistence of these observations to the presence of the aluminium hydroxide adjuvant⁵, citing a sponsored study that showed focal deposition of aluminium around injection sites, which persisted for at least six months and was accompanied by macrophage infiltrates. It is worth mentioning that neither the repeat dose toxicity nor the local tolerance studies employed a reference vaccine (such as Infanrix Hexa) to ascertain the extent of these injection site reactions and whether they were typical for the type of product administered.

⁴ Category B2 for the use of medicines in pregnancy is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

⁵ Verdier F, Burnett R, Michelet-Habchi C, MOrretto P, Fievet-Groyne F, Sauzeat E. Aluminium assay and evaluation of the local reaction at several time points after intramuscular administration of aluminium containing vaccines in the Cynomolgus monkey. *Vaccine*. 2005;23(11);1359-67.

The sponsor surmised that ulceration only occurred in the guinea pig release tests because of a possible error in dose administration (that is, mistakenly using the intradermal instead of the subcutaneous route), while the persistent inflammatory reactions (but no ulceration) in rabbits was an expected finding. As none of the submitted studies addressed this hypothesis and with the sponsor not submitting the actual guinea pig release test report, it is difficult to determine whether the data conclusively rule out any clinical relevance to the guinea pig findings. The sponsor remarked that the affected batches had been also used in Phase III trials without any incidences of lesions or ulceration in subjects, therefore any uncertainties about the local tolerance potential of the product intended for marketing will likely be best addressed by clinical evidence of safety.

Nonclinical summary and conclusions

- The quality of the nonclinical studies included in the dossier was generally satisfactory, with submitted studies meeting relevant guideline requirements and adopting appropriate study designs. The clinical route (IM) and dose (0.5 mL) was used in all submitted nonclinical studies and the animal models demonstrated antigenic reactions to the proposed product.
- Primary pharmacology studies examined the immunogenicity of the new antigen of Hexaxim (HBsAg) and its potential for interfering with the *Haemophilus influenzae* type b antigen (PRP-T). Both antigens evoked significant immunoglobulin production in mice. HBsA brought about higher total immunoglobulin titres than PRP-T. Neither antigen attenuated the immunogenicity of the other when tested either as a combination of the two or as part of the hexavalent vaccine formulation.
- In contrast to all other registered pertussis vaccines, which have at least three pertussis antigen components including pertactin, Hexaxim only has two components (pertussis toxoid and FHA). In a protective efficacy study in mice, immunisation with Hexaxim appeared to be less efficacious than whole cell pertussis vaccine against *B. pertussis*. Notably, since the sponsor developed Hexaxim as an alternative to the registered Infanrix Hexa (which contains pertactin), there was no nonclinical evidence of comparable efficacies and immunogenicities between the two product. Thus, suitability of Hexaxim as an alternative to Infanrix Hexa will rely solely on clinical evidence of efficacy.
- Toxicity testing of the vaccine entailed two repeat dose toxicity studies and one dedicated local tolerance study in rabbits. All treatment related changes were associated with immune responses to the vaccine. Changes to haematological and serum chemistry parameters were anticipated effects of an immune reaction to the vaccine and included increases in lymphocyte counts (eosinophils, neutrophils and basophils), histopathological changes to lymph nodes and alterations to globulin levels.
- Local tolerance effects were noted in all studies and included incidences of erythema and oedema (minimal to mild), which were attributed to needle trauma. As well, there were focal areas of chronic inflammation, characterised by localisation of inflammatory cells, cell debris and foam cell aggregates. These persisted in recovery group rabbits and the cause for these effects were not entirely resolved by nonclinical testing strategies but were surmised by the sponsor to be due to the presence of aluminium hydroxide adjuvant.
- Studies on PK, genotoxicity, carcinogenicity and reproductive toxicity were not submitted, which is acceptable based on the EMA and WHO guidelines on nonclinical testing of vaccine products.

Overall, there are no specific nonclinical objections to the registration of the proposed hexavalent combination vaccine, Hexaxim on the basis of safety. However, in view of the absence of pertactin in the final formulation, an antigen included in all registered pertussis vaccine products, uncertainties about efficacy against pertussis will need to be addressed by clinical demonstration of protection.

There were no comparative studies with Infanrix Hexa, therefore, no comment can be provided on the adequacy of Hexaxim as an alternative to the currently registered hexavalent vaccine.

Revisions to nonclinical statements in the draft PI were recommended; details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The proposed indication is

primary and booster vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive infections caused by Haemophilus influenzae type b.

This hexavalent vaccine offers a potential alternative to the already registered, Infanrix Hexa.

Primary vaccination: three doses of 0.5 mL to be administered at intervals of at least four weeks, in accordance with official recommendations. Table 1 shows the childhood vaccination schedule up to 4 years of age for Australia.

Booster vaccination: After vaccination with three doses of Hexaxim, a booster dose should be given in accordance with official recommendations (see Table 1). The proposed indication reflects the indication approved in the European Union (EU) but the upper age limit of 24 months is not proposed for Australia as the National Immunisation Program (NIP) differs from country to country.

Clinical rationale

In Australia, the current NIP from birth to 4 years is summarised in Table 1 above. The vaccine preventable diseases in which killed (non-live) vaccines (antigen or toxoid) are: 1) hepatitis B; 2) tetanus; 3) diphtheria; 4) pertussis; 5) *Haemophilus type b*; 6) polio; 7) pneumococcus; 8) meningococcus C. The vaccine preventable diseases in which live attenuated vaccines are used are: 1) measles; 2) mumps; 3) rubella; 4) varicella; and 5) rotavirus.

In Australia, several combination vaccines are licensed and at present, Infanrix Hexa (DTPa-hepB-IPV/Hib; sponsor GlaxoSmithKline) is the only hexavalent paediatric vaccine used in the NIP. This hexavalent vaccine was approved by TGA in 2006.

In regards to combination vaccines for childhood use, Sanofi Pasteur's pentavalent acellular pertussis (aP) combination vaccine, Pentavac/Pentaxim (DTPa-IPV/Hib) was first licensed in Sweden in 1997 and is used currently in > 100 countries including 26 in the EU. To date, 142 million doses having been distributed worldwide and the sponsor reports an excellent safety record. Sanofi-Pasteur has effectively extended the pentavalent vaccine with the addition of hepatitis B antigen to make their hexavalent vaccine, Hexaxim.

For the Australian NIP, Hexaxim will represent an alternative to the already approved and in use, Infanrix Hexa. The main difference aside from some component differences is Infanrix Hexa requires reconstitution prior to vaccination, whereas Hexaxim is presented as a fully liquid ready-to-use vaccine. The latter could add efficiency for clinicians/nurses when complying with the NIP schedule for children.

Contents of the clinical dossier

The submission contains 13 clinical study reports consisting of 14 clinical trials evaluating the most common vaccination schedules for a primary series paediatric combination vaccine, which varied according to the targeted country from the most condensed (6, 10, 14 weeks) (Expanded Program on Immunisation, EPI) to the least condensed (2, 4, 6 months), and covered booster vaccination during the second year of life as well as long-term immunity persistence.

Control vaccines were as per standard-of-care used in the countries where the studies were conducted. Co-administration of Hexaxim with other childhood vaccines (measles, mumps rubella, varicella, rotavirus, pneumococcal conjugated), and the effect of the presence or the absence of hepatitis B vaccination at birth, were evaluated.

A summary of the 14 submitted studies is shown in Table 2.

Table 2: Summary of the immunogenicity (efficacy) and safety studies of Hexaxim

Primary vaccination studies (Phase/Comparator/Schedule)	Booster studies (Phase/Comparator/Schedule)
A3L02 – Argentina (Phase II / Pentaxim + Engerix B ⁶ / 2, 4, 6 months)	A3L16 – booster of A3L02 (Phase III / Pentaxim as a booster in both Hexaxim and Pentaxim primed infants and no comparator / 18 months)
A3L04 – Mexico/Peru (Phase III / Tritanrix-Hep B ⁷ /Hib + OPV ⁸ / 2, 4, 6 months)	
A3L10 – Turkey (Phase III safety study / Pentaxim + Engerix B / 2, 3, 4 months)	A3L22 – booster of A3L10 (Phase III / no comparator / 15-18 months)
A3L11 – Mexico (Phase III/ Infanrix Hexa / 2, 4, 6 months)	A3L21 – booster of A3L11 (Phase III / no comparator / 15-18 months)
A3L12 – Thailand (Phase III / Infanrix Hexa / 2, 4, 6 months) concomitant vaccination with Prevenar ⁹	
A3L15ps* - South Africa (Phase III / CombAct-Hib ¹⁰ +Engerix B+OPV / 6, 10, 14 weeks of age)	A3L15bo* (Phase III / CombAct-Hib+OPV / 15-18 months) concomitant use of Mumps, Measles and Rubella (MMR) and Varicella (V) vaccine
	A3L26- South Africa (Phase III / no comparator / no vaccine) Long term following up of Study A3L15
A3L17 – Peru (Phase III / Infanrix Hexa / 2, 4, 6 months)	

⁶ Engerix B: hepatitis B vaccine

⁷ Tritanrix-HepB: Diphtheria (D), tetanus (T), pertussis (whole cell) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

⁸ Hib + OPV: *Haemophilus Influenzae* plus oral poliomyelitis vaccine

⁹ Prevenar: 7 valent pneumococcal conjugate vaccine

¹⁰ CombAct-Hib: Diphtheria (D), tetanus (T), pertussis and *Haemophilus Influenzae* (Hib) vaccine conjugated adsorbed

Primary vaccination studies (Phase/Comparator/Schedule)	Booster studies (Phase/Comparator/Schedule)
A3L24 – Columbia/Costa Rica (Phase III / Infanrix Hexa / 2, 4, 6 months) concomitant vaccination with Prevenar and Rotarix (rotavirus vaccine)	
	A3L01-Argentina (Phase I / Hexavac ¹¹ / 16-19 months)

*A3L15ps (primary series and A3L15bo (booster) are included in one study report

Paediatric data

The submission only included paediatric immunogenicity, efficacy and safety data.

Good clinical practice

The trials were conducted in accordance with the recommendations of the Declaration of Helsinki (revisions, valid at the time of the study) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and with applicable national and local requirements. Clinical trials were designed in accordance with EMA and WHO guidelines on clinical evaluation of new vaccines.

Pharmacokinetics

No studies were provided.

As per the Section 2 of Appendix 15 *Biopharmaceutic Studies* of the *Australian Regulatory Guidelines for Prescription Medicines*, a justification for not providing biopharmaceutic data is not provided. In addition, as stated in the *EMA Note for guidance on the clinical evaluation of new vaccines*¹², PK studies are usually not required for vaccines. PK studies if new delivery systems are employed or when the vaccine contains novel adjuvants or excipients and may include evaluation of the antigens and the excipients. No new adjuvant, toxoid, live/live attenuated virus/bacteria are part of Hexaxim. Hexaxim contains inactivated or purified active ingredients administered by the IM route in a ready-to-use, single dose pre-filled syringe.

Pharmacodynamics

Studies providing pharmacodynamic data

The pharmacological profile of Hexaxim is represented by its immunogenicity profile, and as with many vaccines, efficacy is inferred from immunogenicity data. Table 2 above provides a summary of the submitted immunogenicity studies. None of the immunogenicity studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Immunogenicity findings are considered as part of the efficacy considerations, below.

¹¹ Hexavac: diphtheria, tetanus, acellular pertussis, recombinant hepatitis B surface antigen, inactivated poliomyelitis and *Haemophilus influenzae* type b polysaccharide conjugated to tetanus toxoid vaccine.

¹² EMEA/CHMP/VWP/164653/2005 European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on Clinical Evaluation of New Vaccines. 18 October 2006.

Dosage selection for the pivotal studies

The Hexaxim vaccine in the immunogenicity studies is the same formulation as that used in the *Clinical efficacy* studies and was used as per the primary vaccination schedule (n = 3 vaccines separated by 4 or 8 weeks) in various different countries. Boosting data for Hexaxim (4 doses of Hexaxim in an 18 month period) and longevity of the immune response is provided in Studies A3L22, A3L15 and A3L26 respectively.

Efficacy

Studies providing efficacy data

See Table 2 above.

Evaluator's comment: The distinction between “immunogenicity” studies and clinical efficacy studies in this review is somewhat arbitrary. The reason is that all the studies presented in this submission are immunogenicity studies. This dossier of studies provides only immunological response data (and safety) induced by Hexaxim and the comparator vaccine(s); that is, these are surrogate markers of clinical protection. No actual clinical efficacy data is provided in this submission.

Evaluator's conclusions on efficacy

Immunogenicity for primary vaccination in the first year of life and boosting and protective efficacy

This application provides a comprehensive and appropriately powered swathe of immunogenicity studies of the hexavalent vaccine, Hexaxim. Immunogenicity is used as surrogate of clinical efficacy, the rationale for this approach is discussed above. However, this is not so clearly established for pertussis and discussed further below.

Measures of effectiveness of pertussis vaccines

A correlation between the serological response to antigens and protection against pertussis is currently not well established. Plotkin et al, 2011¹³ reviewed the 16 year clinical data for Pentaxim with the following caveats: it is virtually impossible to detect minor differences between vaccines in efficacy trials and more difficult still, to detect differences in effectiveness by surveillance. The reason for the latter:

- the same vaccine is not exclusively used over a long period of time in exactly the same way (schedule, number of boosters) in a country;
- population demographics and density change over time;
- the natural epidemiology of the infection changes, with cycles of more/less activity;
- vaccine coverage changes;
- the surveillance method used is not usually uniform over time;
- sampling techniques and laboratory methods change and tests used to define the infection change in their sensitivity and specificity.

Surveillance data for pertussis

Despite all the caveats above, it appears that the pertussis toxoid and FHA antigens contained in Hexaxim to control diseases caused by *Bordetella pertussis* have been

¹³ Plotkin SA, Johannes Liese, Shabir A Madhi and Esteban Ortiz. A DTaP-IPV//PRP-T vaccine (Pentaxim): a review of 16 years' clinical experience. *Expert Review of Vaccines*. 2011;10(7):981-1005.

'demonstrated' in a 10 year National surveillance on pertussis in Sweden with the Pentavac/Pentaxim vaccine, which corresponds to the D, T, P, IPV and Hib portion of Hexaxim (Carlsson and Trollfors 2009¹⁴; Hallander and Gustafsson 2009¹⁵; Tindberg 1999¹⁶); national surveillance for pertussis in France (Bonmarin 2007¹⁷) and Austria (Rendi-Wagner 2006¹⁸) also provide similar 'efficacy' data. In regards to the Swedish surveillance data, vaccines containing acellular pertussis were included in the Swedish vaccination program in 1996 (note that whole cell pertussis vaccine was withdrawn in 1977). Vaccine coverage for the three-dose pertussis vaccination at 3, 5, 12 months of age reached 98–99% within a few month of whole cell pertussis withdrawal. Reporting of cases changed from a voluntary to mandatory reporting in October 1997 meaning that all pertussis reports confirmed by culture or polymerase chain reaction (PCR) in Swedish children born in 1996 and onwards have been identified through the computer-linked reporting system; clinical outcomes and detailed vaccination status were obtained by structured telephone interviews. Moreover, since 1996, only two pertussis vaccines have been used in Sweden, the two component vaccine from Sanofi Pasteur and the three-component vaccines from GlaxoSmithKline.

Three years after the introduction of acellular pertussis vaccines, the reported incidence of pertussis had dropped by 80–90% to levels similar to the lowest rates observed in the 1960s when the Swedish whole cell pertussis program was still effective. Moreover, overall incidence of laboratory-confirmed pertussis dropped from 113–150 per 100,000 person-years in 1993–1995 to 11–16 per 100,000 in 2001–2004 and 6–16 per 100,000 in 2001–2007.

A pure cohort of Pentaxim recipients was analysed separately. Over 10 years of vaccine use, the incidence of pertussis was 26 per 100,000 and 12 per 100,000 person-years after the second and third doses, respectively, compared with 232 per 100,000 person-years before the first dose and 209 per 100,000 person-years before the second dose. Additional data document the long-term antibody persistence in the years following booster vaccination. In Sweden, antibody persistence was measured at 5.5 years of age (Carlsson 2002¹⁹). The study found that 89.0–97.0% of children remained seroprotected for diphtheria, tetanus, polio types 1, 2, 3 and PRP antigens, while 91.0–94.0% of children had anti-pertussis toxoid and anti-FHA antibody levels ≥ 4 endotoxin units (EU)/mL (defined at the time of the study) at 5.5 years after receiving the booster dose. Anti-pertussis toxoid geometric mean titres (GMTs) were at 12.8 EU/ml (using seroneutralisation) and anti-FHA GMTs at 24.8 EU/mL (using enzyme linked immunosorbant assay, ELISA). Following a slight increase in incidence of pertussis that was observed among 7–8-year-old children, suggesting waning of vaccine induced protection from pertussis, the Swedish vaccine programme now adopts a booster dose at aged 5-7 years (note the Australian NIP recommends a booster at age 4 years of age).

