ADIS DRUG EVALUATION

DTaP-IPV-HepB-Hib Vaccine (Hexyon®): An Updated Review of its Use in Primary and Booster Vaccination

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Abstract

Hexyon® is a fully-liquid, ready-to-use, hexavalent vaccine approved in the EU since 2013 for primary and booster vaccination in infants and toddlers from age 6 weeks against diphtheria, tetanus, pertussis, hepatitis B (HB), poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib). While the source of HB antigen in Hexyon® is different from other vaccines, the rest of its valences have been extensively used in other approved vaccines. Hexyon® is highly immunogenic for all its component toxoids/antigens when used as primary and booster vaccine in infants and toddlers, irrespective of vaccination schedule. It provides durable protection against hepatitis B. Hexyon® can be used for a mixed primary series of hexavalent-pentavalent-hexavalent vaccines or as a booster in infants primed with Infanrix hexa™ or pentavalent (whole-cell or acellular pertussis) vaccines. Coadministration of Hexyon® with other common childhood vaccines did not affect immune response to any vaccines. Hexyon® has a good reactogenicity/safety profile. The immunogenicity and safety profile of Hexyon® was similar to that of several approved vaccines, including Infanrix hexa™. However, Hexyon® offers the convenience of full-liquid, ready-to-use formulation, which may minimize vaccination errors and preparation time. Thus, Hexyon® is a convenient, useful option for vaccination against childhood diseases caused by six major pathogens.

Hexyon®: clinical considerations
Fully-liquid, ready-to-use, thiomersal-free hexavalent vaccine
Noninferior to many approved vaccines (including Infanrix hexa™) in terms of seroprotection, seroconversion or vaccine response rates
Provides long-term hepatitis B immunity
Generally well tolerated, with a safety profile similar to that of approved vaccines

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1 Introduction

Multivalent vaccines are routinely used in Europe and elsewhere against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B (HB), and invasive diseases caused *Haemophilus influenzae* type b (Hib) [1]. Despite several challenges (e.g. antigen compatibility, complex manufacturing and quality control processes), multivalent vaccines are of great public health and economic value, as they improve vaccine coverage, reduce costs and potential outbreaks, and allow incorporation of new antigens without increasing the number of injections [1, 2].

A combination of diphtheria toxoid (D), tetanus toxoid (T), and acellular pertussis (aP) or whole-cell pertussis (wP) antigens (DTaP or DTwP) serves as a backbone to which poliovirus, HB virus or Hib antigens are added to produce quadrivalent, pentavalent, and hexavalent vaccines. Hexyon® (also known as Hexaxim® or Hexacima®, depending on the country where marketed) is a thiomersal-free, fully-liquid, ready-to-use hexavalent pediatric vaccine (DTaP-IPV-HepB-Hib). One dose (0.5 mL) of Hexyon®, adsorbed on hydrated aluminium hydroxide (0.6 mg), contains the following: D (≥ 20 IU); T (≥ 20 IU); two *Bordetella pertussis* antigens, [pertussis toxoid (PT; 25 µg) and filamentous haemagglutinin (FHA; 25 µg)]; inactivated poliovirus (IPV) type 1, 2,

and 3 (40, 8, and 32 D antigen units, respectively) produced on Vero cells; HB virus surface antigen (HBsAg; 10 µg) produced in yeast *Hansenula polymorpha* cells by recombinant DNA technology; and Hib polysaccharide, polyribosylribitol phosphate (PRP; 12 µg) conjugated to T (22–36 µg) [3]. The source of HBsAg in Hexyon ® is different from other vaccines (Sect. 6). Hexyon® is indicated in the EU and elsewhere for both primary and booster vaccination (Sect. 5) [3].

A review of Hexyon® was published in *Pediatric Drugs* in 2013 [4]. Since then, additional data [5–14] have become available. This article provides an updated review of the immunogenicity, reactogenicity and safety of Hexyon® as primary and booster vaccination against major childhood infectious diseases caused by six pathogens, from a European perspective. The majority of data are from non-European countries. However, these data are relevant to this review, as Hexyon® received a positive scientific opinion from the European Medicines Agency (EMA) under article 58 procedure [15]; the EMA assessment was conducted in consultation with WHO experts using the same criteria for evaluation of vaccines in the EU [16]. The EMA granted a marketing license for Hexyon® in all Europe through a centralized procedure. Hexyon® is in use in national immunization programs worldwide, including Europe.

2 Immunogenicity of Hexyon®

The immunogenicity of Hexyon® as primary vaccination in infants was assessed in a phase 2 (A3L02) and several phase 3 randomized, comparative [8–12, 14, 17–22] or single-arm [7, 13] trials. All trials were open-label and some were observer-blind [8, 10, 14, 19–21]. Safety was the primary objective in one trial (A3L04) [22]. A booster dose of Hexyon® was evaluated in nearly half of the primary series trials [6, 8–10, 14, 21, 23]. Some studies assessed the long-term persistence of antibodies and immune memory against some of the vaccine antigens [5, 24].

The primary series trials were conducted in almost all continents, covering all major ethnicities (African, Asian, Caucasian and Hispanic) [7–14, 17–21] (Table 1). Eligible participants were healthy infants born at full-term pregnancy ($\geq$ 37 weeks), with a $\geq$ 2.5 kg birth weight and age as defined by the vaccination schedule. Typical exclusion criteria were personal and/or maternal history of HIV, HB or hepatitis C infection, history of (or prior vaccination against) diphtheria, tetanus, pertussis, poliomyelitis, HB or Hib infection, history of seizures, immunodeficiency, bleeding disorder contraindicating intramuscular injection, febrile/acute illness, or prior use of blood products. Following local immunization schedules, eligible infants had or had not received HB vaccination at birth. With the exception of routine vaccines [e.g. bacillus Calmette–Guérin vaccine, oral polio vaccine (OPV),

rotavirus vaccines] administered according to the national immunization schedules, infants had not received any other vaccines before study vaccine administration [7–14, 17–22].

Primary series consisted of three vaccine doses administered at age 2, 4, and 6 months (standard schedule; Latin America, Asia) [7, 10, 11, 18–21], 2, 3, and 4 months ('accelerated' schedule; Europe) [8, 9, 12] or 6, 10, and 14 weeks (expanded program of immunization schedule; South Africa, India) [Table 1] [13, 17]. The booster dose was administered at 11–24 months [Table 3] [6, 8–10, 21, 23]. One trial evaluated a 2 + 1 schedule in Europe, with the primary series administered at 3 and 5 months, and the booster dose at 11–12 months [14]. Following local schedules, study vaccines were concomitantly administered with pneumococcal (PCV 7 [10, 20] or PCV 13 [7, 12, 14]), meningococcal (MenC [12] or MenACWY [6]), rotavirus [7, 10, 12] or measles, mumps, rubella + varicella (MMRV) [12, 17] vaccines.