¹⁴ Carlsson RM, Trollfors B. Control of pertussis-lessons learnt from a 10-year surveillance programme in Sweden. *Vaccine*. 2009;27(42):5709-5718.

¹⁵ Hallander HO, Gustafsson L. Efficacy and effectiveness of acellular pertussis vaccines: a 20-year Swedish experience. *Expert Rev Vaccines*. 2009;8(10):1303-1307.

¹⁶ Tindberg Y, Blennow M, Granström M. A ten year follow-up after immunisation with a two component acellular pertussis vaccine. *Pediatr Infect Dis J*. 1999;18(4):361-5; US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007.

¹⁷ Bonmarin I, Levy-Bruhl D, Baron S, Guiso N, Njamkepo E, Caro V, et al. Pertussis surveillance in French hospitals: results from a 10 year period. *Euro Surveill* 200;12 (1– 3);34–38.

¹⁸ Rendi-Wagner P, Kundi M, Mikolasek A, Vécsei A, Frühwirth M, Kollaritsch H. Hospitalbased active surveillance of childhood pertussis in Austria from 1996 to 2003: estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine. *Vaccine*. 2006 Aug 14;24(33-34):5960-5.

¹⁹ Carlsson RM, Claesson BA, Fagerlund E, Knutsson N, Lundin C. Antibody persistence in five-year-old children who received a pentavalent combination vaccine in infancy. *Pediatr. Infect. Dis. J*. 2002;21(6):535–541.

Randomised data

Further data on the protective efficacy of pertussis toxoid against the most severe WHO defined typical pertussis (primary endpoint was ≥ 21 days of paroxysmal cough) was provided in a study conducted in Senegal between 1990-1994 (Simondon, 1997). This was a prospective, double-blind (randomisation was DTaP versus European DTP vaccine at 2, 4, 6 months of age) vaccine study, with estimates of absolute efficacy derived from a nested case-contact study that compared rates of pertussis (after exposure to an index case), among study subjects and non-study subjects, the latter had not received any pertussis vaccination. It is important to note that case detection bias may have occurred as the non-randomised group (no pertussis vaccination) was unblinded to parents and field surveillance workers. The risk of pertussis was 2.42 in the DTaP versus DTP group. When cases (meeting primary case definition) were stratified by age, the relative risk was 1.16 for children younger than 18 months versus 1.76 for older children in the DTaP versus DTP arms respectively, suggesting that protection waned more quickly among DTaP than DTP recipients. Absolute efficacy estimates were 74% for DTaP versus 92% for DTP, but there were very small numbers of cases and the confidence interval (CI) for these estimates are very wide: 51-86% (DTaP) and 81-97% (DTP).

Not all the Hexaxim studies evaluated all 9 antigens for non-inferiority, largely because of the very large experience with the majority of the active components through predecessor vaccines. The focus was on responses to hepatitis B antigen (HbsAg), the only new antigen contained in Hexaxim and all the studies (except the large scale safety Study A3L04) focused on a non-inferiority analysis for this component. In all studies, antigens that were not tested for non-inferiority were evaluated descriptively. Studies were conducted in healthy subjects, in different countries with different ethnicities, with different vaccination schedules (6, 10, 14 weeks; 2, 3, 4 months; 2, 4, 6 months), and with a variety of comparison groups, different immunisation backgrounds for booster studies, and different co-administered vaccines.

Taken collectively, Hexaxim results in high levels of protective immunity to all its antigen components; these levels are equivalent to those produced by comparator vaccines such as Infanrix Hexa, already used in the Australia NIP, at least for the primary vaccine series in infants.

Safety

Studies providing safety data

This application includes 13 completed clinical studies: 8 primary series and 5 booster studies, in which safety data has been collected. These 13 clinical studies were conducted in Latin America, Africa and Eastern Europe (Turkey) and provide key information on safety by gender, ethnicity, in very young infants with the earliest administration at 6 weeks of age, boosting of toddlers, in those with hepatitis B vaccine at birth, co-administered with other childhood vaccines, that is, Prevenar (pneumococcal conjugate vaccine 7-valent, PCV7) and rotavirus (in primary series), measles, mumps, rubella (MMR) and varicella vaccines in booster.

Clinical safety data obtained from 11 of the 13 studies were pooled in an integrated safety analysis (IAP-S) for Hexaxim. The objective of the pooling was to improve:

1. precision of estimation of rate of AEs;
2. probability of detection of any safety signal;
3. safety assessment in larger subgroups of the population.

The following studies were included in the safety integrated analysis plan (IAP-S):

- 7 primary series studies: A3L02, A3L04, A3L10, A3L11, A3L12, A3L15ps, and A3L17
- 4 of the 5 booster studies: A3L01, A3L15bo, A3L21, and A3L22

The booster Study A3L16 (using Pentaxim) is included with this application, but does not contain safety data on Hexaxim and is therefore not included in the IAP-S. Study A3L24 is a confirmatory study evaluating co-administration of Hexaxim with PCV7 and rotavirus vaccines and not part of the integrated analysis for chronological reasons. In addition in the IAP-S, 3 Hexaxim sub-pools are presented based on which control vaccine was used. Studies A3L04 and A3L15 used the whole pertussis combined D, T, pertussis, Hib vaccine Tritanrix-HepB/Hib + OPV and CombAct-Hib + OPV respectively; Studies A3L02 and A3L10 used the pentavalent acellular pertussis combined DTP vaccine Pentaxim; and Studies A3L11, A3L12, and A3L17 used the hexavalent acellular pertussis combined DTP vaccine Infanrix Hexa.

Patient exposure

Overall, in the IAP-S, 3631 infants received ≥ 1 dose of Hexaxim as part of the primary series, and 3434 received the complete 3 doses. One subject received Hexaxim at Dose 2 by mistake, was not included in the safety analysis set (3630 subjects). Of the 3435 subjects who received all doses, 1 subject discontinued after Dose 3. In addition, in Study A3L24, 1030 subjects received ≥ 1 doses of Hexaxim. During the booster, 1511 toddlers received Hexaxim booster. The total exposed population was 4927 subjects, who received at least one Hexaxim dose during the primary series/booster (Table 3).

Table 3: Clinical trial exposure to Hexaxim: subjects who received each dose

Dose of exposure	Study participants (n)
Primary series in integrated safety analysis	
At least one primary vaccine injection received	3631
Safety Analysis Set*	3630
Received Dose 1:	3630
Received Dose 2:	3481
Received Dose 3:	3435
Received complete 3-dose primary series	3434
Booster in integrated safety analysis	
Received Booster:	1511†
Received at least one dose in primary or booster	3897
Not in the integrated safety analysis (A3L24)	
Safety Analysis Set	1030
Received Dose 1:	1030
Received Dose 2:	1013

Dose of exposure		Study participants (n)
Received Dose 3:		1002
Total population exposure		
Received at least one dose in primary or booster		4927

N is the number of subjects who received a dose. *Safety analysis set population does not include the subject who received by mistake the second primary dose with Hexaxim instead of control. † Due to an error of administration or due to subjects not received completed series, 3 subjects have not received the same vaccine for the 3 injections performed during the primary series (these subjects are counted on the total but are not on the sub-totals).

Table 4: Doses for Hexaxim and control vaccines: Safety Analysis Set, IAP-S

	Hexaxim*		Infanrix hexa†		Pentaxim + Engerix B‡		Tritanrix-HepB/Hib or CombAct-Hib + Engerix B§		Subjects primed and boosted with Hexaxim**		Subjects primed with a Control Vaccine and Boosted with Hexaxim††	
	n	%	n	%	n	%	n	%	n	%	n	%
Number of doses administered	12057	100.0	1465	100.0	1383	100.0	2782	100.0	1243	100.0	265	100.0
During primary series	10546	87.5	1465	100.0	1381	99.9	2782	100.0
As booster phase	1511	12.5	.	.	2	0.1	.	.	1243	100.0	265	100.0

n: number of doses; %: percentages are calculated according to the total number of doses of Hexaxim or control vaccine administered; * Primary series: A3L02, A3L04, A3L10, A3L11, A3L12, A3L15, A3L17, Booster phase: A3L01, A3L15, A3L21, A3L22; † A3L11, A3L12, A3L17; ‡ A3L02, A3L10, A3L22; § A3L04, A3L15; ** A3L15, A3L21, A3L22; †† A3L01, A3L21, A3L22

In the integrated analysis:

- 10,546 doses were administered to 3631 infants in the 7 primary series trials; 3434 received a complete 3 doses Hexaxim primary series;
- 1511 doses were administered to toddlers in 4 booster studies; of the 1511 subjects who received a booster dose, 1243 were primed with Hexaxim and 265 were primed with a control vaccine;
- a total of 12,057 doses of Hexaxim were administered. In addition, in Study A3L24, 3045 doses were administered. Overall, 15102 doses were administered in the 12 studies. Of these, 13591 doses were administered to 4661 subjects in the 8 primary series and 1511 doses were administered to toddlers in 4 booster studies.

Adverse events summary

The most frequently reported AE are summarised in Table 5.

Table 5: Summary of most frequently reported AEs after any Hexaxim primary and booster vaccine injection, IAP-S

	Solicited AEs*	%	Unsolicited AEs*	%	SAEs**	%
1	Injection site pain	82.6	Nasopharyngitis (Infections and infestations)	26.1	Gastroenteritis (Infections and infestations)	1.3
2	Irritability	79.5	Pharyngitis (Infections and infestations)	14.1	Bronchiolitis (Infections and infestations)	0.7
3	Crying	72.2	Diarrhoea (gastrointestinal disorders)	10.1	Bronchopneumonia (Infections and infestations)	0.6
4	Injection site	63.6	Upper respiratory	7.3	Pneumonia (Infections)	0.5

	Solicited AEs*	%	Unsolicited AEs*	%	SAEs**	%
	induration (A3L01 and A3L02 only)		tract infection (Infections and infestations)		and infestations)	
5	Injection site erythema	62.7	Cough (Respiratory, thoracic and mediastinal disorders)	7.2	Febrile convulsion (Nervous system disorder)	0.3
6	Somnolence	54.9	Pyrexia (General disorders and administration site conditions)	6.3	Bronchila obstruction (Respiratory, thoracic and mediastinal disorders)	0.3
7	Anorexia	49.1	Rhinitis (Infections and infestations)	5.9	Pneumonia viral (Infections and infestations)	0.2
8	Injection site swelling	46.2	Abdominal pain (gastrointestinal disorders)	5.6		
9	Pyrexia	42.6	Dermatitis diaper (Skin and subcutaneous tissue disorders)	5.2		
10	Vomiting	35.2	Gastroenteritis (Infections and infestations)	4.6		

*AE MedDRA Preferred term, regardless of seriousness; **AE MedDRA Preferred term.

Safety issues with the potential for major regulatory impact

Adverse events of special interest (AESIs) in this setting are: extensive limb swelling (ELS), hypotonic hyporesponsive episode (HHE), febrile convulsions, convulsions, anaphylactic reactions, apnoea, encephalopathy or similar severe neurological conditions, encephalitis or acute demyelinating encephalomyelitis (ADEM), sudden infant death syndrome /sudden unexplained death.

Adverse events of special interest and events possibly related to AESIs occurring within 3 days after any primary or booster vaccination are described below:

56 (3.1%) and 26 (2.7%) subjects experienced at least one AESI and events possibly related to AESIs in the Hexaxim (n = 1803) or Tritanrix-HepB/Hib + OPV or CombAct-Hib + Engerix B + OPV (n = 952) groups, respectively. Most AESIs were in the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) of “Skin and subcutaneous disorders” (1.6% and 1.4% of subjects in the Hexaxim and control vaccine groups, respectively) and “Respiratory, thoracic and mediastinal disorders” (1.2% and 1.2%, respectively). Five (0.3%) subjects in the Hexaxim group and 5 (0.5%) in the control group experienced at least one related AESI. These included rash generalised, injection site rash, injection site dermatitis, and HHE in the Hexaxim group; and rash, rash generalised, swelling face, and injection site rash in control vaccine group;

A total of 3 (0.6%) and 1 (0.2%) subjects experienced at least one AESI and events possibly related to AESIs in the Hexaxim (n = 467) or Pentaxim + Engerix B groups (n = 467), respectively. Of these, subjects experienced AESIs occurring in the SOC of “General disorders and administration site conditions and Skin and subcutaneous disorders” (0.4% and 0.4 % of subjects in the Hexaxim group, respectively) and the one subject from the control vaccine group (0.2%) experienced rash (“Skin and subcutaneous disorders”). Of these 2 (0.4%) subjects experienced at least one related AESI and events possibly related to AESIs in the Hexaxim group (injection site urticaria and oedema

peripheral). No AESIs and events possibly related to AESIs in the control vaccine group were considered as related;

A total of 18 (1.3%) and 5 (1.0%) subjects experienced at least one AESI and events possibly related to AESIs in the Hexaxim (n = 1360) or Infanrix Hexa groups (n = 504), respectively. Of these, most subjects experienced AESIs occurring in the SOCs of “Skin and subcutaneous disorders” in the Hexaxim group (1.1%) and “Respiratory, thoracic and mediastinal disorders” in the control group (0.8%). A subject in Study A3L11 presented with erythema multiforme on the day of Dose 2, post-injection. This was considered not serious and not related. The time to onset (about 3 h post-injection) is not suggestive of a relationship with vaccine administration. Most frequent cause of erythema multiforme is infectious. Of these 5 (0.4%) and 1 (0.2%) subjects experienced at least one related AESI and events possibly related to AESIs in the Hexaxim or Infanrix Hexa groups, respectively. These included the preferred terms rash, rash maculo-papular, and injection site vesicles in the Hexaxim group, and rash generalised in the control vaccine group.

Table 6: AESIs within 3 days after booster of Hexaxim, by SOC and PT per type of vaccine received for primary series: Safety Analysis Set, IAP-S

Subjects experiencing at least one:	Subjects primed and boosted with Hexaxim* (N=1243)								Subjects primed with a Control Vaccine and Boosted with Hexaxim* (N=265)							
	All AESIs				Related AESIs				All AESIs				Related AESIs			
	n	%	(95% CI)	n	n	%	(95% CI)	n	n	%	(95% CI)	n	n	%	(95% CI)	n
AESI	9	0.7	(0.3; 1.4)	9	2	0.2	(0.0; 0.6)	2	1	0.4	(0.0; 2.1)	1	1	0.4	(0.0; 2.1)	1
Skin and subcutaneous tissue disorders	7	0.6	(0.2; 1.2)	7	0	0.0	(0.0; 0.3)	0	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
Rash	5	0.4	(0.1; 0.9)	5	0	0.0	(0.0; 0.3)	0	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
Dermatitis	1	0.1	(0.0; 0.4)	1	0	0.0	(0.0; 0.3)	0	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
Dermatitis allergic	1	0.1	(0.0; 0.4)	1	0	0.0	(0.0; 0.3)	0	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
General disorders and administration site conditions	2	0.2	(0.0; 0.6)	2	2	0.2	(0.0; 0.6)	2	1	0.4	(0.0; 2.1)	1	1	0.4	(0.0; 2.1)	1
Extensive swelling of vaccinated limb	1	0.1	(0.0; 0.4)	1	1	0.1	(0.0; 0.4)	1	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
Injection site urticaria	1	0.1	(0.0; 0.4)	1	1	0.1	(0.0; 0.4)	1	0	0.0	(0.0; 1.4)	0	0	0.0	(0.0; 1.4)	0
Injection site pruritus	0	0.0	(0.0; 0.3)	0	0	0.0	(0.0; 0.3)	0	1	0.4	(0.0; 2.1)	1	1	0.4	(0.0; 2.1)	1

Hexaxim prime series and boost: A total of 9 (0.7%) and 1 (0.4%) subjects experienced at least one AESI and events possibly related to AESIs after receiving a Hexaxim booster when primed with either Hexaxim or control vaccine, respectively. Of these, most subjects experienced AESIs and events possibly related to AESIs occurring in the SOCs of “Skin and subcutaneous disorders” in the group primed with Hexaxim (0.6%). There were 2 (0.2%) and 1 (0.4%) subjects experienced at least one related AESI and events possibly related to AESIs in the group primed with Hexaxim or control vaccine, respectively. These included ELS, injection site urticaria and injection site pruritus.