Established antibody threshold levels and validated assays were used for assessing seroprotection for anti-D and anti-T ($\geq$ 0.01 IU/mL; ELISA assay), anti-IPV 1, 2, and 3 ($\geq$ 8 1/ dil), anti-HB ($\geq$ 10 mIU/mL), and anti-Hib ($\geq$ 0.15 µg/mL) [6–14, 17–23]. Most trials also evaluated long-term protective threshold (LTPT) rates (i.e. proportion of participants achieving antibody titer levels of $\geq$ 0.1 IU/mL for anti-D and anti-T, $\geq$ 100 mIU/mL for anti-HB, and $\geq$ 1 µg/mL for anti-Hib). In the absence of generally accepted seroprotective threshold levels for pertussis antigens, seroconversion rates at established thresholds (i.e. $\geq$ 4-fold increase from baseline in antibody concentrations) and/or vaccine response rates were used as surrogates of protection against pertussis. Geometric mean concentrations (GMCs) of anti-D, anti-T, anti-PT, anti-FHA, anti-HB, and anti-Hib antibodies or geometric mean titers (GMTs) of anti-polio antibodies were also evaluated. Immunogenicity was assessed 1 month after the last dose of the primary series (post-primary), before the booster dose (pre-booster, i.e. antibody persistence), and 1 month after the booster dose (post-booster), with prevaccination assessments also made for some antigens [6–14, 17–23]. For concomitant vaccines, the following seroprotective thresholds were used: $\geq$ 0.35 µg/mL for each of PCV7 [10] or PCV13 [14] antigens; serum bactericidal antibody titers $\geq$ 8 for MenC [12] and each of MenACWY [6] antigens; $\geq$ 20 U/mL for anti-rotavirus IgA [10]; $\geq$ 300 mIU/mL for anti-measles and anti-varicella, $\geq$ 500 EU/mL for anti-mumps, and $\geq$ 10 IU/mL for anti-rubella [23].

In many primary series trials, the primary immunogenicity objective was noninferiority of Hexyon® to the comparator group with respect to seroprotection, seroconversion or vaccine response rates [8–12, 17–20]. In two primary series trials, the primary or coprimary objective was equivalence of three lots of Hexyon® (i.e. lot-to-lot consistency) with respect to anti-HB GMC ratio and seroprotective, seroconversion or vaccine response rates for all antigens [10, 21].

Table 1 Post-primary seroprotection, seroconversion or vaccine response rates for Hexyon® and comparators

Study (country)	Vaccine[a] (no. of subjects)	Anti-D	Anti-T	Anti-PT [VR[b]]	Anti-FHA [VR[b]]	Anti-IPV1	Anti-IPV2	Anti-IPV3	Anti-HB	Anti-Hib
Primary series at 2, 4, 6 months of age										
A3L24 [10] (Colombia, Costa Rica)	HEX[c] (935) [+HB]	100[d]	100[d]	89.6 [97.5[d]]	94.7 [99.8[d]]	100[d]	100[d]	100[d]	99.7[d]	94.6[d]
	IFX (316) [+HB]	100	100	89.7 [98.4]	91.0 [99.4]	100	100	99.7	100	95.9
A3L11 [21] (Mexico)	HEX[c] (695) [−HB]	96.4	100	97.4	98.4	99.9	100	99.9	98.3	98.8
	IFX (119) [−HB]	99.2	100	95.8	96.5	100	100	100	100	99.2
A3L12 [20] (Thailand)	HEX (189) [+HB]	97.4	100	93.7	94.7	100	100	100	99.5[d]	97.9[d]
	IFX (190) [+HB]	100	100	93.7	95.2	100	100	100	99.5	96.3
A3L17 [19] (Peru)	HEX (132) [−HB]	95.5	NE	NE	NE	NE	NE	NE	99.2[d]	100
	IFX (130) [−HB]	100	NE	NE	NE	NE	NE	NE	100	99.2
A3L31 [11] (South Korea)	HEX (132) [+HB]	100[d]	99.2[d]	94.6[d] [98.4]	91.7[d] [97.7]	100[d]	100[d]	100[d]	97.7[d]	100[d]
	PEN+EUV (131) [+HB]	100	100	93.0 [98.4]	89.3 [96.2]	100	100	100	96.9	100
A3L02 [18] (Argentina)	HEX (260) [−HB]	100[d]	100[d]	91.8[d]	93.2[d]	100[d]	100[d]	100[d]	99.2[d]	94.6[d]
	PEN+ENG (271) [−HB]	99.6	100	92.9	90.0	100	100	100	100	97.4
A3L39 [7] (Spain)	HEX-PEN-HEX (236) [+HB]	100	100	89.7 [99.5]	95.5 [100]	100	99.5	100	99.1	100
Primary series at 2, 3, 4 months of age										
A3L39 [8] (Germany, Czech Republic)	HEX (237) [−HB]	100	100	90.4 [98.3[d]]	89.2 [99.1[d]]	100	100	100	95.7[d]	91.1[d]
	IFX (239) [−HB]	100	100	90.9 [97.8]	76.4 [94.8]	100	100	100	98.7	86.3
HXM01C [12] (Finland)	HEX+MenC (162) [−HB]	100	100	88.3 [98.7]	89.6 [99.4]	100	100	100	97.5[d]	98.1
	HEX (160) [−HB]	99.4	100	88.3 [100]	91.5 [100]	98.7	100	99.3	96.1	94.3
A3L10 [9] (Turkey)	HEX (145) [−HB]	99.3	100	93.6	81.9	97.7	94.7	97.4	94.0[d]	90.7
	PEN+ENG (141) [−HB]	97.1	100	94.2	83.1	97.9	94.0	100	96.1	97.8
Primary series at 6, 10, 14 weeks of age										
A3L15 [17] (South Africa)	HEX (220) [−HB]	97.6[d]	100[d]	93.6	93.1	100[d]	98.5[d]	100[d]	95.7[d]	95.4[d]
	CMB+ENG+OPV (212) [−HB]	96.1	100	83.2	57.7	93.0	100	98.3	95.4	100
	HEX (123) [+HB]	95.1	100	95.1	90.0	99.0	98.2	100	99.0	97.5
A3L33 [13] (India)	HEX (156) [+HB, +OPV]	99.3	100	NE [93.8]	NE [99.3]	100	100	100	100	100
Primary series at 3, 5 months of age										
A3L38 [14] (Sweden, Finland)	HEX (249) [−HB]	99.6	100	NE [98.4]	NE [99.6]	90.8	95.0	96.7	97.2	71.5
	IFX (248) [−HB]	99.6	100	NE [99.2]	NE [98.3]	95.4	96.6	98.3	98.4	57.9

+HB/−HB, with/without HB vaccine at birth, AbC antibody concentration, CMB CombAct-Hib®, D diphtheria, ENG Engerix B® Pediatrico, EUV Euvax B®, FHA filamentous haemagglutinin, HB hepatitis B, HEX Hexyon®, Hib H. influenzae type b, IFX Infanrix hexa®, IPV inactivated polio virus, LLOQ lower limit of quantification, MenC meningococcal serogroup C conjugate vaccine, NE not evaluated, OPV oral polio vaccine, PCV pneumococcal conjugate vaccine, PEN Pentaxim®, PT pertussis, T tetanus, VR vaccine response