Related AESIs with onset > 3 Days: Three related AEs were reported more than 3 days post vaccination: 2 were injection site rash occurring for subjects in the Hexaxim group, at day 11 post-injection 1 and day 5 post-booster, and 1 was injection site dermatitis at day 5 post-injection 3, occurring in a subject who received Tritanrix-HepB/Hib + OPV or CombAct-Hib + Engerix B+OPV.

Integrated analysis: No differences in frequency of AESIs were observed between Hexaxim and control vaccines (subject exposure in control groups: Infanrix Hexa (primary) n = 504; Pentaxim + Engerix B (primary) n = 467; Tritanrix-HepB/Hib + OPV or CombAct-Hib + Engerix B+OPV (primary) n = 962; CombAct-Hib (booster) n = 254).

See Attachment 2 (CER Extract) for further details of safety findings.

Evaluator’s conclusions on safety

Thirteen clinical studies conducted in Latin America, Africa and Eastern Europe (Turkey) provide key information on safety of Hexaxim by gender, different ethnicities, in very

young infants, with the earliest administration at 6 weeks of age, boosting of toddlers, in those with hepatitis B vaccination at birth, co-administration with other childhood vaccines, that is, Prevenar and rotavirus (in primary series), MMR and varicella vaccines in booster. In total, 4927 subjects have received at least one Hexaxim dose during primary series or as a booster.

The data presented clearly demonstrate Hexaxim as a safe (and effective) hexavalent vaccine for primary series use in infants and/or boosting in toddlers. Overall the vaccine was very tolerated, with very few SAEs and no suspected, unexpected, serious adverse reaction.

Injection site reactions were almost universal (83%) in recipients and rates were slightly higher than those with Pentaxim + Engerix B (75%); the reactions were generally mild to moderate, occurred soon after vaccination and were short lived. However, Grade 3 solicited injection site reactions were reported at a higher frequency for those who received Hexaxim (28.0%) than those who received Pentaxim + Engerix B (15.1%). The frequency of reported solicited injection site reactions at each post-injection decreased from the previous injection in other words there was no incremental increase in solicited local reactions with each successive dose.

Solicited systemic reactions also occurred in the majority, around 85%, as expected, and although these were mostly mild to moderate a higher percentage of Hexaxim recipients had Grade 3 solicited systemic reactions (39%) than those who received Pentaxim + Engerix B (29%). Pyrexia was the most common solicited systemic reaction; again the majority were mild to moderate in intensity and short-lived post vaccination.

There were no safety concerns when infants previously given hepatitis B vaccine were exposed to a primary series of Hexaxim plus a subsequent Hexaxim boost, representing 5 doses of hepatitis B vaccine exposure within an approximate 18 month period. This is an important finding as the current Australian NIP recommends four hepatitis B vaccines in year 1. The co-administration of the other vaccines that are part of the Australian NIP in year 1 and 2 of life, that is pneumococcal conjugate (note only the 7-valent form was assessed here, whereas the 13-valent conjugate is recommended as part of the NIP) and Rotarix (rotavirus vaccine) in year 1 and MMRV in year 2 were not associated with any safety concerns or negative impact on immunogenicity of vaccine components.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Hexaxim in the proposed usage are:

- Single use, ready-to use vaccine that is immunogenic and safe for all the antigens it contains;
- The antigens contained within Hexaxim represent 6 of the primary series antigens that children are recommended to receive (Australian NIP, 2013) as part of their year 1 vaccines.

First round assessment of risks

The risks of Hexaxim in the proposed usage are:

- This dossier of studies provides only immunological response data (and safety) induced by Hexaxim and the comparator vaccine(s), that is, these are surrogate markers of clinical protection. No actual clinical efficacy data is provided in this submission. The correlates of protection have not been established for pertussis

antigens. This submission provided limited published support for efficacy of the acellular pertussis (pertussis toxoid, FHA) component of Hexaxim to control disease caused by *Bordetella pertussis*;

- No data are provided for the use of Hexaxim with the currently recommended pneumococcal conjugate vaccines, which is the 13-valent form;
- The Australia NIP does not recommend boosting at 18 months with all the antigens contained in Hexaxim. It only recommends a *Haemophilus Influenza* type b booster at month 12 and aDTPa-IPV booster at 4 years of age. No hepatitis B booster is recommended after the “at birth” followed by 3 vaccinations as part of the primary series in year 1 (total n = 4). Therefore, Hexaxim as a booster at 18 months does not align with the present Australian NIP. There are reasonable arguments too, that 3 hepatitis B vaccinations are protective in the majority of infants so as a 4th vaccination is already part of the Australian NIP it seems hard to justify giving a 5th dose as a matter of course. Moreover, it could be argued as to whether a 4th dose is even needed as the very high rates of response to even a 4th vaccination attest to the fact that there appears to be protective immunity following 3 hepatitis B vaccine doses even in those with surface antibody levels < 10 mIU/mL;
- Whilst the booster studies in this application do not appear associated with harm in the just over 1500 subjects tested in these studies, nevertheless, it is an important discussion point as to the appropriateness of toddlers receiving a booster vaccine with all 6 of these antigens when they don’t “need” two of them, that is, hepatitis B and *Haemophilus Influenza* type b (already received the booster at month 12 as per the Australia NIP) for protective immunity;
- There is no data provided in premature infants of low birth weight < 2.5 kg as these were exclusions for participation;
- There is no data on the immunogenicity or safety of Hexaxim in immunocompromised infants and toddlers, as again these subjects were specifically excluded from the studies.

First round assessment of benefit-risk balance

The benefit-risk balance of Hexaxim, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Hexaxim is a reasonable alternative to Infanrix Hexa for first series vaccinations, but its role in boosting is unclear. While this hexavalent vaccine is clearly safe and immunogenic as a booster, its use in this way would not be in alignment with the current recommendations in the Australian NIP.

The issue regarding pertussis protection is not considered to be unique to Hexaxim; it applies equally to other already registered combination vaccines that contain acellular pertussis and as such it does not alter the recommendation regarding authorisation of this product.

Clinical questions

Pharmacodynamics (immunogenicity)

What are the sponsor’s plans to assess safety and immunogenicity of Hexaxim when co-administered with pneumococcal 13 valent conjugated vaccine (PCV13)? Are there any

plans to look at immunogenicity and safety when co-administered with meningococcal vaccines?

Product Information: Indication

The Australian PI should not state that Hexaxim is indicated for boosting. This would definitely not align with the current Australia NIP. The PI should be amended to reflect that while boosting with Hexaxim appears safe and effective, the use of a hexavalent vaccine such as Hexaxim is not recommended for boosting at 18 months or even 4 years of age (no data in this age group, plus not recommended that a hexavalent boost is received here) in the current Australian NIP guidelines.

The sponsor's responses to these questions are assessed as part of the Delegate's Overview (under *Overall conclusion and risk-benefit assessment*, below).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), EU RMP Version 8.0, no date assigned, (data lock point 11th August 2011), with Australian Specific Annex (ASA) Version 1.0 dated October 2013, which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 7.

Table 7: Summary of Ongoing Safety Concerns

Ongoing safety concerns	
Important Identified Risks	Events labelled <ul style="list-style-type: none"> • Hypotonic Hyporesponsive episode • Extensive Limb Swelling
Important Potential Risks	Events usually labelled with similar vaccines: <ul style="list-style-type: none"> • Convulsion • Anaphylaxis Events under close supervision for class effects or historical reasons: <ul style="list-style-type: none"> • Apnoea • Encephalopathy, Encephalitis Events under close supervision, without evidence of causality relationship with vaccination <ul style="list-style-type: none"> • sudden infant death syndrome, sudden unexplained death, apparent life threatening event (ALTE)
Important Missing Information	DTaP-IPV-Hep B-PRP-T has not been studied in <ul style="list-style-type: none"> • Premature infants • Immunocompromised individuals (from disease or treatment) • Subjects suffering from acute or chronic illness including cardiac or renal insufficiency • Subjects with a history of seizures • Population with genetic polymorphism has not been studied nor excluded

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns. Additional pharmacovigilance activities (nine clinical studies) are also proposed for the following risks:

- Hypotonic hypotensive episode
- Extensive limb swelling
- Convulsions
- Anaphylaxis
- Apnoea
- Encephalopathy, encephalitis
- Sudden infant death syndrome and Sudden unexplained death
- Apparent life threatening event (ALTE)
- Immunocompromised patients

The sponsor does not propose additional pharmacovigilance activities for the following risks: “premature infants”; “subjects suffering from acute or chronic illness”; “subjects with a history of seizures”; “population with genetic polymorphism”.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all ongoing safety concerns. The sponsor makes the following statement in the ASA regarding the need for additional risk minimisation activities: *“The important identified and potential risks will be communicated to healthcare professionals and patients through the Australian product Information and Consumer medicine Information (provided in the Annex 1 and 2). No additional risk minimization measures beyond routine pharmacovigilance activities are considered necessary at this time.”*

OPR reviewer comment: The sponsor’s conclusions regarding risk minimisation activities are acceptable.

Planned actions

The sponsor proposes routine risk minimisation in the form of statements in the Australian PI document, for all important identified risks, important potential risks and important missing information, except “sub-populations with genetic polymorphism”.

Reconciliation of issues outlined in the RMP report

A summary of the OPR’s recommendations from the first round evaluation of the RMP, the sponsor’s responses to issues raised by the OPR and the OPR’s evaluation of the sponsor’s responses is below:

OPR recommendation 1

Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor's response

The sponsor acknowledges this request.

OPR evaluator's comments

Based on the clinical evaluator's comments (see below) the sponsor should amend the ASA accordingly before this application is approved.

OPR recommendation 2

The sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

Sponsor's response

The table outlining the forthcoming studies is included as part of the updated ASA.

OPR evaluator's comments

This is acceptable.

OPR recommendation 3

The OPR evaluator would like to draw the Delegate and clinical evaluator's attention to the additional phrase within the approved EU indication that does not appear in the proposed Australian indication: *"from six weeks to 24 months of age"*.

Sponsor's response

The Paediatric Use section of the PI has been revised to include the following statement *"The safety and efficacy of Hexaxim in children over 24 months of age have not been established"* to help minimise the risk of the vaccine used in children older than 24 months.

OPR evaluator's comments

This remains an outstanding recommendation to the Delegate.

OPR recommendation 4

Furthermore, the proposed dose and route of administration does not contain specific information regarding the administration schedule for Hexaxim. The phrase *"in accordance with official recommendations"* is not adequate to assist prescribers with safe and appropriate administration. This is also not the usual practice for vaccinations, with other products containing specific dosing schedule information.

Sponsor's response

The sponsor now proposes to include the phrases: *"in accordance with the national recommendation as per the current Immunisation Handbook"* and *"for further information, refer to the current Immunisation Handbook"*.

OPR evaluator's comments

This response is considered inadequate and consequently this recommendation remains an outstanding issue.

OPR recommendation 5

The OPR evaluator would also like to draw the Delegate's attention to the proposed use of Hexaxim as a booster after 3 doses. This does not align with the Australian NIP and will result in over-exposure of toddlers to hepatitis B and *Haemophilus Influenza* type b antigens.

Sponsor's response

The sponsor maintains that with regards to *Haemophilus Influenza* type b, in Australia, a booster dose of *Haemophilus Influenza* type b is given during the second year of life so Hexaxim can be used as a booster of *Haemophilus Influenza* type b for this age group.

OPR evaluator's comments

This remains an outstanding recommendation to the Delegate.

OPR recommendation 6

In regards to the quality of the written submission, the submitted EU-RMP is out of date and not presented in the new EU format. The sponsor is requested to re-submit a current EU-RMP and up to date ASA, ensuring relevant dates and status for the current pharmacovigilance plan are clarified.

Sponsor's response

The sponsor states that it plans to issue a new RMP (second) by the end of the year (2014) which will be compliant with the revised EU format, and will provide a compilation of safety data from all the clinical studies that will be completed as of 17 October 2014.

OPR evaluator's comments

Consequently no wording can be suggested for specific conditions of registration as they pertain to the RMP and this recommendation remains an outstanding issue.

OPR recommendation 7

The OPR evaluator would like to draw the Delegate's attention to potential deficiencies in the safety data submitted. The integrated safety analysis is dated 2010 and potentially excludes the results of multiple subsequent completed studies, including Study A3L24 (submitted separate to the integrated safety analysis, although complete 2 years before submission to the TGA) and A3L27. The status of Studies A3L31, A3L33 and A3L36 remains unclear.

Sponsor's response

The sponsor acknowledges that the integrated safety analysis does not include the Study A3L24 and A3L27 in the application as this has not been requested by EMA during the registration process in Europe. In addition the integrated safety analysis is performed on the completed studies and hence the next integrated safety analysis will include all the completed studies including A3L24 and A3L27 and the studies expected to be completed later this year.

OPR evaluator's comments

This remains an outstanding recommendation to the Delegate.

OPR recommendation 8

The sponsor is requested to ensure that all study reports that are submitted to the EU are also submitted to Australia with the same timelines.

Sponsor's response

The sponsor commits to provide the final Clinical Study Reports in accordance with their European due date.

OPR evaluator's comments

This is acceptable.

OPR recommendation 9

The sponsor is requested to provide details of the antigen content of the vaccine within the RMP.

Sponsor's response

The ASA has been revised to include details of the antigen content of Hexaxim.

OPR evaluator's comments

This is acceptable.

OPR recommendation 10

Pending the evaluation of the nonclinical and clinical aspects of the Safety Specification (see below), the following should be added as important missing information unless the sponsor can provide compelling justification for their exclusion:

- Long-term vaccine effectiveness.
 - This is an important ongoing safety concern that requires further investigation. Some issues identified to support this recommendation include:
 - The diphtheria toxoid content (20 IU) in the vaccine dose for initial inoculation does not comply with conventional standards (30 IU) set by the WHO, specified by the Ph. Eur. 6.0, article 2067.
 - In regards to *Haemophilus Influenzae* type b, The Australian Immunisation Handbook 10th Edition 2013 makes the following statement "*Some Hib combination vaccines containing acellular pertussis are known to produce lower Hib antibody responses than similar formulations containing whole-cell pertussis.*"
- Vaccine failure
- Children with low birth weight
- Safety and effectiveness of Hexaxim in infants vaccinated for Hepatitis B at birth
- Interactions with other vaccines, especially those on the Australia NIP Schedule that would be given with Hexaxim. This includes rotavirus vaccination and the 13 valent pneumococcal vaccine. The clinical studies reported for Hexaxim only investigated interaction with the Prevenar 7 valent pneumococcal vaccine. However, the 13 valent pneumococcal vaccine is used in Australian children.
- Fever
- Guillain Barré Syndrome
- Kawasaki disease

Above ongoing safety concerns should be assigned appropriate pharmacovigilance and risk minimisation activities.

Sponsor's response

The sponsor provided justification for not including any of the proposed important missing information in the ASA.

In regard to the important missing information: 'Long-term vaccine effectiveness', the sponsor states: "*As adequate clinical data have been generated with at least three different Hexaxim batches presenting lower limits of the 95% CI of their observed diphtheria potency being below 30 IU/dose and above 20 IU/dose (22 IU/dose, 28 IU/dose, 29 IU/dose), it can be concluded that this difference of antigenic potency expression is not clinically relevant for Hexaxim.*" and "*When administered as a Hib-containing combined vaccine variable reduced immunogenicity of the Hib component (while still high in terms of the accepted*

seroprotective level of 0.15 µg/mL) compared to administration of the Hib standalone vaccines has been a widely-discussed and sometimes controversial topic. The origin of these observations is due to both immune and pharmaceutical interference. Such interference is not clinically significant and in primed children, Hib conjugate vaccines (like Hexaxim) induce a T-lymphocyte-dependent immune response and immune memory (even in those with antibody levels < 0.15 µg/mL). Primed children who do not receive a dose of Hib vaccine during their second year of life may be at increased risk of Hib disease however in Australia, a booster dose is given at 12 months of age. Post-marketing and surveillance studies have shown that the use of combination vaccines do not affect the effectiveness of the Hib vaccines, where the key determinant is the existence of a Hib booster vaccination performed at toddler age, and this whatever the nature of the Hib vaccine used for this (Hib standalone or Hib-containing combination vaccine). Based on the information provided above, the sponsor considers there is no need to include this information as missing information in the RMP.”

In regard to the AESI ‘Vaccine failure’, the sponsor states: *“In the next PBRERs the sponsor will provide an analysis of all vaccine failure reported cases, if any.”* and concedes: *“No vaccine provides 100% protection and the Product Information already has included a statement ‘As with any vaccine, vaccination with Hexaxim may not protect 100% of susceptible individuals’”*.