[a] Concomitantly administered with PCV 7 (A3L24, A3L12, A3L39), PCV 13 (A3L24, A3L39, HXM01C, A3L38) and rotavirus vaccine (A3L24, A3L39, HXM01C)

[b] In A3L24, post-primary AbC ≥ LLOQ or ≥ prevaccination levels in initially seronegative or seropositive subjects, respectively. In all other studies, post-primary AbC ≥ 4 × LLOQ or ≥ prevaccination levels in subjects with prevaccination levels < 4 × LLOQ or ≥ 4 × LLOQ, respectively

[c] Subjects were randomized to 1 of 3 batches [batch to batch equivalence criteria met (primary objective)]; data reported are for pooled batches

[d] Noninferior to comparator vaccine

If equivalence was demonstrated, data were pooled and tested for noninferiority of Hexyon® to the comparator as a coprimary or secondary objectives [10, 21]. In the trial evaluating the 2 + 1 schedule, noninferiority was tested after the primary series (observational objective) and the booster dose (primary objective) [14]. Pre-defined equivalence or noninferiority margins were 10% (for anti-D, anti-T, anti-PT, anti-FHA, anti-HB, and anti-Hib) or 5% (for anti-polio types 1–3) [8–12, 17–21]; for equivalence, 95% CI of the anti-HB GMC ratio between any two batches should be within 0.5–2 [10, 21]. Comparisons were descriptive in some primary series trials [7, 13, 14] and most of the booster trials [6, 8–10, 21, 23]. The principal immunogenicity analyses were conducted in the per-protocol populations.

2.1 Antibody Response to Hexyon®

There was a good lot-to-lot consistency between three manufacturing lots of Hexyon® based on immunogenicity equivalence [10, 21]. A 3-dose Hexyon® primary series administered in various schedules beginning at 1.5–2 months was highly immunogenic for all its component toxoids/antigens [8–13, 17–21]. Post-primary seroprotection rates were 95–100% for anti-D and anti-polio, 99–100% for anti-T, 94–100% for anti-HB, and 91–100% for anti-Hib. For anti-PT and anti-FHA, seroconversion rates were 88–97% and 82–98%, and the vaccine response rates were ≥ 94% (Table 1). When Hexyon® was used in a 3-dose mixed primary series of hexavalent-pentavalent-hexavalent vaccines, seroprotection or vaccine response rates were > 99% for all antigens [7]. Following a 2-dose Hexyon® primary series, anti-Hib seroprotection rate was 72% and seroprotection or vaccine response rates were 91–100% for other antigens [14]. In infants receiving a 3-dose Hexyon® primary series, there was a good antibody persistence in the second year of life, with most participants remained protected against each antigen before the booster dose (Table 2) [6, 8–10, 21, 23].

A single booster dose of Hexyon® at 11–24 months produced a strong immunogenic response, irrespective of the primary vaccines or schedules used. In participants boosted with Hexyon®, post-booster seroprotection rates were 96–100% for anti-D, anti-T, anti-polio types 1–3, anti-HB, and anti-Hib, and seroconversion rates were 79–97% for anti-PT and 60–97% for anti-FHA (vaccine response rates > 94% for both) (Table 3) [6, 8–10, 21, 23]. The 2 + 1 schedule of Hexyon® also elicited robust booster response, with seroconversion or vaccine response rates > 96% [14]. Post-booster LTPT rates were 94–100% for anti-D, anti-T, and anti-Hib, and 88–99% for anti-HB [6, 8–10, 14, 21, 23]. Persistence of antibodies to Hexyon® antigens in the longer term are discussed in Sects. 2.2 and 2.4 [5, 24].

In the study that randomized infants to receive HB vaccination at birth or not (A3L15 [17]), anti-HB post-primary (Table 1) and post-booster (Table 3) seroprotection rates were numerically similar in both groups, although HB vaccination at birth was associated with numerically higher LTPT rates and GMCs at all assessment timepoints. This finding was broadly supported by individual studies which included infants who had [7, 10, 11, 13, 20, 21] or had not [8, 9, 12, 14, 18, 19] received HB vaccination at birth and a pooled analysis of infants who had not received HB vaccination at birth [25]. Post hoc analyses showed that anti-HB post-booster seroprotection rate was independent of pre-booster GMCs (< 10 vs. ≥ 10 mIU/mL) [9, 23].

2.2 Compared with a Hexavalent Vaccine

The immunogenicity of Hexyon® primary series was compared with that of Infanrix hexa™ (DTPa-HBV-IPV/Hib) in six trials (A3L24 [10], A3L11 [21], A3L12 [20], A3L17 [19], A3L39 [8] and A3L38 [14]) (Table 1). Four of these trials were followed by booster studies [8, 10, 14, 21], with two studies investigating interchangeability of the study vaccines [10, 21] (Table 3). Pre-booster antibody persistence was evaluated in all booster studies (Table 2). In addition, two of the core trials (A3L24 and A3L12) were followed-up to assess the long-term persistence of antibodies [5, 24].

Following a 3-dose primary series, Hexyon® was noninferior to Infanrix hexa™ with respect to post-primary seroprotection or vaccine response rates for all component antigens [10], anti-PT and anti-FHA [8], anti-HB [8, 10, 19, 20] or anti-Hib [8, 10, 20] (primary objective) [Table 1] and seroprotection rate for anti-D (secondary objective) [21]. Following a 2-dose primary series, Hexyon® was noninferior to Infanrix hexa™ with respect to seroprotection or vaccine response rates for anti-D, anti-T, anti-PT, anti-FHA, anti-IPV3, anti-HB and anti-Hib, although noninferiority criteria was not met for anti-polio types 1 and 2 (observational objective) [14]. Apart from statistical comparisons, where reported, seroprotection or vaccine response rates were numerically similar between the two vaccines [8, 19–21]. Hexyon® induced numerically similar (for anti-D, anti-T, anti-PT, anti-FHA), lower (for anti-polio types 1–3) or higher (for anti-Hib) levels of GMCs/GMTs relative to Infanrix hexa™, although these differences did not reflect in seroprotection or vaccine response rates [8, 10, 19–21].

Seroprotection data are supported by LTPT rates. Following the standard schedule, post-primary LTPT rates in the Hexyon® group were 58–76% (vs. 56–75% with Infanrix hexa™) for anti-D, 99–100% (vs. 100%) for anti-T, 92–99% (vs. 99–100%) for anti-HB, and 78–93% (vs. 71–91%) for anti-Hib [10, 19–21]. With the accelerated primary schedule, there were some differences between Hexyon® and Infanrix hexa™ in LTPT rates for anti-HB (72% vs. 86%) and anti-Hib (59% vs. 37%) [8].