In regard to the important missing information: ‘Children with low birth weight’, the sponsor states: *“Prematurity is already included as a safety concern and children with low birth weight will be monitored as per the premature infants (refer to the Summary of the AUS RMP in the ASA).”* However, children with low birth weight are not necessarily premature.

In regard to the important missing information: ‘Safety and effectiveness of Hexaxim in infants vaccinated for Hepatitis B at birth’, the sponsor states: *“It should also be noted that three studies provided in Module 5 had included hepatitis B vaccination at birth and the data from these studies confirm the safety and efficacy of 4 doses of hepatitis B.”*

In regard to the AESI ‘Guillain Barré Syndrome’ and ‘Kawasaki disease’, the sponsor states: *“In the next PBRERs the sponsor will provide an analysis of all GBS reported cases. GBS is included in the PI as a potential adverse event and hence it is not missing information.”* and *“Although, there is no new safety concern, in the next PBRERs the sponsor will provide an analysis of all Kawasaki’s disease reported cases.”* respectively.

OPR evaluator’s comments

As the OPR has not evaluated the clinical efficacy data supporting this application the Delegate needs to advise whether the sponsor’s response is acceptable. If not, it is reiterated that the ongoing safety concern: ‘Long-term vaccine effectiveness’ should be included and consideration given to appropriate pharmacovigilance and risk minimisation activities, to be reflected in an amended ASA, before this application is approved.

The ongoing safety concern: ‘Vaccine failure’, and in fact all the AESI not currently included in the Summary of Ongoing Safety Concerns (that is, neuritis, vasculitis, Bell’s palsy and demyelinating disorders) should be included as important potential risks and consideration given to appropriate pharmacovigilance and risk minimisation activities, to be reflected in an amended ASA, before this application is approved.

The ongoing safety concern: ‘Children with low birth weight’ should be included as important missing information and consideration given to appropriate pharmacovigilance and risk minimisation activities, to be reflected in an amended ASA, before this application is approved.

As the OPR has not evaluated the clinical efficacy and safety data supporting this application the Delegate would need to advise as to whether the response regarding the ongoing safety concern: ‘Safety and effectiveness of Hexaxim in infants vaccinated for

Hepatitis B at birth' is acceptable. If not, it is reiterated that the ongoing safety concern: 'Safety and effectiveness of Hexaxim in infants vaccinated for Hepatitis B at birth' should be included and consideration given to appropriate pharmacovigilance and risk minimisation activities, to be reflected in an amended ASA, before this application is approved.

The ongoing safety concerns: 'Guillain Barré Syndrome' and 'Kawasaki disease' should be included as important potential risks and consideration given to appropriate pharmacovigilance and risk minimisation activities, to be reflected in an amended ASA, before this application is approved.

OPR recommendation 11

The submitted pharmacovigilance plan within the EU-RMP is out of date and inadequate to investigate the ongoing safety concerns associated with Hexaxim. Unfortunately, the ASA does not provide an update on the status of each study. Furthermore, it appears that the ASA refers to studies that are now complete (such as A3L24, A3L26 and A3L27). There are also a number of studies (including A3L31, A3L33 and A3L36) that are not included in the pharmacovigilance plan and their current status remains unclear. The sponsor is requested to confirm the current status of each of these studies, especially as the sponsor has stated that these studies "should allow collection of both efficacy and safety data in these countries".

Sponsor's response

The sponsor states: "Study A3L24 is included in this application but Sanofi Pasteur acknowledges that the integrated safety analysis does not include this study as it was not requested by EMA during the registration process in Europe. Study A3L26 is included in this application and it was a long term follow up study for antibody persistence and as such no product was administered. It has been improperly designated as an efficacy study in the RMP. The only safety data collected has been the occurrence of related-SAEs, which have been analysed as such. Study A3L27 has been completed since the submission of the application and has not raised any clinical concerns. For the status of studies A3L31 and A3L33, please refer to the [table provided in the response]. Study A3L36 is a study that was under discussion at the time of dossier submission and that has been cancelled since then."

OPR evaluator's comments

The sponsor has previously stated that it plans to issue a new RMP (second) by the end of the year (2014) which will be compliant with the revised EU format, and will provide a compilation of safety data from all the clinical studies that will be completed as of 17 October 2014. Consequently no wording can be suggested for specific conditions of registration as they pertain to the RMP and this recommendation remains an outstanding issue.

OPR recommendation 12

The proposed pharmacovigilance plan contains major deficits (deficiencies of the 9 studies mentioned in the RMP).

Sponsor's response

The sponsor states: "Study A3L27 has been completed and has not raised any clinical concerns. Study A3L26 was a long term follow up study for antibody persistence and as such no product was administered. It has been improperly designated as an efficacy study in the RMP. The only safety data collected has been the occurrence of related-SAEs, which have been analysed as such. Study A3L28 is similar in its design and objective as Study A3L26. The follow up to the cohort is still ongoing. The protocol for this study is provided in Annex 3 of the ASA. For the current status of studies A3L38, A3L39 and A3L40, [refer to the table in the sponsor response]. The same table contains the details of study HXM01C (also known as

A3L43-EXT). The protocols for the clinical Studies A3L38, A3L39, A3L40 and A3L43-EXT/HXM01C are provided in an Annex of the ASA.

Study A3L24 is included in this application but Sanofi Pasteur acknowledges that the integrated safety analysis does not include this study as it was not requested by EMA during the registration process in Europe.”

OPR evaluator’s comments

See Recommendation 11.

OPR recommendation 13

The OPR evaluator would like to draw the Delegate’s attention to potential deficiencies in the safety data submitted. The integrated safety analysis is dated 2010 and potentially excludes the results of multiple subsequent completed studies, including Study A3L24 (submitted separate to the integrated safety analysis, although complete 2 years before submission to the TGA) and A3L27. The status of Studies A3L31, A3L33 and A3L36 remains unclear.

Sponsor’s response

See Recommendations 7 and 11.

OPR evaluator’s comments

This remains an outstanding recommendation to the Delegate.

OPR recommendation 14

The sponsor is requested to submit the latest Periodic Safety Update Report (PSUR) for Hexaxim to the TGA for review.

Sponsor’s response

The sponsor states: “The 1st Periodic Benefit-Risk Evaluation Report (PBRER) taking a data lock point (DLP) of June 4th, 2013 (covering the December 5th, 2012 to June 4th, 2013 period) is provided but it should be noted that it provides no additional information compared to the 1st RMP. The second PBRER taking a DLP of October 17th, 2013 (covering the June 5th, 2013 to October 17th, 2013 period) is provided and it provides a first analysis of the first months of post-marketing of this product. The 3rd PBRER taking a DLP of April 17th, 2014 (covering the October 18th, 2013 to April 17th, 2014 period) will be issued by July 2014 and the sponsor commits to submit it as soon as available.”

OPR evaluator’s comments

This is acceptable and the second PBRER concludes “Based upon this review of the data, no new safety concerns have been identified during the current review period.”

OPR recommendation 15

It is noted that the sponsor has not proposed additional pharmacovigilance activities for premature infants. Some adverse events are possibly associated with prematurity such as HHE, apnoea, ALTE, and sudden infant death syndrome. This has also been noted by the EMA and the sponsor has been requested to update the RMP accordingly (EMA/373868/2013). It is recommended that the sponsor provide details of this additional pharmacovigilance activity with the s31 responses.

Sponsor’s response

The sponsor states: “The pharmacovigilance activities currently in place are described in the PBRER Number 2 provided and they are identical to the pharmacovigilance activities in the RMP. No specific pharmacovigilance activities have been implemented for premature infants and therefore no additional pharmacovigilance activities are described in the PBRER

Number 2. The topic of “risks” associated with prematurity and vaccination with DTaP-backed products will be discussed and updated in the next RMP update and the next PBRER.”

OPR evaluator’s comments

See Recommendation 11.

OPR recommendation 16

The sponsor is requested to update the pharmacovigilance plan to include the additional safety concerns recommended by the OPR evaluator.

Sponsor’s response

See Recommendation 10.

OPR evaluator’s comments

See Recommendation 10.

OPR recommendation 17

The studies referenced in the EU-RMP will generate safety data and thus the sponsor is advised to provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

Sponsor’s response

The ASA has been updated to include a table outlining the summary of recently completed and ongoing clinical studies.

OPR evaluator’s comments

This is acceptable.

OPR recommendation 18

In light of pending safety study reports, lack of post-marketing data plus the potential for large uptake of Hexaxim across Australia, the sponsor should complete an Australian specific safety study. Furthermore, the OPR will be seeking advice from the Advisory Committee on the Safety of Vaccines (ACSOV) in regards to the adequacy of the proposed pharmacovigilance plan for Hexaxim (see below for ACSOV comments on this matter).

Sponsor’s response

The sponsor states: “Due to similarities in population, standards of care and indication, the totality of clinical data from both clinical studies and post-marketing experience are considered relevant to the Australian population and environment and no specific local safety study is deemed necessary. Routine pharmacovigilance activities will ensure that any identified changes to safety information will be addressed and that risk minimisation activities remain appropriate for each safety concern.”

OPR evaluator’s comments

This response is considered inadequate and consequently this recommendation remains an outstanding issue.

The remaining OPR recommendations relate to revisions to the draft PI and Consumer Medicine Information (CMI) documents in the context of routine risk minimisation activities. Details of these are beyond the scope of the AusPAR.

Summary

Outstanding issues

Issues in relation to the RMP

Outstanding matters in relation to the RMP are described above under *Reconciliation of issues outlined in the RMP report* and were referred to the Delegate. In particular, recommendations 3, 5, 7, 13, and those regarding the PI and CMI were highlighted as open for the Delegate's consideration.

In addition, the 'Summary of Safety Concerns and Planned Pharmacovigilance Actions' of the EU-RMP makes reference to "standardised follow-up forms for AESIs/important identified and potential risks". The sponsor should confirm that these standardised follow-up forms are used in Australia and if so provide copies of these forms.

Advice from the Advisory Committee on the Safety of Vaccines

The ACSOV considered the Overview of Clinical Safety, Summary of Safety and the EU-RMP provided by the sponsor and concluded that the adequacy of the pharmacovigilance plan for Hexaxim was likely to be inadequate. Furthermore, ACSOV noted that there was limited information regarding Hexaxim in the Australian context and the committee advised that this also needs to be addressed.

The full ratified advice regarding Hexaxim from the ACSOV meeting was provided to the Delegate. In particular:

- ACSOV advised that, once the sponsor has submitted the most up to date information to the TGA for review, the adequacy of the RMP can be reassessed.
- The committee also noted that immunisation has been associated with an increased risk of apnoea in premature infants, and while there were no reports of apnoea associated with Hexaxim in the clinical trials, premature infants had been excluded from the clinical trials. In this context, ACSOV advised that premature infants should be included in future safety studies. It was further noted that some adverse events are possibly associated with prematurity such as HHE, the ELS, ALTE and sudden infant death syndrome. The committee advised that any enhanced post-licence surveillance in premature infants should monitor for these events.
- As there was no clinical trial data in Aboriginal and Torres Strait Islander (ATSI) infants, ACSOV advised that use in the ATSI population should be added as missing information to the ongoing safety concerns.
- The sponsor should address the committee's concerns by providing updated RMP documentation and the requested clinical trial data (see above) for ACSOV to consider at a future meeting.

Comments on the safety specification of the RMP

Clinical evaluation report

The Safety Specification in the draft RMP is not entirely satisfactory and should be revised, having regard to the comments below:

1. [the sponsor should] insert the amount of antigen for each of the components in Hexaxim;
2. Please add some wording regarding avoidance of giving the vaccine intradermally;
3. [the sponsor] should point out that the diphtheria component in Hexaxim differs from that in Infanrix Hexa, even though the immunogenicity was not affected, nevertheless

the amount of diphtheria antigen is currently less than that recommended by WHO and was a reason why at least one country to date has deferred approval;

4. [the sponsor] should add some specific wording on the safety of Hexaxim in primary series in infants already vaccinated at birth for hepatitis B;
5. [the sponsor should] mention the lack of data in those of low birth weight.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for D, T, aP, IPV, Hb, Hib vaccine (Hexaxim) detailed in the Safety Specifications of the draft RMP are in general concordance with those of the nonclinical evaluator. No comment can be made, however, regarding local reactions in guinea pigs, as these studies were not submitted in Module 4 for evaluation.

Suggested wording for conditions of registration

No wording can be suggested until the EU-RMP and an ASA have been adequately and appropriately revised and updated (see above).

Key changes to the updated RMP

In the response to the TGA request for information the sponsor provided an updated ASA (Version: 1.1, dated April 2014). Key changes from the versions evaluated at Round 1 are summarised below:

Table 8: Australian Specific Annex: key changes from Version 1.1 compared with Version 1.0

ASA: Key changes from version 1.0 to version 1.1
<ul style="list-style-type: none"> • Section 1 Introduction - update to include sub-sections on Product Profile, Regulatory History and Indication • Section 4.1 Australian RMP - update routine risk minimization measures reflecting changes in PI • Section 4.2 Ongoing and Completed Clinical Studies - new section • Annex 1 and 2 Update PI/CMI • Annex 3 – Study protocols

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's Overview and recommendations:

Background

This is a submission to obtain registration for Hexaxim, a preservative free liquid formulation hexavalent vaccine for IM administration. The six antigen components are diphtheria, tetanus, pertussis (acellular, component), hepatitis B (recombinant), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed).

The sponsor explains that Hexaxim is a fully liquid ready-to-use, preservative free vaccine, presented as a suspension for injection adjuvanted onto aluminium hydroxide in a single monodose prefilled syringe. It is based on the pentavalent combination vaccine, Pentavac/Pentaxim which was initially licensed in Sweden in 1997 and combined with a

new recombinant HBsAg produced from *Hansenula polymorpha* yeast. According to the sponsor, Pentavac/Pentaxim is currently in use in more than 105 countries and has an excellent safety profile.

In Australia, Infanrix Hexa (DTPa-hepB-IPV/Hib, licensed by GlaxoSmithKline) is currently the only hexavalent paediatric vaccine used in the NIP. Hexaxim eliminates the need for reconstitution and therefore the potential for administration errors. (Infanrix Hexa requires reconstitution by adding the entire contents of the supplied syringe containing the liquid component to the vial containing the Hib pellet²⁰).

The main differences in antigenic components for Hexaxim and Infanrix Hexa are that Infanrix Hexa contains a three component pertussis vaccine while Hexaxim contains a two component pertussis vaccine. Hexaxim contains a new recombinant HBsAg and a slightly higher quantity of *Haemophilus* type B polysaccharide conjugated to tetanus protein. The specification for diphtheria potency is ≥ 20 IU for Hexaxim versus ≥ 30 IU for Infanrix Hexa.

A very similar vaccine, Hexavac was approved in the EU in 2000, with the marketing authorisation suspended in 2005 on the recommendation of the Agency's Committee for Medicinal Products for Human Use (CHMP), further to review of the short and long-term protection afforded by recombinant hepatitis B vaccines (EMA public statement on Hexavac²¹). Hexavac contains the same pentavalent vaccine Pentavac as Hexaxim, with a recombinant Hepatitis B vaccine H-B-VAX II.(Merck & Co; registered in Australia). The sponsor voluntarily withdrew the marketing authorisation for Hexavac in the EU in 2012 for commercial reasons (EMA public statement on Hexavac).

The equivalent to Hexaxim (under the trade name Hexyon) was registered in the EU in April 2013. The European Public Assessment Report (EPAR) for Hexyon (EMA/373968/2013, Procedure no: EMEA/H/C/002796, dated 5 March 2014) was referred to in the preparation of this Overview.

Vaccine-preventable diseases included in Hexaxim

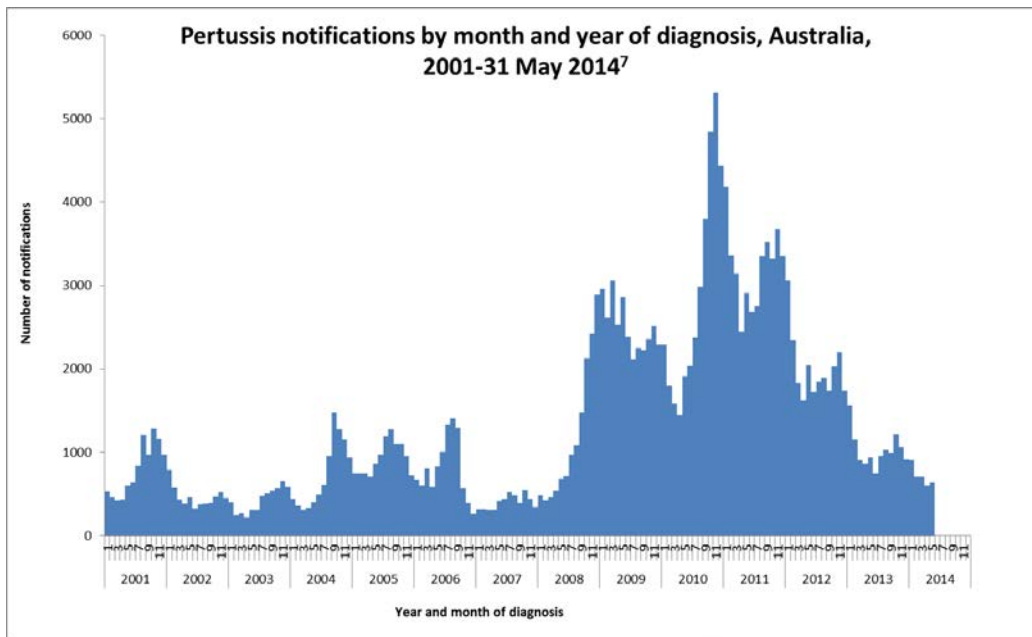
Globally, Australia has the highest reported rates of pertussis in the world²². Pertussis remains the least well-controlled of all vaccine-preventable diseases, with epidemics occurring every three to four years (Australian Immunisation Handbook²³).

²⁰ Infanrix Hexa Product Information. Date of most recent amendment: 4 February 2014

²¹ European Medicines Agency. Public statement on Hexavac [diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, hepatitis b (recombinant) and haemophilus influenzae type b conjugate vaccine, adjuvanted] Withdrawal of marketing authorisation in the European Union. 24 July 2012

²² McIntyre, PB, Nolan, TM. Pertussis control: where to now? MJA 2014;200(6):306-307

²³ The Australian Immunisation Handbook. Australian Government. Department of Health. 10th Edition. 2013 (updated January 2014).

Figure 1: Pertussis notifications in Australia 2001-2014

The epidemiology of diphtheria in Australia is similar to other developed countries, with cases predominantly associated with imported infections.

With respect to hepatitis B infection, Aboriginal and Torres Strait Islander people, migrants born in Asia, Pacific islands, North Africa, Middle Eastern and Mediterranean countries have a significantly increased prevalence of chronic hepatitis B infection compared with the rest of the Australian-born population. Following acute infection, approximately 1 to 10% of persons infected in adulthood become chronically infected with hepatitis B, compared with up to 90% of those infected in early infancy (Australian Immunisation Handbook).

The introduction of the 7 valent pneumococcal vaccine has led to a substantial reduction in the incidence of invasive pneumococcal disease in Australia, with the adoption of the 13 valent pneumococcal vaccine in the National Immunisation Program since July 2011 affording protection against additional serotypes (Australian Immunisation Handbook). Similarly, with the introduction of routine *Haemophilus Influenza* type b vaccines more than 20 years ago, there has been a reduction of more than 95% of notified cases, particularly significant in Indigenous children.

Tetanus is a rare disease in Australia, occurring mainly in older adults who were never vaccinated or who were vaccinated many years previously. Australia (as part of the Western Pacific region) was certified polio-free by the WHO in 2000, with the most recent case of laboratory confirmed wild-type disease in Australia in 2007 acquired overseas (Australian Immunisation Handbook).

The NIP for vaccine preventable diseases includes a three dose primary schedule for infants at 2, 4 and 6 months of age, with a booster dose at 4 years of age (Table 1 above) It is noted that the submitted data for this submission includes studies where a booster dose is given at 15-18 months of age, which does not align with the current Australian schedule.

Quality

Subject to appropriate clinical comment on matters related to the final product diphtheria potency specification and stability of PRP-T (*Haemophilus Influenza* type b) conjugates, the Module 3 evaluator recommended the application to register Hexaxim be approved with conditions detailed below:

1. The company should make a commitment to monitor depolymerised PRP levels in final lots derived from bulk product showing depolymerised PRP levels close to 20% at release by enrolling such lots in ongoing 36 month stability studies.
2. Standard Lot Release and CPD requirements should also be applied.

With respect to the final product diphtheria potency specification, the Module 3 evaluator commented that the Ph. Eur. Monograph 2067, *Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus type b conjugate vaccine (adsorbed)* requires that the minimum potency for Diphtheria stated on the label is 30 IU per single human dose unless otherwise justified and authorised. It also requires that the LCL ($p = 0.95$) of the estimated potency determined in the test is not less than the minimum potency stated on the label.

The company has proposed the following specification for Diphtheria potency: activity ≥ 30 IU/dose with a LCL of the estimated potency ≥ 20 IU/dose. Justification of this specification is based on the argument that clinical batches of vaccine that, when tested in the diphtheria potency test, resulted in LCL estimation between 20 and 30 IU/dose were efficacious in clinical studies and were not demonstrated to be inferior to batches for which LCL above 30 IU/dose were measured with respect to the observed percentage of subjects attaining the established seroprotection rate of major clinical relevance (≥ 0.01 IU/mL). The clinical studies were A3L10; A3L11; A3L12; A3L15ps; A3L17; A3L24.

Details regarding stability of PRP-T (*Haemophilus Influenza* type b) conjugates are discussed under *Quality findings* above.

Nonclinical

Overall, there were no specific nonclinical objections to the registration of the proposed hexavalent combination vaccine, Hexaxim, on the basis of safety. However, the nonclinical evaluator commented that in view of the absence of pertactin in the final formulation (an antigen included in all registered pertussis vaccine products in Australia), uncertainties about efficacy against pertussis will need to be addressed by clinical demonstration of protection.

The evaluator commented that *“none of the studies compared the overall efficacies of Hexaxim and its registered counterpart, Infanrix Hexa (which contains pertactin) to demonstrate that the proposed product is a viable and comparable alternative hexavalent vaccine to the existing registered option. Nonclinical demonstration of equivalent immunogenicity would have been helpful in establishing comparable activities of the two vaccines, in view of the differences in pertussis antigen composition; although clinical demonstration of equivalent immunogenicity may be more pertinent and useful.”*

Thus, suitability of Hexaxim as an alternative to Infanrix Hexa will rely solely on clinical evidence of efficacy and no comment can be provided on the adequacy of Hexaxim as an alternative to the currently registered hexavalent vaccine.

The quality of the nonclinical studies included in the dossier was generally satisfactory, with submitted studies meeting relevant guideline requirements and adopting appropriate study designs. The clinical route (IM) and dose (0.5 mL) was used in all submitted nonclinical studies and the animal models demonstrated antigenic reactions to the proposed product.

Primary pharmacology studies examined the immunogenicity of the new antigen of Hexaxim (HBsAg) and its potential for interfering with the *Haemophilus influenzae* type b antigen (PRP-T). Both antigens evoked significant immunoglobulin production in mice. HBsAg brought about higher total immunoglobulin titres than PRP-T. Neither antigen

attenuated the immunogenicity of the other when tested either as a combination of the two or as part of the hexavalent vaccine formulation.

Studies on PK, genotoxicity, carcinogenicity and reproductive toxicity were not submitted, which is acceptable based on the EMA and WHO guidelines on nonclinical testing of vaccine products.

Clinical

Efficacy

The submission contained 13 clinical study reports consisting of 14 clinical trials evaluating the most common vaccination schedules for a primary series paediatric combination vaccine, which varied according to the targeted country from the most condensed (6, 10, 14 weeks) (EPI) to the least condensed (2, 4, 6 months). It also covered booster vaccination during the second year of life as well as long term immunity persistence.

As there were few issues raised by the clinical evaluator following round 1 and the responses to these were reviewed by the Delegate, a second round clinical evaluation report (CER) was not required.

Overview of studies and comparison with the National Immunisation Program Schedule

There were eight infant primary studies and five booster studies conducted at 15-18 months of age, with one Phase III trial (A3L26) addressing long-term antibody persistence.

The submitted studies included immunogenicity data with no clinical efficacy data provided.

Hexaxim was compared to Infanrix Hexa, Pentaxim, Hexavac, CombAct-Hib, Tritanrix-HepB/Hib, Engerix B and the oral polio vaccine using non-inferiority study designs. Of these vaccines, Infanrix Hexa and Engerix B are currently registered in Australia. The oral polio vaccine is no longer available in Australia. The comparators for each study are summarised in Table 9.

Table 9: Summary of comparator vaccines for submitted studies

Study	Comparator	Comments
A3L11, A3L12, A3L17, A3L24	Infanrix Hexa	Infanrix Hexa is registered in Australia
A3L02, A3L10	Pentaxim with Engerix B	Engerix B is registered in Australia
A3L15ps and A3L15bo	CombAct-Hib (Diphtheria-Tetanus-Pertussis (whole cell)-Hib) with Engerix B and oral polio vaccine.	Comparator includes whole cell pertussis and live attenuated (oral) polio vaccine. CombAct-Hib and oral polio vaccines are not available in Australia.

Study	Comparator	Comments
A3L04	Tritanrix-Hib (Diphtheria-Tetanus-Pertussis (whole cell)-Hep B-Hib and oral polio vaccine	Comparator includes whole cell pertussis and live attenuated (oral) polio vaccine. Tritanrix-Hib and oral polio vaccine are not available in Australia.
A3L16, A3L21, A3L22, A3L26	Nil	Booster or long-term studies
A3L01	Hexavac	Hexavac is no longer registered in the EU.

The clinical evaluator commented that not all the submitted studies evaluated all antigens for inferiority, largely because of the extensive experience with the majority of active components through previous vaccines. All studies focused on a non-inferiority analysis for the new Hep B antigen component (with the exception of the safety Study A3L04) with other antigens evaluated descriptively.

Clinical non-inferiority margins were the same for all clinical trials and were established according to acceptable margins already used for combined vaccines. Accepted correlates of protection were used to assess non-inferiority of the antibody responses. These parameters (specific immunoresponse cut-offs) are well established for diphtheria, tetanus, poliovirus types, hepatitis B and *Haemophilus Influenza* type b antigens. Surrogates of protection were used for pertussis antigens.

The immunogenicity margins (differences between test and control vaccines) were classical boundaries for this vaccine. The margins were set at a non-inferiority delta limit of 10% for all antigens except poliovirus, which was set at 5%, as requested by the US FDA for other Sanofi Pasteur combined vaccines, and in order to harmonise comparisons with internal studies. The delta limit for equivalence between 2 paired lots was: a) 10% for hepatitis B, diphtheria, tetanus, PRP (*Haemophilus Influenza* type b), pertussis toxoid and FHA, and b) 5% for poliovirus (same limits used for non-inferiority immunogenicity margins between the Hexaxim and marketed controls).

Secondary immunogenicity endpoints and immunogenicity parameters for booster studies are outlined in the CER (see AusPAR Attachment 2).

Table 10: Primary immunogenicity endpoints by antigen for primary series studies

Antigen	Primary immunogenicity endpoints	A3L02	A3L10	A3L11	A3L12	A3L15	A3L17
Diphtheria	Ab titre ≥ 0.01 IU/mL*	X		X		X	
Tetanus	Ab titre ≥ 0.01 IU/mL*	X		X		X	
PT, FHA	≥ 4 -fold titre increase-baseline to post dose 3 vaccine†	X		X			
Poliovirus types 1,2,3	Ab titre ≥ 8 (1/dil)*	X		X		X	
Hep B	Ab titre ≥ 10 mIU/mL*	X	X	X	X	X	X
PRP	Ab titre ≥ 0.15 μ g/mL*	X		X	X	X	

Ab: antibody, PT: pertussis toxoid, FHA: filamentous haemagglutinin, PRP: Hib capsular polyribosylribitol phosphate, *Sero-protection level, †Seroconversion

Co-administration with other childhood vaccines was assessed in two primary series studies (Prevenar, 7vPCV) in A3L12 and A3L24; Rotarix (rotavirus vaccine) in A3L24 and one booster study (MMR and varicella in A3L15), following local recommended schedules.

With respect to the NIP, the 13 valent pneumococcal vaccine (Prevenar 13) is the currently recommended pneumococcal vaccine. The NIP includes concurrent administration of DTPa, HiB, IPV, HepB and pneumococcal vaccines with oral rotavirus vaccines (Rotarix or RotaTeq) at 2 and 4 months or 2, 4 and 6 months respectively²⁴. MMR and varicella vaccines are mostly administered at different times from DTPa, HiB, IPV, HepB: 12 months and 18 months, (although Hib is given with MMR at 12 months and MMR may be given at 4 years with DTPa-IPV if it was omitted at 18 months).

The effect of the presence or the absence of hepatitis B vaccination at birth was also evaluated. In Australia, the hepatitis B infant schedule consists of a monovalent hepatitis B vaccine (Engerix B or H-B-Vax II) at birth and three doses of a hepatitis B-containing combination vaccine at 2, 4 and 6 months.

The 14 submitted immunogenicity (efficacy) and safety studies are summarised in Table 2 above and described below:

Phase II study

Study A3L02 (non-inferiority to Pentaxim and Engerix B with respect to all valences)

This was a single centre, Phase II, open-label, randomised, active controlled trial conducted to assess the immunogenicity and safety of Hexaxim in 624 infants born to HBsAg seronegative mothers in Argentina.

The primary objective was to demonstrate that the immune response of Hexaxim is non-inferior for all valences (D, T, polio types 1, 2, 3, hepatitis B, PRP, PT, and FHA) to those of Pentaxim and Engerix B one month after a three dose (2, 4, 6 month) primary series.

300 and 304 subjects completed the trial in the Hexaxim and Pentaxim and Engerix groups respectively. Overall, the evaluator concluded that this was an appropriately designed study. The primary objective of the trial was met: Hexaxim was non-inferior for all valences to the control vaccines Pentaxim and Engerix B at one month after a three dose primary series at 2, 4 and 6 months. Hexaxim was associated with more solicited injection site reactions (particularly severe reactions) and severe systemic reactions: Day 0 to Day 7: 90.0% and 83.3% for Hexaxim and Pentaxim + Engerix B, respectively, severe injection site reactions, 35.0% and 17.3%, respectively and severe systemic reactions, 40.2% and 30.8%, respectively.

Phase III studies

Study A3L10 (non-inferiority of Hexaxim with respect to hepatitis B protection)

This was a Phase III, single centre, open-label, randomised, controlled trial conducted to assess the immunogenicity and safety of Hexaxim in 310 infants in Turkey who had not been previously vaccinated against pertussis, tetanus, diphtheria, polio, *Haemophilus Influenza* type b or hepatitis B infection. The primary objective was to demonstrate that the immune response to the hepatitis B antigen of Hexaxim is non-inferior to that of Pentaxim + Engerix B 1 month after a three dose primary series at 2, 3, and 4 months of age.

302 of 310 subjects completed the study and the groups were comparable at baseline. In the per protocol analysis set, observed difference in the anti-hepatitis B antigens (anti-HBs) seroprotection rate at 1 month post 3rd vaccine dose between the Hexaxim group and the Pentaxim + Engerix B group was -2.06% (two-sided 95% CI: -7.88; 3.65). Non-

²⁴ The Australian Immunisation Handbook 10th Edition. Australian Government. Department of Health. 2013. (Updated January 2014)

inferiority criteria were met as the lower limit of the 95% CI was > -10. Overall, the evaluator concluded that this was appropriately designed study with both vaccines safe and effective with equivalent seroprotection rates to anti-HBs elicited in both groups. The study was not powered to compare the immunogenicity for the other vaccine valences.

Study A3L17 (non-inferiority of Hexaxim with respect to hepatitis B protection)

This was a randomised, blind-observer, controlled, single-centre, Phase III trial in 263 healthy Peruvian infants born to HBsAg negative mothers. The primary objective was to demonstrate that Hexaxim induces an immune response that is at least as good as Infanrix Hexa in terms of seroprotection rates to hepatitis B, 1 month after a three-dose primary series (2, 4, 6 months).

All subjects completed the study. The primary objective was met: Hexaxim was non-inferior to Infanrix Hexa in terms of anti-HB seroprotection rates (≥ 10 mIU/mL) at 1 month after the third vaccine. Similar results were obtained for the ITT Analysis Set.

As stated in the EPAR for Hexyon (dated 5 March 2013), slightly lower GMTs and a lower seroprotection rate based on the ≥ 100 mIU/mL threshold criterion were observed for Hexyon (equivalent to Hexaxim) compared to Infanrix Hexa (GMTs: 986 versus 1139; ≥ 100 mIU/mL: 93.9% versus 99.2%, respectively) for the anti-HB response.

Studies addressing non-inferiority of Hexaxim with respect to D, T, polio, Hep B and PRP.