There were no clinically relevant differences between Hexyon® and Infanrix hexa™ in pre-booster seroprotection

Table 2 Pre-booster seroprotection or seroconversion rates for Hexyon® and comparators

Booster study (primary study)	Vaccine (no. of subjects)	Anti-D	Anti-T	Anti-IPV1	Anti-IPV2	Anti-IPV3	Anti-HB	Anti-Hib
Primary series at 2, 4, 6 months of age and booster at 12–24 months of age								
A3L27 [10] (A3L24)	HEX (396) [+HB]	97.9	100	98.8	99.4	95.9	97.5	73.4
	IFX (260) [+HB]	95.7	100	98.6	100	99.1	99.2	76.4
A3L21 [21] (A3L11)	HEX (177) [+HB]	92.0	100	100	100	96.5	89.8	86.9
	IFX (65) [+HB]	96.9	100	100	100	98.5	95.4	92.3
Primary series at 2, 3, 4 months of age and booster at 11–18 months of age								
A3L40 [8] (A3L39)	HEX (225) [–HB]	98.5	100	83.7	83.3	91.3	86.0	72.0
	IFX (218) [–HB]	99.5	100	93.6	90.7	93.5	97.2	57.7
HXM01C [6]	HEX + MenC (87) [–HB]	98.0	100	80.8	64.9	82.0	90.1	86.8
	HEX (91) [–HB]	99.3	100	84.7	76.0	82.0	90.1	77.3
A3L22 [9]	HEX (145) [–HB]	90.4	100	98.9	100	85.2	80.7	85.0
	PEN + ENG (141) [–HB]	88.3	100	98.8	97.7	96.3	99.0	83.3
Primary series at 6, 10 and 14 weeks of age and booster at 15–18 months of age								
A3L15 [23]	HEX (–HB) (204)	93.4	100	97.4	98.4	98.4	78.9	81.4
	CMB + ENG + OPV (–HB) (202)	86.1	100	94.2	99.5	97.9	92.0	92.5
	HEX (+HB) (116)	84.5	100	96.4	98.2	99.1	94.7	75.9
Primary series at 3, 5 months of age and booster at 11–12 months of age								
A3L38 [14] (A3L38)	HEX (249) [–HB]	98.3	100	62.9	60.7	66.1	87.6	50.6
	IFX (248) [–HB]	97.5	100	76.7	72.7	76.2	97.5	40.8

+HB/–HB, with/without HB vaccine at birth, *CMB* CombAct-Hib®, *D* diphtheria, *ENG* Engerix B® Pediatrico, *FHA* filamentous haemagglutinin, *HB* hepatitis B, *HEX* Hexyon®, *Hib H. influenzae* type b, *IFX* Infanrix hexa®, *IPV* inactivated polio virus, *MenC* meningococcal serogroup C conjugate vaccine, *OPV* oral polio vaccine, *PEN* Pentaxim®, *PT* pertussis, *T* tetanus

rates in infants primed at 2, 4 and 6 months [10, 21] (Table 2). However, in those primed at 2, 3 and 4 months [8] or 3 and 5 months [14], Hexyon® was associated with numerically lower (for anti-HB and anti-polio types 1–3) or higher (for anti-Hib) seroprotection rates than Infanrix hexa™ (Table 2). There were some numerical differences between the study vaccines in pre-booster GMCs/GMTs (e.g. lower for anti-polio types 1–3 [10, 21] and anti-HB [8, 14] in the Hexyon® group).

A booster dose of Hexyon® was associated with high seroprotection, seroconversion or vaccine response rates irrespective of whether the primary series vaccine was Hexyon® or Infanrix hexa™ [10, 21], suggesting that these two vaccines may be interchangeable for the booster dose (Table 3). Hexyon® booster was numerically similar to Infanrix hexa™ booster with respect to seroprotection or vaccine response rates for all antigens when the same vaccines had been used for a 3-dose primary series (Table 3) [8]. Following the 2 + 1 schedule, Hexyon® was noninferior to Infanrix hexa™ in terms of postdose 3 (i.e. post-booster) LTPT (anti-D, anti-T, anti-Hib), seroprotection (anti-HB, anti-polio types 1–3) or vaccine response (anti-PT, anti-FHA) rates (Table 3) [14]. Furthermore, post-booster LTPT rates with Hexyon® booster were similar to that with Infanrix hexa™ booster for anti-D (97–100% vs. 100%), anti-T (99–100% vs. 100%), anti-HB (91–99% vs. 98%), and anti-Hib (94–100% vs. 95–99%) [8,

10, 14, 21]. Administration of an extra polio vaccination with OPV (n = 164) between the primary series and the booster dose had no clinically relevant effect on the booster response to the IPV antigens of either Hexyon® or Infanrix hexa™ [10].

Infants vaccinated in A3L24 showed good persistence of antibodies to Hexyon® antigens up to pre-school age [5]. At 4.5 years, in infants primed and boosted with Hexyon®, seroprotection rates were 92% for anti-HB and 98–100% for anti-D, anti-T, anti-polio types 1–3, and anti-Hib, GMCs were 3.2 and 33.8 EU/mL for anti-PT and anti-FHA, and LTPT rates were 57.2%, 80.8%, 74.0%, and 85.6%, for anti-D, anti-T, anti-HB, and anti-Hib, respectively. Similar results were seen when primary or booster vaccines were interchanged between Hexyon® and Infanrix hexa™ [5]. In infants primed with Hexyon® or Infanrix hexa™ in A3L12, revaccination with a monovalent HB vaccine at age 9–10 years induced a strong anti-HB anamnestic response in both groups (seroprotection rate 92.8 vs. 98.7%; LTPT rate 89.9 vs. 97.4%; GMCs: 3692 vs. 4241 mIU/mL) [24].

2.3 Compared with Pentavalent (aP or wP) + Hepatitis B + Oral Polio Vaccines

The immunogenicity of Hexyon® primary series has been compared with that of a pentavalent vaccine, Pentaxim®

Table 3 Post-booster seroprotection, seroconversion and vaccine response rates for Hexyon® and comparators