Study A3L15ps. Comparator was CombAct-Hib with Engerix B and OPV

This was a randomised, open-label, controlled, multicentre (two sites), Phase III trial in 635 infants in South Africa who received Hexaxim (Group 1, n = 286), CombAct-Hib and Engerix B Pediatric with oral polio vaccine (Group 2, n = 286), or Hexaxim with Engerix B Paediatric at birth (Group 3, n = 143). The study assessed the most condensed schedule (6, 10 and 14 weeks of age). The primary objective was non-inferiority of immune response against tetravalent whole cell pertussis combined vaccine (CombActHib) + OPV + Engerix B one month after the three-dose primary vaccination for D, T, polio, Hep B and PRP.

The ITT population included 622 subjects, as 93 of the 715 subjects initially randomised withdrew prior to group allocation. Overall, all primary endpoints concerning non-inferiority were met: Hexaxim was shown to be non-inferior compared to priming with CombAct-Hib + Engerix + OPV for D, T, PRP, Hep B and polio.

Anti-hepatitis B and anti-PRP antibodies persistence were lower in subjects primed with Hexaxim (78.9% and 81.4%, respectively) than with CombAct-Hib + Engerix B + OPV (92.0% and 92.5%, respectively), based on surrogate thresholds for seroprotection; Anti-D (diphtheria) antibody persistence was higher in subjects primed with DTaP-IPV-Hep B-PRP-T (93.4%) than with CombAct-Hib + Engerix B + OPV (86.1%), although the 95% CIs overlapped.

It is noted that the comparator for this study included whole cell pertussis and live attenuated (oral) polio vaccines, neither of which are currently used in Australia. The study used a condensed schedule which differs from the primary schedule for Australia (2, 4 and 6 months), although EU guidance states that demonstration of satisfactory immunological responses with the most challenging schedules (for example, 2, 3 and 4 months or the WHO EPI schedule starting at 6 weeks of age) may be extrapolated to less condensed schedules (for example, 2, 4 and 6 months²⁵.)

²⁵ EMEA/CHMP/VWP/164653/2005. *Guideline on Clinical Evaluation of New Vaccines*. 18 October 2006.

Studies addressing lot-to-lot consistency**Study A3L11**

This was a Phase III, randomised, blind-observer, multicentre, controlled, four-arm study conducted in 1189 infants in Mexico. All subjects received three doses (at 2, 4, 6 months of age of either one of the three batches of the Hexaxim vaccine, (Groups 1, 2, and 3) or the Infanrix Hexa vaccine (Group 4). All infants were followed up for a total of 10 months. The primary objective was to provide clinical confirmation that the manufacturing process of the second drug product generation of the investigational Hexaxim vaccine was consistent between three industrial scale batches, in terms of immunogenicity and safety.

1056 of 1189 randomised subjects completed the trial. The evaluator commented that of all the studies, this one was the most problematic in terms of attrition or non-compliance with the protocol. Overall, the primary objectives of the study were met: individual batches were consistent using both 'per protocol' and 'intention to treat' analysis sets. The three individual batches showed broadly similar seroprotection/seroconversion rates at protocol-specified thresholds, however some differences were observed at higher thresholds.

With respect to other efficacy outcomes, non-inferiority with Infanrix Hexa was demonstrated. The clinical evaluator highlighted the following points: given the amount of diphtheria antigen is less in Hexaxim than in Infanrix Hexa, the pooled batches elicited a non-inferior anti-D seroprotection rate (at the ≥ 0.01 IU/mL threshold) compared to Infanrix Hexa. Descriptively, seroprotection/seroconversion rates and GMTs were generally in a similar range for pooled Hexaxim batches and Infanrix Hexa, demonstrating that both vaccines were protective against the six targeted diseases.

Studies addressing concomitant use with other vaccines**Study A3L12. Concomitant use with 7-valent pneumococcal vaccine**

This was a Phase III, multicentre, blind-observer, randomised, controlled trial conducted in 412 infants in Thailand. The primary objective was to demonstrate that Hexaxim induces an immune response at least as good as the response following Infanrix Hexa in terms of hepatitis B and PRP (*Haemophilus B*) seroprotection 1 month after a three-dose primary series (at 2, 4, 6 months), when co-administered with Prevenar(7 valent pneumococcal vaccine).

393 of 412 subjects completed the trial and the two groups were comparable. The non-inferiority criteria were met for hepatitis B and *Haemophilus Influenza* type b.

The study was not designed to demonstrate an effect of Hexaxim on the immunogenicity of the serotypes present in Prevenar (7-valent).

Study A3L24. Lot-to lot consistency and concomitant use with 7-valent pneumococcal vaccine and rotavirus vaccine

This was multi-centre, randomised, observer blinded, Phase III trial in 1376 Latin American infants. It was a four-arm trial with subjects randomly allocated to receive 1 of 3 lots of Hexaxim (consistency testing), or the control vaccine Infanrix Hexa (non-inferiority testing). All doses of the investigational or control vaccine were co-administered with Prevenar at 2, 4, and 6 months of age and Rotarix at 2 and 4 months of age.

The primary objectives were to demonstrate immunogenicity equivalence of three lots of Hexaxim (final bulk product) one month after a 3 dose primary series (2, 4, 6 months) when co-administered with Prevenar and Rotarix in terms of GMTs for hepatitis B, seroprotection rates for diphtheria, tetanus, hepatitis B, PRP, and poliovirus, and seroresponse rates for anti-pertussis toxoid and anti-FHA. The other primary objective was to demonstrate the non-inferiority of the hexavalent vaccine to the licensed Infanrix

Hexa vaccine in terms of seroprotection or seroresponse rates to all antigens, one month after a 3-dose primary series when co-administered with Prevenar and Rotarix.

Of the 1376 subjects initially randomised, only one subject discontinued. Overall, lot to lot consistency was demonstrated for the per protocol analysis set in terms of hepatitis B GMTs and seroprotection/vaccine response rate for all antigens. The intent-to-treat (ITT) set was used for confirmation. Non-inferiority of Hexaxim (pooled batches) versus Infanrix Hexa regarding seroprotection/vaccine response rates was demonstrated for all antigens.

Booster studies

Study A3L15bo. MMR and varicella vaccine

The aim of this study was to demonstrate that toddlers aged 15-18 months could be administered Trimovax (MMR vaccine) and Varilrix (varicella vaccine) concomitantly with Hexaxim. This was the only study where the same vaccine was used for both priming and booster immunisation. Overall, booster Hexaxim at 15 to 18 months with MMR and varicella co-administration induced a similar or better response for all antigens assessed (D, T, IPV and PRP) versus CombAct-Hib and oral polio vaccine.

Study A3L16 (booster for A3L02). Pentaxim used as booster vaccine

This study is of limited relevance to this submission given the booster was Pentaxim. The clinical evaluator concluded that the majority of subjects had seroprotective levels of antibodies at 16 to 18 months following priming with Hexaxim or Pentaxim and the majority of subjects developed similar robust anamnestic responses to the valences in Pentaxim vaccine regardless of their priming three series.

Study A3L21 (booster of A3L11). Comparison of booster effect of Hexaxim at 15-18 months following a primary series of either Hexaxim or Infanrix Hexa

This aim of this study was to determine that a booster with Hexaxim was immunogenic regardless of the priming vaccine (Infanrix Hexa or Hexaxim). 881 of 1056 subjects who completed the primary study were enrolled in the booster study. Of these 881 subjects, 768 had received Hexaxim and 113 had received Infanrix Hexa in the previous study. Immunogenicity was assessed in a subset of 310 subjects. Overall, the booster dose of Hexaxim produced similar results regardless of the priming vaccine, with antibody persistence similar between groups for most antigens.

Study A3L22 (booster for A3L10). Comparison of booster effect of Hexaxim at 15-18 months following a primary series of either Hexaxim or Pentaxim and Engerix B

The primary objective was to describe the antibody persistence against all antigens in either Hexaxim or Pentaxim and Engerix B and to describe the immunogenicity of a booster dose of Hexaxim. 254 of 302 subjects who completed the primary study were enrolled. The clinical evaluator concluded that pre-booster antibody persistence for all valences except anti-hepatitis B was similar in both primary vaccination groups; for anti-hepatitis B, pre-booster antibody persistence was lower in subjects primed with Hexaxim than those primed with Pentaxim + Engerix B. Post-booster anti-hepatitis B seroprotection rates (≥ 10 mIU/mL) were similar. For all the remaining valences the percentage of subjects attaining thresholds for seroprotection at 1 month after boosting was similar for the Hexaxim and Pentaxim + Engerix B primed groups.

Study A3L01. Phase I, safety of a booster dose

This was a study conducted in 60 infants in Argentina who received either Hexaxim or Hexavac as a booster dose following primary immunisation according to local schedules. The primary objective was safety, with immunogenicity a secondary objective. The clinical evaluator concluded that hepatitis B and *Haemophilus Influenza* type b had higher GMTs

with Hexaxim. Both vaccines were generally well tolerated. Local and systemic AEs were slightly less frequent with Hexaxim than with Hexavac.

Study A3L26. Antibody persistence

This was a Phase III, multi-centre study describing the long-term antibody persistence at 3.5 (2 years post-booster dose) and 4.5 years (3 years post-booster dose) in South African children who had completed a 3-dose primary series (Hexaxim with or without hepatitis B vaccine at birth, or CombAct-Hib + OPV + Engerix B) and the booster phase (Hexaxim or CombAct-Hib + OPV) in Study A3L15. Subjects were followed for one year. 453 children were included in the 3.5 year analysis and 436 for the 4.5 year analysis.

It was concluded by the evaluator that long term humoral immunity towards antigens following completion of a 3 dose primary series and a booster at 15-18 months (with or without hepatitis B vaccine at birth) induced strong antibody responses which were persistent in a significant percentage of study participants at the time points tested (that is, approximately 2 and 3 years after the toddler dose). Hexaxim long term antibody persistence did not differ from that observed with the control vaccines.

Pooled analyses of immunogenicity performed across trials

All studies (regardless of schedules, concomitant vaccines and choice of comparators) were conclusive in showing non-inferiority of Hexaxim, compared with control vaccines. The clinical evaluator drew attention to the following points:

Diphtheria antigen

Non-inferiority analysis of immunoresponses against diphtheria of Hexaxim versus controls was assessed in Studies A3L15 and A3L02. The acceptable non-inferiority margin for D was 10%. The estimated difference in the rates of diphtheria seroprotection (≥ 0.01 IU/mL) was equal to 1.46% (-2.20; 5.31) in Study A3L15 (control = CombAct-Hib + Engerix B + OPV), and 0.369% (-1.12; 2.06) in Study A3L02 (control = Pentaxim + Engerix B). The lower bound of the 95% 2-sided CI of the difference was $> -10\%$ for both studies, demonstrating non-inferiority of Hexaxim with respect to the diphtheria antigen.

Hepatitis B

Hexaxim seroprotection rates for hepatitis B (≥ 10 mIU/mL) were high ($\geq 94.0\%$) and similar to those in all the control groups, regardless of the immunisation schedule used. In terms of GMTs, variability was observed across studies, for example, in Studies A3L10 and A3L04, Hexaxim GMTs were lower than control. Given seroprotection rates for hepatitis B were high for these studies, GMT differences were deemed unlikely to be significant.

Haemophilus influenzae type b

No differences in anti-PRP responses in terms of seroprotection rate (≥ 0.15 $\mu\text{g/mL}$) were observed between the Hexaxim and control groups, except for Study A3L15. In terms of GMTs, variability was observed across studies which were deemed unlikely to be clinically significant, given the high seroprotection rates.

Ongoing, non-evaluated or awaited studies

1. Study A3L27 (booster of A3L24): Completed study. *Evaluation of Antibody Persistence Following a Primary Series at 2, 4, and 6 Months on Trial A3L24 and Booster Effect of the DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix Hexa concomitantly Administered with Prevenar (7-valent) at 12 to 24 Months of Age in Healthy Latin American Infants.* The study was completed in October 2013 and therefore not included in the initial application submitted to the TGA. It has not been evaluated by the TGA but is available on request to the sponsor.
2. Study A3L28 (long-term persistence study of A3L24/A3L27): Ongoing study. *Evaluation of Antibody Persistence at 3.5 and 4.5 Years in Healthy Children After*

Primary Series and Booster Vaccination with an Investigational (DTaP-IPV-Hep B-PRP-T) or Infanrix Hexa vaccines in Latin America.

3. Study A3L38: Ongoing study assessing concomitant administration with Prevenar-13. *Immunogenicity and Safety Study of a Hexavalent DTaP-IPVHep B-PRP-T Combined Vaccine or Infanrix Hexa Concomitantly Administered With 13-Valent Pneumococcal Conjugate Vaccine (PCV13), at 3, 5, 11 to 12 Months of Age in Healthy Infants in Europe.*
4. Study A3L39: Ongoing study assessing concomitant administration with Prevenar-13 and rotavirus vaccine. *Immunogenicity and Safety Study of a Hexavalent DTaP-IPV-HB-Hib Combined Vaccine in a 3-dose Primary Series (Hexavalent or Hexavalent/Pentavalent Combined Vaccine) in Healthy Infants in Europe.*
5. Study A3L43-EXT: Ongoing study assessing concomitant administration with the meningococcal C vaccine. *A phase III open-label randomised study to evaluate the immunogenicity and safety of the concomitant administration of a new Hexavalent DTaP-IPV-HepB-PRP-T combined vaccine (Hexavalent vaccine) given at 2, 3, and 4 months of age with a meningococcal serogroup C conjugate (MenC) vaccine given at 2 and 4 months.*
6. Study A3L40: Planned booster study for A3L39, assessing concomitant use with a Prevenar-13 booster.

Safety

Of the 14 studies included with this submission, 11 studies (7 primary and four booster studies) were included in the integrated safety analysis.

Study A3L04 was primarily a safety study. It was included in the integrated safety analysis and essentially demonstrated that Hexaxim and OPV placebo did not induce a higher incidence rate of high fever than Tritanrix-Hep B/Hib (DTP (whole cell)-Hep B-Hib) and OPV after any of the three vaccinations at 2, 4, and 6 months of age.

The integrated safety analysis did not include Studies A3L24 and A3L27 as this was not requested during the registration process in Europe. Study A3L26 (long-term antibody persistence) was also excluded as was Study A3L16 (Study A3L16 included Pentaxim as a booster).

The total exposed population who received at least one Hexaxim dose during the primary series or as a booster was 4927 subjects. This included 11 studies in the integrated safety analysis in addition to subjects in study A3L24. Overall, 15,102 doses of Hexaxim were administered in these 12 studies. Of these, 13,591 doses were administered to 4661 subjects in the 8 primary series, and 1511 doses were administered in 4 booster studies.

For the integrated safety analysis, no differences in frequency of AESI were observed between Hexaxim and control vaccines (subject exposure in control groups: Infanrix Hexa (primary) n = 504; Pentaxim + Engerix B (primary) n = 467; Tritanrix-HepB/Hib + OPV or CombAct-Hib + Engerix B+OPV (primary) n = 962; CombAct-Hib (booster) n = 254).

Solicited injection site reactions were reported at a higher frequency for those who received Hexaxim (83.4%) than those who received Pentaxim + Engerix B (75.4%).

The most frequently reported AEs are summarised in Table 5 above.

The EMA EPAR for Hexyon noted a tendency for higher reactogenicity of Hexaxim compared to Infanrix Hexa, especially for injection site reactions. In addition, a higher percentage of injection site reactions and fever for Hexaxim concomitantly administered with Prevenar as compared to Infanrix Hexa + Prevenar was observed.

The clinical evaluator commented that frequency of reported solicited injection site reactions at each post-injection decreased from the previous injection (that is, there was no incremental increase in solicited local reactions with each successive dose).

Of note, two subjects had potential ELS following administration of Hexaxim.

Deaths and serious adverse events

Overall, within the eleven studies included in the integrated analysis, 205 of 3896 subjects (5.3%) reported a total of 247 serious adverse events following Hexaxim administration. Of the 247 SAEs reported, one was considered related to the administration of Hexaxim: a case of HHE was reported in a 7 week old infant seven hours after administration of the first dose of Hexaxim.

The most frequently reported SAEs were of an infectious nature. In addition, 14 subjects experienced two episodes of convulsions and 13 episodes of febrile convulsions in the Hexaxim or Hexaxim + OPV placebo groups. All cases but one were considered serious and none were considered by the investigator to be related to vaccination.

No cases of encephalopathy or ADEM were reported after vaccination with Hexaxim. No cases of anaphylaxis were identified.

Eleven subjects died while included in the Hexaxim arms of the completed studies. None of the deaths were considered to be related to vaccination.