Booster study (primary study)	Vaccine (primary→booster) (no. of subjects)	Anti-D	Anti-T	Anti-PT [VR[b]]	Anti-FHA [VR]	Anti-IPV1	Anti-IPV2	Anti-IPV3	Anti-HB	Anti-Hib
Booster at 12–24 months of age following primary series at 2, 4, 6 months of age										
A3L27 [10] (A3L24)	HEX → HEX (396)	100	100	92.9 [98.7]	87.5 [96.4]	100	100	100	99.7	99.7
	HEX → IFX (393)	100	100	93.9 [97.6]	88.8 [97.6]	100	100	100	99.5	100
	IFX → HEX (260)	100	100	92.9 [97.2]	93.3 [98.8]	100	100	100	100	100
A3L21 [21] (A3L11)	HEX → HEX (177)	99.4	100	91.8	86.7	100	100	100	99.4	100
	IFX → HEX (65)	98.5	100	88.9	87.3	100	100	100	100	100
Booster at 11–18 months of age following primary series at 2, 3, 4 months of age										
A3L40 [8] (A3L39)	HEX → HEX (225)	100	100	78.8	60.4	99.5	100	100	99.6	100
	IFX → IFX (218)	100	100	79.6	80.7	100	100	100	100	99.5
HXM01C [6] (HXM01C)	HEX ± MenC → HEX + Men-ACWY (87)	100	100	83.5 [98.8]	96.5 [100]	98.9	100	100	98.9	100
	HEX ± MenC → HEX (91)	100	100	88.4 [98.8]	92.1 [100]	98.9	100	100	98.9	100
A3L22 [9] (A3L10)	HEX → HEX (145)	100	100	96.5	91.8	100	100	100	97.3	100
	PEN + ENG → HEX (141)	100	100	96.2	97.4	100	100	100	98.6	100
Booster at 15–18 months of age following primary series at 6, 10 and 14 weeks of age										
A3L15 [23] (A3L15)	HEX (–HB) → HEX (204)	100	100	94.8	91.2	100	100	100	98.5	100
	CMB + ENG + OPV (–HB) → CMB + OPV (202)	100	100	83.5	96.5	97.4	100	98.9	NE	100
	HEX (+HB) → HEX (116)	100	100	93.9	94.7	100	100	100	100	100
Booster at 11–12 months of age following primary series at 3, 5 months of age										
A3L38[c] [14] (A3L38)	HEX → HEX (249)	100	100	94.0 [98.0[d]]	96.6 [100[d]]	100[d]	100[d]	99.6[d]	96.4[d]	99.6
	IFX → IFX (249)	99.6	100	99.2 [99.6]	95.8 [99.6]	100	100	99.6	99.6	98.8

+HB/−HB, with/without HB vaccine at birth, *AbC*, antibody concentration, CMB CombAct-Hib®, *D* diphtheria, *ENG* Engerix B® Pediatrico, *FHA* filamentous haemagglutinin, *HB* hepatitis B, *HEX* Hexyon®, *Hib H. influenzae* type b, *IFX* Infanrix hexa®, *IPV* inactivated polio virus, *LLOQ* lower limit of quantification, *MenACWY* meningococcal serogroup ACWY conjugate vaccine, *MenC* meningococcal serogroup C conjugate vaccine, *NE* not evaluated, *OPV* oral polio vaccine, *PEN* Pentaxim®, *PT* pertussis, *T* tetanus, *VR* vaccine response

[a]Coadministered with PCV 7 (A3L27), PCV 13 (A3L40, A3L38) or measles, mumps, rubella and varicella (A3L15) vaccines

[b]In A3L27, post-booster AbC ≥ LLOQ or ≥ prevaccination levels in initially seronegative or seropositive subjects, respectively. In all other studies, post-booster AbC ≥ 4 × LLOQ or ≥ prevaccination levels in subjects with prevaccination levels < 4 × LLOQ or ≥ 4 × LLOQ, respectively

[c]HEX was noninferior to IFX for anti-D ≥ 0.1 IU/mL (100 vs. 99.2%), anti-T ≥ 0.1 IU/mL (100 vs. 100%) and anti-Hib ≥ 1 μg/mL (93.5 vs. 85.2%)

[d]Noninferior to IFX

(DTaP-IPV liquid suspension used to reconstitute freeze-dried Hib), co-administered with a monovalent HB vaccine (Engerix B®, Euvax B® or Engerix B™ Pediatrico) in three trials (A3L10 [9], A3L31 [11] and A3L02 [18]). Participants in A3L31 had received HB vaccination at birth while those in A3L10 and A3L02 had not. All study vaccines were administered according to the standard [11, 18] or accelerated [9] schedule, with the exception of Euvax B® which was administered only at age 1 and 6 months [11]. A3L10 was followed by a booster study in which all eligible subjects received Hexyon® booster at age 15–18 months [9].

Hexyon® primary series was also compared with another pentavalent vaccine, Tritanrix-Hep B™/Hib [DTwP-Hep B suspension used to reconstitute freeze-dried Hib vaccine (Hiberix™)] + OPV, at age 2, 4 and 6 months in a safety study (A3L04) conducted in Latin America [22].

Hexyon® was noninferior to Pentaxim® + HB vaccine with respect to post-primary seroprotection or seroconversion rates for all antigens [11, 18] or anti-HB [9] (primary immunogenicity objective; Table 1). The vaccine response rates for anti-PT and anti-FHA were high and numerically similar between the vaccines (Table 1) [11]. There were some differences between Hexyon® and comparators in LTPT rates for

anti-D (64 vs. 68% [18]; 34 vs. 44% [9]), anti-HB (65 vs. 78% [9]) or anti-Hib (87 vs. 97% [11]; 73 vs. 77% [9]). Numerical differences noted between the groups in GMCs/GMTs were not considered to be clinically relevant [9, 11, 18]. In A3L04, post-primary seroprotection rate was 100% for anti-HB in both Hexyon® and Tritanrix-Hep B™/Hib groups, with a LTPT rate of ≥ 96.2%; however, anti-HB GMC was 3-fold lower with Hexyon® versus comparator [22].

The majority of participants primed with Hexyon® or Pentaxim® + Engerix B® remained seroprotected against anti-D, anti-T, anti-polio types 1–3, anti-HB and anti-Hib before the booster dose (Table 2) [9]. However, pre-booster seroprotection rate and GMCs for anti-HB were significantly (based on 95% CI) lower in the Hexyon® than in the comparator group, with 33.9 and 76.7% of participants in the respective groups achieving anti-HB LTPT [9].

A Hexyon® booster dose was associated with high and similar seroprotection or seroconversion rates for all antigens, irrespective of the primary series vaccine used (Hexyon® or Pentaxim® + Engerix B®) (Table 3) [9]. While the post-booster anti-HB seroprotection rate was similar between the groups, GMCs were significantly (based on 95% CI) lower in infants primed with Hexyon®. Post-booster LTPT rates were similar in infants primed with Hexyon® and those primed with Pentaxim® + Engerix B® for anti-D (99.1 vs. 100%), anti-T (100 vs. 100%), anti-HB (86.5 vs. 93%), and anti-Hib (98.2 vs. 100%) [9].

2.4 Compared with Quadrivalent (DTwP/Hib) + Hepatitis B + Oral Polio Vaccines

The immunogenicity of Hexyon® primary series administered at age 6, 10 and 14 weeks has been compared with that of a quadrivalent vaccine, CombAct-Hib™ (DTwP liquid suspension used to reconstitute freeze-dried Hib vaccine) + Engerix B™ Pediatric + OPV (A3L15) [17]. Both study arms enrolled infants who had not received a HB vaccine at birth. A3L15 also included a Hexyon® arm that enrolled infants who had received a HB vaccine at birth. Thus, this study allowed directly comparing aP versus wP, IPV versus OPV, and Hexyon® with or without HB vaccination at birth. Eligible participants completing the primary series received a booster dose of the respective primary vaccines (Engerix B™ Pediatric was not included in the comparator arm) at age 15–18 months [23]. A3L15 was followed up to 4.5 years to evaluate the long-term persistence of antibodies [5]. Results for Hexyon® and the comparator vaccine arms are discussed here; results for Hexyon® arms with or without HB vaccine at birth are discussed in Sect. 2.1.

Hexyon® was noninferior to CombAct-Hib™ + Engerix B® Pediatric + OPV with respect to post-primary seroprotection rates for anti-D, anti-T, anti-polio types 1–3, anti-HB, and anti-Hib (primary objective;

Table 1) [17]. Anti-PT and anti-FHA seroconversion rates were numerically higher with Hexyon® than with the comparator. In Hexyon® recipients, LTPT rates were numerically higher for anti-D (40 vs. 14%) and lower for anti-Hib (80 vs. 93%) than in those receiving the comparator. Anti-HB GMC was 2.2-fold higher and anti-FHA GMC was 5.5-fold higher with Hexyon® relative to the comparator [17].

The majority of participants in both groups remained seroprotected against all antigens before the booster dose, with seroprotective rates (and GMCs) for anti-HB and anti-Hib being numerically lower with Hexyon® (Table 2) [23].

Post-booster seroprotection or seroconversion rates with Hexyon® were numerically similar (anti-D, anti-T, anti-polio types 1–3, anti-Hib), higher (anti-PT), and lower (anti-FHA) relative to the comparator (Table 3) [23]. LTPT rates were high and similar between the groups for anti-D (100 vs. 99%), anti-T (100 vs. 100%), and anti-Hib (99 vs. 99%). The seroprotection and LTPT rates for anti-HB were 98.5 and 93.9% with Hexyon®. GMCs/GMTs were numerically higher with Hexyon® for all antigens, although these differences were not reflected in the seroprotection or seroconversion rates [23].

Antibody persistence was demonstrated for all antigens in Hexyon® and comparator groups at 3.5 and 4.5 years [5]. At 4.5 years, in the Hexyon® group, seroprotection rates were 98.2, 100, 73.3 and 98.8% for anti-D, anti-T, anti-HB, and anti-Hib, respectively (vs. 87.5, 100, 68.5 and 98.8% with comparator). LTPT rates were numerically higher in the Hexyon® than in the comparator group for anti-D (75 vs. 33%) and anti-HB (40 vs. 17%), and were similar in both groups for anti-T (90 vs. 85%) and anti-Hib (85 vs. 84%). GMCs were higher with Hexyon® for anti-D (5.7-fold), anti-T (2-fold), anti-FHA (3.3-fold) and anti-HB (2.4-fold), and were similar between the groups for anti-PT and anti-Hib [5].

3 Coadministration with Other Vaccines

Coadministration of Hexyon® primary series with MenC (NeisVac-C®) did not affect the immunogenicity of either vaccine in a comparative study (HXM01C) [12]. Participants were randomized to Hexyon® accelerated schedule, with or without MenC administered at age 2 and 4 months. In both groups, PCV13 was administered at age 2 and 4 months, and rotavirus vaccine at age 2, 3, and 4 months. Hexyon® + MenC was noninferior to Hexyon® with respect to anti-HB post-primary seroprotection rate (coprimary objective; Table 1). For all other antigens, seroprotection, seroconversion or vaccine response rates were numerically similar between the groups (Table 1), with some minor differences observed in GMCs/GMTs. Post-primary seroprotection rate for MenC was 100% (95% CI 97.7–100), which met the acceptability criteria of the lower bound of the 95% CI being > 90% (coprimary objective) [12].

The use of MenC in primary series did not preclude the use of MenACWY (Nimenrix®) for booster vaccination [6]. Participants who completed HXM01C were randomized to booster vaccination at 12 months with Hexyon® + MenACWY, Hexyon® alone or MenACWY alone (groups A, B, and C, respectively). Post-booster seroprotection or vaccine response rates for all Hexyon® antigens were numerically similar in groups A and B (Table 3) [6]. The proportion of participants with an antibody titer level of ≥ 8 1/dil for anti-MenA, anti-MenC, anti-MenW, and anti-MenY was high in both group A (98.9–100%) and group C (95.7–100%) [6].

In A3L39, coadministration of one dose of MenC at age 2 months with the mixed hexavalent-pentavalent-hexavalent primary series did not adversely affect the immune response to Hexyon® antigens; PCV13 and rotavirus vaccine were also coadministered in this study [7].

Coadministration of PCV7 and rotavirus vaccine [10] or PCV7 [20] with Hexyon® primary series, and PCV7 [10], PCV13 [14] or MMRV [23] with Hexyon® booster did not adversely affect immune responses to any vaccines. Post-primary seroprotection rates were > 95% for each of the seven PCV7 antigens and 84% for anti-rotavirus [10]. Post-booster seroprotection rates were > 95% for 12 of the 13 PCV13 antigens, anti-measles, anti-mumps, and anti-rubella (86% for anti-pneumo 3 and 74–75% for anti-varicella) [14, 23].

4 Reactogenicity and Safety of Hexyon®

Hexyon® as primary and booster vaccination was well tolerated in infants aged < 24 months in clinical trials discussed in Sect. 2. The incidences of severe solicited adverse reactions (SARs), vaccine-related unsolicited adverse events (UAEs) and serious adverse events (SAEs) were low in Hexyon® recipients [6–14, 17–23]. In an integrated analysis of 11 primary and booster studies of Hexyon® (n = 3896), 205 Hexyon® recipients (5.3%) reported a total of 247 SAEs, of which only one (hypotonic hyporesponsive episode) was considered related to the vaccine [26]. The most frequently reported SAEs were of infectious nature and included gastroenteritis (51 participants), bronchiolitis (30), bronchopneumonia (23), and pneumonia (22). SAEs also included febrile convulsions (13) and convulsion (1). The incidence of SAEs was generally similar between Hexyon® and comparator groups [26]. The reactogenicity and safety profile of Hexyon® booster dose did not vary according to the primary vaccine received (Hexyon®, Infanrix hexa®, or Pentaxim® + Engerix B®) [9, 10, 21]. Hexyon® was also generally well tolerated when coadministered with pneumococcal, rotavirus, MMRV or meningococcal vaccines [6, 7, 10, 12, 14, 17, 20], although there was a trend towards increased reactogenicity when coadministered with meningococcal vaccines [6, 12].

The reactogenicity and safety of Hexyon® in 399 preterm infants (25–36 weeks of gestation), as reported by their parents after the first dose, was evaluated in a post-marketing surveillance in 2017 in Italy (poster [27]). The most common injection site reactions were pain (35.7%), redness (27.1%), swelling (26.5%), nodule (25.7%), and induration (24.8%). The most common systemic adverse events were irritability (27.4%), fever (≥ 38 °C; 22.4%), somnolence (16.2%) and loss of appetite (8.8%). In preterm infants, injection site induration and nodule, and cutaneous rash were more frequent, while loss of appetite, vomiting and persistent crying were less frequent, compared with the expected frequencies in full-term-born infants [27].