It is noted in the sponsors response to the TGA request for information that *“between 01 July 2013 and 17 February 2014, a total of 16 non-serious reports were received from Germany reporting sluggish pre-filled syringe plunger or increased pressure needed for injection, often combined with reports of increased pain or increased crying during vaccination sessions or potential under-dosing due to these problems. Some of these 16 reports referred to clusters of subjects, therefore the total number of concerned vaccinees was estimated to be at minimum 135 subjects (in six reports, the actual number of subjects concerned was not indicated).”*

The sponsor acknowledged the fact that the gliding force needed to actuate the syringe for all batches of Hexaxim pre-filled syringes is higher than the average of other vaccines manufactured by the company. They have initiated activities to modify the syringe design and the new design plunger syringes are expected to be available early 2015, prior to the planned launch in Australia.

Clinical evaluator’s recommendation

The clinical evaluator has recommended approval, based on a favourable risk-benefit balance and appropriately powered immunogenicity studies for Hexaxim. However, immunogenicity as a surrogate of clinical efficacy for pertussis is not clearly established and is a problem which is not unique to Hexaxim.

Risk management plan

The submitted RMP was evaluated for the OPR evaluator with the following issues highlighted:

The OPR evaluator commented that the submitted EU-RMP was out of date, contained major deficiencies and was inadequate to investigate the ongoing safety concerns associated with Hexaxim. The sponsor states that it plans to issue a new RMP by the end of 2014 which will be compliant with the revised EU format, and will provide a compilation of safety data from all the clinical studies that will be completed as of 17 October 2014. Two PBRER were provided which confirmed there had been no new safety concerns identified that would warrant an update to the RMP. A further PBRER is anticipated as

part of the response to the Delegate's Overview and the ASA will be reviewed to ensure any relevant new information is incorporated.

Several recommendations are made by the RMP evaluator. Recommendations 3, 5, 7, 13, and those regarding the PI and CMI were highlighted as open for consideration. These were anticipated to be resolved prior to a final decision being made on this application.

ACSOV advice

The RMP was presented to the ACSOV in March 2014, which noted that it was difficult to provide comment on the adequacy of the pharmacovigilance plan for Hexaxim; however it was likely to be inadequate. Furthermore, ACSOV noted that there was limited information regarding Hexaxim in the Australian context and that this needed to be addressed.

Immunisation has been associated with an increased risk of apnoea in premature infants, and while there were no reports of apnoea associated with Hexaxim in the clinical trials, premature infants had been excluded from the clinical trials.

Hexaxim has mainly been studied with the booster dose at 15-18 months. This difference was discussed, particularly in the context of the current NIP schedule. ACSOV advised that the administration of a booster at this time point would expose children to antigens that are not normally given at 18 months. As the current NIP schedule is 'tetanus toxoid heavy' the additional tetanus load may pre-dispose children to more severe local reactions. Furthermore, a booster dose of pertussis in the second year of life is known to be associated with an increased likelihood of local adverse events, including ELS.

Risk-benefit analysis

Delegate's considerations

- The overall strengths of this submission include the use of appropriate comparator vaccines and the inclusion of studies conducted in accordance with EU Guidelines on the evaluation of new vaccines²⁶.
- The submitted studies were mostly conducted in Latin and South America. The applicability of these ethnicities was addressed in the EMA EPAR for Hexyon and deemed comparable to the EU population. While the ethnicities are probably also acceptable in Australia, several of the submitted studies are of limited relevance to Australia, due to different schedules and choice of comparators.
- Furthermore, giving Hexaxim at 18 months as a booster does not align with the current NIP. The Delegate agrees with the clinical evaluator in recommending that the indication is not appropriate for boosting and noted that this had been addressed by the sponsor in the response to the TGA request for information.
- Recommendations for the NIP frequently change and it is understood that an 18 month booster dose for pertussis is likely to be re-introduced by the Australian Technical Advisory Group on Immunisation (ATAGI, as indicated at its 53rd meeting, 20-21 February 2014). In this case, the 15-18 month booster data from this submission would be of greater relevance to Australia, however whether a hexavalent vaccine is appropriate as a booster is yet to be determined.

The Delegate considered the sponsor should complete a study with the booster in the Australian context (that is, a study which includes the use of a quadrivalent booster (DTPa-IPV), rather than a hexavalent booster), as per ACSOV advice.

²⁶ EMEA/CHMP/VWP/164653/2005 *Guideline on Clinical Evaluation of New Vaccines*. 18 October 2006.

- Weaknesses of this submission are the exclusion of premature and immunocompromised infants (groups at increased risk of adverse events). The dossier relies on surrogate markers of clinical protection rather than clinical efficacy data.
- Correlates of protection have not been established for pertussis vaccines and the submission provides limited support for efficacy of the acellular pertussis component to control disease caused by *Bordetella pertussis*.
- The EPAR for Hexyon suggested that efficacy of the hepatitis B vaccine component for Hexyon (Hexaxim equivalent) may be dependent on inclusion of the booster dose. In the Australian context, this may be less relevant given the inclusion of the monovalent hepatitis B vaccine at birth in the NIP.
- Variability in GMTs for hepatitis B was observed across studies and while the evaluator concluded that this was unlikely to be clinically significant (given seroprotection rates for Hepatitis B were high), ACPM advice is to be sought.
- The limitations of studies with Prevenar have been addressed in the sponsor's response to the TGA request for information, given studies with concomitant use of Prevenar 13 are currently being conducted.

The sponsor would be requested to provide the TGA with the completed study reports for Studies A3L38, A3L39, A3L40 and A3L430Ext assessing concomitant administration with Prevenar 13 and with the meningococcal type C vaccine when available and to update the Hexaxim PI accordingly.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Hexaxim should be approved for registration.

The Delegate proposed to recommend this submission be rejected given the submitted studies are inadequate for demonstrating efficacy against pertussis. This is particularly pertinent to Australia, where rates of pertussis are the highest in the world.

Questions to sponsor

In the response to the Delegate's Overview, the sponsor was requested to address the following specific concerns:

1. Extrapolation of data to Australia

Hexaxim contains a two component pertussis vaccine. It is known that two component pertussis vaccines are less efficacious than vaccines containing three or more components and this has been demonstrated in a systematic review where efficacy of multi-component (at least three) vaccines varied from 84% to 85% in preventing typical whooping cough compared with 59% to 75% for one- and two component vaccines (Zhang et al., 2011²⁷). However, it has equally been demonstrated that long term large scale use of licensed two component vaccines, primarily in Sweden and Japan, have demonstrated high levels of pertussis prevention irrespective of antigen content (WHO²⁸). Conclusions from 10 year surveillance data in Sweden sponsored by vaccine manufacturers suggesting a significant reduction in pertussis in pre-school children are limited by the use of several different acellular vaccines during the period of follow-up and by cyclic fluctuations in reported cases of pertussis at different times and in different parts of the country (Carlsson and

²⁷ Zhang L, Prietsch SOM, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. [Review] [Update of Cochrane Database Syst Rev. 2011;(1):CD001478; PMID: 21249646]

²⁸ WHO. Pertussis vaccines: WHO position paper. *Weekly Epidemiol Record* 2010;85:385-400.

Trollfors²⁹). Furthermore, differences in surveillance systems and vaccination programs between countries make international comparisons difficult, and reporting rates may differ considerably, based on factors such as case definition and availability of laboratory reporting (Clark 2014³⁰, Edwards et al, 2013³¹). Recent Australian data suggest that *Bordetella pertussis* strains are changing in response to vaccine selection pressure with pertactin deficient strains emerging during the 2008-2012 outbreak of pertussis. It is unknown whether these strains will continue to increase and affect vaccine effectiveness and bacterial pathogenicity (Lam et al., 2014³²).

Caution is warranted in applying overseas data to Australia and approving a vaccine which is potentially less efficacious in a country where the burden of disease for pertussis remains high. Furthermore, while current acellular vaccines are highly effective in preventing severe pertussis in the first two years of life, effectiveness rapidly wanes from 2 years after the last dose and better vaccines are needed³³ (see also Clarke, 2014).

2. Non-clinical data

The non-clinical evaluator commented that since Hexaxim has been developed as an alternative to the registered Infanrix Hexa, there was no nonclinical evidence of comparable efficacies and immunogenicities between the two products. Thus, suitability of Hexaxim as an alternative to Infanrix Hexa will rely solely on clinical evidence of efficacy and no comment can be provided on the adequacy of Hexaxim as an alternative to the currently-registered hexavalent vaccine.

3. Diphtheria potency

It is of concern that the diphtheria potency for this vaccine does not comply with conventional standards (30 IU) set by the WHO (specified by the Ph. Eur. 6.0, article 2067), and that this was a reason for rejection by Russian Federation regulatory authorities and highlighted by ACSOV and the Module 3 (quality) evaluator. While the Ph. Eur. Monograph 2067 requires that the minimum potency for Diphtheria stated on the label is 30 IU per single human dose “unless otherwise justified and authorised”, it is requested that the sponsor provide an explanation for the basis for which the EU accepted the lower diphtheria toxoid content.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. The efficacy of a two component versus three component pertussis vaccine and the extrapolation of overseas data to the epidemiology of pertussis in Australia.
2. Related to this, the proposal by ATAGI to re-instate an 18 month booster for pertussis, in light of the submitted data.
3. The diphtheria toxoid content (20 IU) being less than conventional standards (30 IU) set by the WHO, specified by the Ph. Eur., and the regulatory implications for this in Australia.

²⁹ Carlsson RM, and Trollfors B. Control of pertussis-lessons learnt from a 10-year surveillance programme in Sweden. *Vaccine*. 2009;27(42):5709-5718.

³⁰ Clark TA. Changing Pertussis Epidemiology: Everything Old is New Again. *J Infect Dis* 2014;209:978–981.

³¹ Edwards KM, and Decker MD. Pertussis Vaccines. Section two: Licensed Vaccines In: *Vaccines*, 6th edition 2013; pp: 447-492. Plotkin, SA; Orenstein W; Offit PA (editors).

³² Lam C, Octavia S, Ricafort L, Sintchenko V, Gilbert GL, Wood N, et al. Rapid increase in pertactin-deficient *Bordetella pertussis* isolates, Australia. *Emerg Infect Dis*. 2014 April.

³³ McIntyre, PB, Nolan, TM. Pertussis control: where to now? *MJA* 2014;200(6):306-307.

4. The efficacy against hepatitis B, given the variability in geometric mean titers observed across studies and that this is a new hepatitis B vaccine.

Response from sponsor

The sponsor comments on the issues for which the advice of the ACPM is sought, as outlined in the Delegate's Overview (above) are presented below.

Hexaxim (DTPa-hepB-IPV-Hib) is a fully liquid ready-to-use hexavalent vaccine for infants and toddlers presented in a single-dose prefilled syringe for intramuscular injection. It provides protection against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b that are associated with significant morbidity and mortality. Optimal effectiveness of immunisation programs is directly influenced by vaccination coverage rates and compliance with vaccination schedules. From a public health perspective a high rate of vaccination coverage is critical to achieving 'herd immunity' to prevent or control resurgence of these diseases. Herd immunity makes it difficult for the infectious agent to find new hosts. This helps to protect infants who are too young to be vaccinated, or individuals whose immunity from vaccination has waned or for whom immunisation is contraindicated.

Hexaxim provides several important clinical benefits to support vaccine uptake:

- Wide coverage for six infectious diseases with a single injection;
- No reconstitution is needed simplifying administration, minimising vaccination errors and aiding clinicians/nurses;
- Reduction in injection burden facilitates compliance with vaccination schedules.

Hexaxim has been extensively investigated in clinical studies. With the exception of the hepatitis B antigen, all the antigens in Hexaxim have accumulated substantial post-marketing experience over more than a decade as part of various licensed vaccines produced by Sanofi Pasteur including Tetravac/Tetraxim (DTPa-IPV), Pentavac/Pentaxim (DTPa-IPV//Hib), Act Hib (Hib) and IPOL (IPV). Hexaxim is approved in 48 countries including the 28 EU Member States as of 7 July 2014, and in March 2014 it was approved in New Zealand for primary and booster vaccination of infants and toddlers from 6 weeks of age.

Hexaxim was first launched in Germany in July 2013 and cumulative global post marketing exposure as of 17 April 2014 is estimated from sales data as between 270 958 and 812 873 vaccinees (that is, vaccinees receiving 1 to 3 doses in accordance with the recommended three dose primary series schedule).

Since approval of Hexaxim in the EU on 17 April 2013, there have been no newly identified safety concerns from global surveillance activities that have warranted any changes to the EU-RMP, which is proposed for adoption in Australia in conjunction with an ASA.

The clinical evaluator has recommended that Hexaxim should be approved based on a favourable risk-benefit balance and appropriately powered studies demonstrating the safety and immunogenicity of all six components of Hexaxim. The Delegate has acknowledged the overall strengths of the data package which include the use of appropriate comparator vaccines, the inclusion of studies conducted in accordance with the EU guidelines and the applicability to Australia of the ethnicities used in the studies, as addressed during the EU evaluation.

The Delegate has provisionally recommended rejection of the application on the ground that the submitted studies are inadequate for demonstrating efficacy against pertussis, whilst noting that immunogenicity as a surrogate of clinical efficacy for pertussis is not clearly established and is a problem not unique to Hexaxim. This point was addressed by the clinical evaluator in recommending approval of Hexaxim, noting the pertussis problem

applies equally to other already registered combination vaccines that contain acellular pertussis antigens. The Delegate deemed this particularly pertinent to Australia, where rates of reported pertussis are among the highest in the world. Consequently, the Delegate describes perceived differences in the effectiveness of two component acellular pertussis versus three component acellular pertussis vaccines as a reason to exercise caution in extrapolation of overseas data.

The sponsor concurs with the conclusions of the clinical evaluator that Hexaxim should be approved. This response will address the concerns raised by the Delegate, particularly in relation to the extrapolation of overseas data to the Australian setting, on the basis of the overall supporting evidence which demonstrates:

- The vaccination schedule as a contributory factor to the high rates of pertussis in Australia compared to other countries where vaccination schedules are optimised. This supports the extrapolation of data for Hexaxim to Australia and the proposal by ATAGI to re-instate an 18 month booster.
- High levels of pertussis prevention in countries using one component acellular pertussis vaccine or two component acellular pertussis vaccine or both as well as other multi-component acellular pertussis vaccines. This supports the effectiveness of immunisation regardless of the number of acellular pertussis components.
- Effectiveness of the pertussis component of Hexaxim based on immunogenicity, efficacy and epidemiologic evidence including:
 - Evidence of effectiveness from use of Pentavac/Pentaxim containing the same two component acellular pertussis antigens as Hexaxim since first launch in 1997, expansion to registration in over 100 countries with more than 200 million doses distributed worldwide.
 - Comparative immunogenicity data demonstrating non-inferiority of all Hexaxim antigens to those in Infanrix Hexa, the only hexavalent paediatric vaccine currently approved in Australia.
 - A very recent review of evidence by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Pertussis Working Group that concludes³⁴ *“Evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component acellular pertussis vaccines; there is no conclusive data yet establishing the superiority of one acellular pertussis vaccine versus another.”* (April 2014)
 - Biases of the 2011 Cochrane review cited by the Delegate as the basis for concluding two component acellular pertussis vaccines are less efficacious than three component acellular pertussis vaccines in contrast to the very recent 2014 WHO SAGE Pertussis Working Group review.
 - Lack of any concerns raised by other global regulators on the effectiveness of the pertussis component of Hexaxim.
- Major differences between Hexaxim and Hexavac, which was withdrawn in the EU based on concerns relating to long-term immunogenicity of the hepatitis B component, due to hepatitis B antigens produced in different expression systems at different facilities and in different quantities. The new hepatitis B antigen in Hexaxim has been proven to induce protective immunity non-inferior to that induced by comparator vaccines such as Engerix B and Infanrix Hexa.
- Compliance with the Ph. Eur. monograph for diphtheria potency based on the same specification as approved in the EU. The Ph. Eur. is an accepted reference

³⁴ World Health Organization, “WHO SAGE pertussis working group Background paper SAGE April 2014” 14 March 2014.

pharmacopeia in both the EU and Australia and the same standards are therefore applicable.

Overall these data demonstrate the favourable benefit-risk profile of Hexaxim and justify its approval for use in Australia. The simplified administration option based on the ready-to-use presentation will aid compliance and support achieving high vaccination coverage rates for six infectious diseases that cause significant morbidity and mortality and for which community protection is an important public health benefit.

Impact of vaccination schedule on resurgence of pertussis in Australia

Proposal by ATAGI to re-instate an 18 months booster for pertussis, in light of the submitted data:

The natural history of pertussis is cyclical, with peaks of disease incidence occurring every 3-5 years. This occurred in the pre-vaccination era, the era of whole cell vaccine and continues in the acellular vaccine era. Historical efficacy data combined with epidemiologic observations in countries where pertussis vaccination was broadly implemented provide clear evidence of the effectiveness of acellular pertussis vaccines regardless of brand, in preventing the disease and controlling pertussis at a population level.

The 2008-2012 pertussis epidemiology data in Australia were reviewed as part of the 2014 WHO SAGE Pertussis Working Group review and key conclusions drawn from this review are:

- Pertussis is a major public health issue in Australia, with a continuous increase observed since 2008, most recently in younger children consistent with waning immunity.
- Resurgence of pertussis is particularly evident in children less than 10 years of age, especially in 2 to 4 year olds and 7 to 9 year olds.
- No other country using acellular pertussis vaccines has seen such a major increase in 2 to 3 year old children; other countries have seen increased cases from 6 years of age, but these apparent increases have been magnified by changes and increases in diagnostic testing.
- Cessation of the 18 month booster dose (DTPa) appears to be an important contributor to resurgence in 2 to 4 year olds, with early waning immunity following the last acellular pertussis vaccine dose at 6 months.
- There are Australian data to support a shorter duration of immunity among children who have received acellular pertussis vaccines than in those who received the Australian manufactured whole cell pertussis vaccine (which was used from 1975 to 1996).
- The resurgence was not associated with any increase in infant pertussis deaths, which have remained similar or lower to that of previous pertussis epidemics in the past 2 decades despite more sensitive diagnostic tests.

It is documented that immunity in response to the childhood DTPa vaccination series wanes over time (after approximately 5-10 years), which is why several national advisory committees on immunisation including the ATAGI in Australia recommend an acellular pertussis containing booster dose for adolescents and adults, especially those who have close contact with an infant.

In Australia, the recommended primary schedule for pertussis was originally three doses at 2, 4 and 6 months of age, with booster doses at 18 months and 4 years. In September 2003 the 18 month booster dose was removed and replaced with an adolescent (11 to 17 years) booster dose.

Recognising the removal of the 18 month booster as a contributing factor to the increasing incidence of pertussis, in 2013 the ATAGI re-instated its recommendation to administer an additional dose of pertussis containing vaccine in the second year of life. This additional dose in the second year of life has yet to be included on the NIP.

On the basis of the above the sponsor considers the high rates of pertussis in Australia are not based on population specific attributes that could limit the extrapolation of data to assess safety and effectiveness of Hexaxim, but rather on the use of sub-optimal vaccination schedules compared to other countries where higher levels of protection are observed.

In addition, a study with the booster in the Australian context using a quadrivalent booster (DTPa-IPV) was recommended by the Delegate and ACSOV. It should be noted that Sanofi Pasteur's DTPa vaccine, Tripacel, was used as the 18 month booster prior to its removal in 2003, and Quadracel (DTPa-IPV), which is approved for the 4th dose for children from 15 months to six years of age, is currently used as the 4th dose at four years of age on the NIP. There are post marketing experiences generated through the use of these two vaccines in Australia and hence the sponsor does not consider an Australian specific study is necessary.

Effectiveness of two component pertussis vaccines

The efficacy of a two component versus three component pertussis vaccine and the extrapolation of overseas data to the epidemiology of pertussis in Australia

The Delegate has referenced the 2011 Cochrane systematic review by Zhang et al. in support of a statement that it is known that two component vaccines are less efficacious than vaccines containing three or more components. This is in contrast to the very recent 2014 WHO SAGE Pertussis Working Group review of evidence that indicated there is no conclusive data on the superiority of one acellular pertussis vaccine over another. Reference is also made by the Delegate to the Australian data that suggest that *Bordetella pertussis* strains are changing in response to vaccine selection pressure with pertactin deficient strains emerging during the 2008-2012 outbreak.

- There were a number of biases that were not accounted for in the Cochrane systematic review:
 - The majority of currently licensed pertussis vaccines have not been compared in head to head efficacy trials. Most critically there are no clinical trials that directly compare the efficacy of licensed two component acellular pertussis vaccines with that of licensed three component acellular pertussis or 5 component acellular pertussis vaccines. In fact, the only study in which two component acellular pertussis vaccine was less efficacious than multi-component acellular pertussis vaccines involved an experimental two component acellular pertussis vaccine that was never licensed due to its limited efficacy. The bias of using an incorrect comparator (an unlicensed two component acellular pertussis vaccine) is not clearly discussed and remains a significant flaw in this Cochrane review.
 - The review did not account for any of the observational studies that give a reflection of the real world data.
 - Considerable published effectiveness data clearly support the effectiveness of both one and two component acellular pertussis vaccines as well as other multi-component acellular pertussis vaccines.
- As highlighted in Sanofi Pasteur's letter in response to the Cochrane systematic review [not reproduced here], rather than discussing the results of the historical vaccine efficacy trials performed with different acellular pertussis vaccines, the focus should be on the pragmatic evaluation of the vaccine effectiveness and programmatic effects

of all the acellular pertussis vaccines where they are in use. In these analyses, it is important to take into consideration the recommended vaccination schedules in the countries from which these vaccine effectiveness data are generated, and the vaccination coverage rates achieved within each of these countries.

- There is no evidence at this time that changes in circulating *Bordetella pertussis* strains are due to vaccine selection pressure or that such changes have reduced the effectiveness of licensed pertussis vaccines. The most common strains of *Bordetella pertussis* circulating in the U.S. or elsewhere have been the same for the past 30 years, so any studies of DTPa or dTpa would have been on the same strains as seen today. Although it has been shown that *Bordetella pertussis* bacteria have mutated over the past 10-20 years, there is no evidence that this is due to vaccine pressure or that this has led to increased rates of pertussis disease.

As previously stated, the sponsor wishes to re-emphasise that the pertussis antigens included in the Sanofi Pasteur's two component acellular pertussis vaccines are well-established and highly immunogenic. Data from large scale Sanofi Pasteur two component acellular pertussis vaccine-based field vaccination programs have shown their ability to successfully reduce the incidence of pertussis within 5-7 years following a complete primary vaccination (primary series followed by a toddler booster). On the basis of the available evidence the sponsor considers there are no grounds to conclude that there is a difference in effectiveness between two and three component acellular pertussis vaccines. The concerns raised by the Delegate in relation to extrapolation of overseas data can therefore be addressed by understanding the influence of the changes in vaccination schedule on the resurgence of pertussis in Australia and acknowledging the lack of inferiority demonstrated for all antigens including pertussis in Hexaxim compared to Infanrix Hexa, the only hexavalent vaccine currently approved in Australia.

Nonclinical data

No nonclinical evidence of comparable efficacies and immunogenicities between Hexaxim and Infanrix Hexa:

The nonclinical studies undertaken on Hexaxim were compliant with the relevant EU nonclinical guidelines that are adopted by the TGA. The goal was to determine the safety profile of Hexaxim and evaluate its primary pharmacodynamics. Whilst a nonclinical comparative study of Hexaxim and Infanrix Hexa is not a requirement in these guidelines, Infanrix Hexa was used as the main comparator vaccine in a number of the pivotal clinical studies (A3L11, A3L12, A3L17 and A3L24).

As noted by the TGA nonclinical evaluator, clinical demonstration of equivalent immunogenicity is more pertinent and useful. The conclusion drawn by the clinical evaluator in the CER is *"taken collectively, Hexaxim results in high levels of protective immunity to all its antigen components; these levels are equivalent to those produced by comparator vaccines, for example, Infanrix Hexa, already used in the Australian NIP, at least for the primary vaccine series in infants"*.

Diphtheria potency

The diphtheria toxoid content (20 IU) being less than conventional standards (30 IU) set by the WHO, specified by the Ph. Eur. and the regulatory implications for this in Australia:

In Europe, the proposed specification for the diphtheria component of Hexaxim has been considered compliant with both the Ph. Eur. (Monograph 01/2008:2067) and WHO (Technical Report Series No. 927, 2005) requirements (EPAR for Hexacima³⁵. The

³⁵ European Medicines Agency Assessment Report (EPAR) for Hexacima (Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type B conjugate vaccine (adsorbed)), 5 March 2013 EMA/373868/2013.

specification was justified based on relevant data on clinical lots and consequently approved. The same standards apply in Australia as in the EU.

The immune response of Hexaxim in terms of seroprotection to diphtheria (defined by a titer ≥ 0.01 IU/mL) was descriptively analysed in a number of studies and the data show that at the ≥ 0.01 IU/mL threshold, no differences in anti-diphtheria responses were observed between Hexaxim and comparator vaccines including Infanrix Hexa. As noted by the Delegate and the clinical evaluator, in the non-inferiority analysis against Infanrix Hexa in Study A3L11, *“the pooled batches elicited a non-inferior anti-D seroprotection rate (at the ≥ 0.01 IU/mL threshold) compared to Infanrix Hexa”*.

Efficacy against hepatitis B

The efficacy against hepatitis B, given the variability in geometric mean titres observed across studies and that this is a new Hepatitis B vaccine:

Development of an anti-HBs antibody titer exceeding 10 mIU/mL is generally accepted as a correlate for protective immunity against hepatitis B. During the Hexaxim clinical development program, anti-HBs ≥ 10 mIU/mL was used as the primary study endpoint parameter. In addition, to comply with the current recommendations, anti-HBs ≥ 100 mIU/mL and GMTs were also descriptively analysed as secondary study endpoint parameters.

The primary endpoint was met in all clinical studies conducted with Hexaxim following primary series (seroprotection rates between 94.0 and 100%).

As the hepatitis B antigen is the only new antigen contained in Hexaxim, it was descriptively analysed in 13 out of 14 studies (no immunogenicity analysis in the large scale safety Study A3L04) and tested for non-inferiority against controls in 6 primary series studies:

- In primary series studies, Hexaxim was tested for non-inferiority against Engerix B in A3L15, A3L10 and A3L02 and Infanrix Hexa in A3L12, A3L17 and A3L24. In all 6 studies, Hexaxim was shown to be non-inferior to control vaccines based on anti-HBs ≥ 10 mIU/mL 1 month post-dose 3.
- The protection conferred by Hexaxim with or without hepatitis B vaccination at birth was also shown to be comparable to Infanrix Hexa using the 2-4-6-month vaccination schedule in Studies A3L12 and A3L24 (with hepatitis B at birth) and A3L11 and A3L17 (without hepatitis B at birth). In Australia, the first hepatitis B vaccination is given at birth, thus the data from A3L12 and A3L24 are most applicable to the Australian population. For the 4 studies in which Hexaxim and Infanrix Hexa were administered, the percentages of individuals with anti-HBs ≥ 10 mIU/mL were similar and higher than 98.3%. When planned in the protocol (all studies except A3L11), non-inferiority of Hexaxim compared to Infanrix Hexa was demonstrated in terms of seroprotection rate (anti-HBs ≥ 10 mIU/mL).
- The immune responses were also comparable between the two vaccines in terms of GMTs. The percentages of individuals with anti-HBs ≥ 100 mIU/mL were also in the same ranges in Studies A3L12, A3L17 and A3L24, but lower in the Hexaxim group than in the Infanrix Hexa group in study A3L11 (91.7% versus 99.2%). These differences, as well as differences in GMT, are expected to be of no meaningful clinical relevance.

Overall, Hexaxim was shown to induce high seroprotection rates (anti-HBs ≥ 10 mIU/mL), and similar seroprotection rates to Infanrix Hexa, indicating adequate priming and effective protection against hepatitis B infection.

RMP evaluation

As referenced in the Delegate's Overview, the comments that the submitted EU-RMP was out of date is an error of fact and was addressed in the sponsor's response to the RMP evaluation report. The EU-RMP remains current and fully addresses all safety concerns in alignment with the approval of Hexaxim in the EU. In addition the latest PBREER confirms no new safety signals that warrant any additional update to the RMP.

Summary

In summary, the evidence supporting the safety and effectiveness of Hexaxim confirms a favourable benefit-risk profile and supports its approval for use in Australia:

- Hexaxim provides protection against six infectious diseases (diphtheria, tetanus, pertussis, tetanus, hepatitis B, poliomyelitis and *Haemophilus Influenzae*) associated with significant morbidity and mortality.
- Immunogenicity data confirms the non-inferiority of Hexaxim compared to other well established comparators including Infanrix Hexa, the only hexavalent vaccine currently approved in Australia.
- Because of its fully liquid formulation, Hexaxim provides a safe and efficacious option compared to the alternative combination paediatric vaccine approved in Australia. It simplifies vaccine administration and supports compliance conferring optimal individual and population immunity.
- No new safety signals have been identified from post marketing experience that warrant any updates to safety concerns reflected in the EU-RMP.

The overall body of evidence supports the effectiveness of the two component acellular pertussis antigen in Hexaxim. The very recent 2014 WHO SAGE Pertussis Working Group review of evidence, in contrast to the 2011 Cochrane review, found no conclusive data to establish superiority of one acellular pertussis vaccine over another.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's Overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Hexaxim solution for injection containing 0.5 mL of diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) [DTPa-hepB-IPV-Hib] to have an overall positive benefit-risk profile for the indication;

Hexaxim is indicated for primary and booster vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b.

The ACPM advised that, as with all new vaccines, post-market monitoring would be important, especially in relation to differentiating efficacy and safety of the two component compared to the three component pertussis vaccines.

Conditions of registration

The ACPM proposed the following:

- Subject to satisfactory negotiation of the Risk Management Plan with the TGA,
- Negotiation of PI and CMI to the satisfaction of the TGA.

Proposed PI/CMI

The ACPM advised that the amendments to the PI and CMI should be limited to the following:

- The statement about use with Prevenar should make it clear that these data pertain only to use with 7 valent PCV, not the 13 valent currently used in Australia.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI should make clear the lack of experience in premature infants.
- A statement in the *Precautions* section of the PI should caution against intradermal use.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. The efficacy of a two component versus three-component pertussis vaccine and the extrapolation of overseas data to the epidemiology of pertussis in Australia.

Swedish experience suggests two component pertussis vaccine is adequate. Although not ideal data they support the efficacy of two component vaccine.

While the strong emergence of pertactin deficient strains of pertussis has been documented Australia the significance of this for the two component compared to the three component vaccines is unknown.

2. Related to this, the proposal by ATAGI to re-instate an 18 month booster for pertussis, in light of the submitted data.

The evidence submitted supports the adequate immunological response following a booster dose. Acellular vaccines are effective against severe disease even after one dose but effectiveness wanes within 2 years. The relationship between Australia's resurgence of disease and the withdrawal of the 18 month booster dose is unknown.

3. The diphtheria toxoid content (20 IU) being less than conventional standards (30 IU) set by the WHO, specified by the European Pharmacopoeia and the regulatory implications for this in Australia.

The ACPM noted that the relevant Ph. Eur. Monograph requires that the minimum potency for Diphtheria stated on the label is 30 IU per single human dose unless otherwise justified and authorised. The submitted data show excellent immunogenicity of the Diphtheria component of Hexaxim.

4. The efficacy against hepatitis B, given the variability in geometric mean titers observed across studies and that this is a new Hepatitis B vaccine.

Non-inferiority criteria were met, showing the antigenicity of the HBsAg in Hexaxim to be similar to that in Infanrix Hexa and Engerix B.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Hexaxim DTPa-hepB-IPV-Hib suspension for injection in pre-filled syringe, indicated for:

Hexaxim is indicated for vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b.

Use of this vaccine should be in accordance with the national recommendation as per the current Immunisation Handbook.

Specific conditions of registration applying to these goods

- Risk Management Plan for Hexaxim Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) [DTPa-hepB-IPV-Hib]:
 - The European Risk Management Plan Version 8.0 (data lock point 11 August 2011) with an Australian Specific Annex (ASA) Version: 1.1 (dated April 2014), to be revised as specified in the sponsor's correspondence dated 28 April and 28 August 2014, and any subsequent revisions as agreed with the TGA, must be implemented.
 - Hexaxim will not be launched in Australia until the next planned PBRER and EU-RMP due in December 2014 has been submitted and evaluated and any relevant updates incorporated into the ASA to the satisfaction of the TGA.
- It is a condition of registration that all independent batches of Hexaxim diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus influenzae* type b conjugate vaccine (adsorbed) [DTPa-hepB-IPV-Hib] imported into Australia are not released for sale until samples and the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).
- Conditions of registration – Lot Release³⁶:

Attachment 1. Product Information

The Product Information approved for Hexaxim at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

³⁶ Details are beyond the scope of the AusPAR.

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