4.1 Solicited Adverse Reactions

Solicited injection-site (pain, erythema, and swelling) and systemic (pyrexia, vomiting, crying, somnolence, anorexia, and irritability) reactions occurring within the first 7 days after each vaccination were the main focus of the reactogenicity assessment in all studies [6–14, 17–23]. The majority of Hexyon® primary series recipients experienced SARs, although most reactions were grade 1 or 2 in severity. Across the trials (n = 132–1423), the incidences of SARs after any primary dose of Hexyon® were: pain, any grade 62–90% (grade 3, 2–27%), erythema 34–68% (0.7–4.5%), swelling 24–55% (0.5–5%), pyrexia 20–75% (0–4%), vomiting 18–50% (0–18%), crying 48–81% (1–17%), somnolence 43–86% (2–20%), anorexia 25–56% (0–11%), and irritability 52–94% (0–20%) [8–12, 14, 17–22]. The incidences of SARs after the booster dose were generally lower than after a primary dose [8–10, 21, 23].

Hexyon® was largely similar to Infanrix hexa™ in terms of SARs [8, 10, 14, 19–21]. The incidence of SARs in the two vaccine groups in a representative large trial is shown in Fig. 1 [10].

Hexyon® was slightly more reactogenic than Pentaxim® regarding solicited injection site reactions [9, 11, 18], particularly after the first and second primary dose [9, 11]. Hexyon® was also associated with a slightly higher incidences of any grade pyrexia and crying, compared with Pentaxim® + Euvax B®/Engerix B® [9, 11, 18]. The incidences of grade 3 SARs were generally similar between the study vaccines [9, 11, 18].

Hexyon® appeared to be less reactogenic than CombAct-Hib™ with respect to each type of solicited injection site reaction in the primary [17] and booster [23] studies. Hexyon® was generally similar to CombAct-Hib™ + Engerix B® Pediatric + OPV with regards to solicited systemic reactions, with the exception of any grade pyrexia (44.5 vs. 33.2%) and anorexia (46.6 vs. 55.9%) [17].

The reactogenicity profile of Hexyon® was slightly better than that of Tritanrix-Hep B™/Hib + OPV in the safety study

(A3L04) [22]. Hexyon® was similar to the comparator with respect to the incidence of severe fever after any dose (3.97% vs. 5.55%; risk ratio 0.715; 95% CI 0.48–1.066) [primary safety assessment]. However, apart from vomiting (which was generally similar between the groups), the incidence of solicited injection-site and systemic reactions were numerically lower with Hexyon® than with the comparator [22].

4.2 Unsolicited Adverse Events

Immediate UAEs (occurring within 30 minutes of vaccination) were absent [9, 11, 13, 19–21] or were reported in 0.2–5% of Hexyon® recipients [8, 10, 17, 18]. Those considered vaccine-related included rhinopharyngitis, enteritis, erythema, and cough. UAEs occurring within 30 days of vaccination were reported in 11–82% and 15–48% of participants receiving Hexyon® primary series and the booster dose, respectively [6, 8–14, 17, 19–23]; however, where reported, the incidence of vaccine-related 30-day UAEs was 0–6% [8, 10, 11, 19–21]. There were no clinically relevant differences between Hexyon® and comparator vaccines with respect to immediate or 30-day UAEs.

5 Dosage and Administration of Hexyon®

Hexyon® is available as a fully liquid 0.5 mL suspension for intramuscular injection and is indicated in the EU for primary and booster vaccination of infants and toddlers from age 6 weeks against diphtheria, tetanus, pertussis, HB, poliomyelitis and invasive diseases caused by Hib [3].
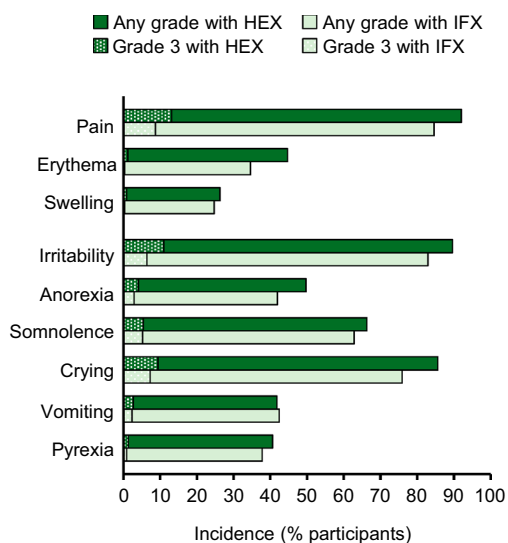

Fig. 1 Incidence of solicited adverse events occurring within 7 days after any primary vaccination in Hexyon® (*n* = 1030) and Infanrix hexa™ (*n* = 345) recipients in a representative study (A3L24) [10]. *HEX* Hexyon®, *IFX* Infanrix hexa™

Primary vaccination consists of two doses at least 8 weeks apart or three doses at least 4 weeks apart and can be administered irrespective of whether or not a dose of HB vaccine has been administered at birth. Hexyon® can be used for a mixed primary vaccination schedule of hexavalent-pentavalent-hexavalent vaccines. A booster dose of Hexyon® must be given at least 6 months after the last priming dose. In addition, where required, Hexyon® can be considered for HB or polio vaccine booster dose and may be used as a booster following another hexavalent vaccine or a pentavalent vaccine plus a monovalent HB vaccine. All doses of Hexyon® should be administered in accordance with the official recommendations [3]. Consult local prescribing information for full details of administration method, contraindications, special warnings and precautions, and potential risks.

6 Place of Hexyon® in the Prevention of Major Childhood Diseases

Vaccination against diphtheria, tetanus, pertussis, poliomyelitis, and invasive diseases caused by HB and Hib is recommended (mandatory in 11 countries) in Europe [28, 29]. Owing to their benefits (Sect. 1), hexavalent vaccines have become a cornerstone in pediatric immunization against these diseases worldwide. Hexavalent vaccines are used in almost all EU countries. Currently, three hexavalent vaccines (Hexyon®, Infanrix hexa™, and Vaxelis®) are available in Europe [1]. These vaccines differ from each other in formulation and/or composition [4, 30, 31].

All components used in Hexyon®, except the HB antigen, have been extensively used in other approved pediatric vaccines (Pentavac®/Pentaxim®; Tetravac®/Tetraxim®; Imovax Polio®; Act-HIB®), and have well established immunogenicity and reactogenicity profiles [32, 33]. Furthermore, the immunogenicity of Hexyon® was evaluated in a large number of well-designed clinical trials, following WHO and EMA recommendations for evaluating new vaccines [26]. Hexyon® was tested in all major primary vaccination schedules (including those recommended by WHO [26]), using approved vaccines as comparators. In these trials, Hexyon® primary series starting at 6 weeks of age induced high levels of seroprotection, seroconversion or vaccine response rates for all its components, regardless of vaccination schedules; good antibody persistence was seen before the booster dose (Sect. 2.1). A Hexyon® booster dose at age 11–24 months further strengthened or maintained the immune responses, irrespective of the primary series vaccines used. Of note, after the Hexyon® booster dose, the majority of participants achieved antibody threshold levels indicative of long-term protection for anti-D, anti-T, anti-Hib, and anti-HB. Coadministration of

Hexyon® with other childhood vaccines did not adversely affect the immunogenicity of any vaccines.

Hexyon® was noninferior to Infanrix hexa™, with respect to post-primary (after a 3-dose primary series) or post-booster (after a 2 + 1 schedule) seroprotection or vaccine response rates for all Hexyon® antigens (Sect. 2.2). At 4.5 years, seroprotection rates remained high and similar in Hexyon® and Infanrix hexa™ recipients. Hexyon® was also noninferior to approved pentavalent (Sect. 2.3) or quadrivalent (Sect. 2.4) vaccines coadministered with monovalent HB vaccines or OPV in terms of post-primary seroprotection or seroconversion rates.

The HBsAg used in Hexyon® is derived from the yeast *H. polymorpha*, whereas that used in Infanrix hexa™ or monovalent HB vaccines is derived from the yeast *Saccharomices cerevisiae*. Thus, the anti-HB response to Hexyon® is of particular interest. The immunogenicity and safety of *H. polymorpha*-derived HBsAg was confirmed in adolescents and adults before inclusion in Hexyon® [34]. In Hexyon® recipients, anti-HB seroprotection rates were ≥ 94% after primary series, ≥ 96% after the booster dose, and 92% at 4.5 years of age (Sect. 2). Administration of HB vaccination at birth had a positive effect on anti-HB response to Hexyon®. Pre-booster and post-booster GMCs, and post-booster LTPT rates were numerically lower with Hexyon® than with comparator vaccines. Although higher anti-HB GMCs may, theoretically, be associated with greater antibody persistence, breakthrough HB infection seems to be dependent on immune memory rather than anti-HB antibody levels [26]. In fact, revaccination of Hexyon® primary series recipients with a HB vaccine at age 9–10 years induced a strong anti-HB anamnestic response (Sect. 2.2). Thus, the available data indicate a good persistence of anti-HB immunity during the first 2 years of life and a strong anamnestic response in the long term after vaccination with Hexyon®, irrespective of the vaccination schedule [35].

Hexyon®, Infanrix hexa™, and Vaxelis® contains 2, 3, and 5 aP antigens, respectively [36]. As stated in the most recent WHO position paper, current evidence is inadequate to establish any significant difference in vaccine effectiveness of aP vaccines with differing number of aP antigens [37]. In a large-scale Swedish pertussis surveillance program, the level of pertussis control achieved among cohorts vaccinated with Pentavac® (which contains the same pertussis antigens as Hexyon®) was similar to that observed in the overall population receiving 2- or 3-component aP vaccines [38]. When a two component aP vaccine (containing the same antigens as Hexyon®) was compared with a wP vaccine in a randomized, double-blind trial, the absolute vaccine efficacy based on PCR confirmation was 85% (95% CI 66–93) and 96% (95% CI 86–99), respectively [39]. The efficacy of aP vaccines tends to wane over time and a booster dose at age 5–7 years is necessary [40–42].

The Hib antigen (PRP) in Hexyon® and comparator vaccines are conjugated to T, with the exception of Vaxelis® in which PRP is conjugated to the outer membrane protein complex (OMPC) of *Neisseria meningitides*. PRP-T elicits a strong immune response after a full primary series and a booster dose; whereas, PRP-OMPC is known to elicit a strong immune response just after one primary dose and a relatively weaker response after a booster dose [43]. Although protective efficacy and effectiveness data for Hexyon® against Hib are not available, surveillance data indicate that the introduction of Hib conjugated vaccines in general dramatically decreased the incidences of invasive Hib diseases in Europe [44]. For example, in France, where PRP-T vaccines are used, the incidence of invasive Hib disease declined by 96% in children aged < 5 years in 15 years after its introduction [45]. In Germany, the effectiveness of full immunization with PRP-T-containing hexavalent vaccines against Hib diseases was estimated to be 100% during the post-licensure period of 5 years [46].

Hexyon® was well tolerated in clinical trials, including when coadministered with common childhood vaccines, in infants aged < 24 months (Sect. 4). Hexyon® was slightly more reactogenic than Infanrix hexa™ or Pentaxim® and slightly less reactogenic than CombAct-Hib™ or Tritanrix-Hep B™/Hib + OPV. However, the overall safety profile of all vaccines was broadly similar.

Hexyon® (and Vaxelis®) is a fully-liquid, ready-to-use vaccine, whereas Infanrix hexa™ requires reconstitution of the Hib antigen with other components prior to administration. Compared with vaccines which require reconstitution, fully-liquid vaccines reduce vaccination errors and preparation time, and therefore, provide greater satisfaction among healthcare professionals [47]. For example, a survey of French physicians suggest that vaccine reconstitution is a complicating factor in pediatric immunization and is associated with errors and time loss, although it allows more time to talk to parents or distract the infant [48]. Similarly, German healthcare professionals preferred fully-liquid hexavalent vaccines over those requiring reconstitution because of decreased preparation time and reduced risk of handling and dosage errors [49]. These findings are supported by an open-label, randomized Belgian study in which a fully-liquid vaccine reduced preparation time (36 vs. 70.5 s) and immunization errors (10 vs. 47 on 192 preparations) versus a non-fully liquid vaccine, with 98% of healthcare professionals preferring the fully-liquid vaccine [50].

Given the availability of several combination vaccines, interchangeability of vaccines is important because the previous vaccine given may not be known, not accessible or no longer available. Hexyon® offers the convenience of interchangeability; Hexyon® may be used for a mixed primary schedule or as a booster in infants primed with Infanrix hexa™ or pentavalent vaccines [3].

Currently, there is limited data on the immunogenicity and safety of Hexyon® in immunosuppressed or premature

infants. Furthermore, there is no direct data on the protective efficacy and effectiveness of this vaccine against its target diseases.

In conclusion, Hexyon® was highly immunogenic, safe and generally well tolerated when used as primary and booster vaccination of infants and toddlers from 6 weeks of age against diphtheria, tetanus, pertussis, poliomyelitis and invasive diseases caused by HB and Hib, irrespective of immunization schedules. Hexyon® provides durable protection against HB. The immunogenicity and safety profile of Hexyon® was similar to that of Infanrix hexa™ and pentavalent or quadrivalent combination vaccines. However, Hexyon® offers the convenience of a fully-liquid, ready-to-use- vaccine, which may minimize vaccination errors and preparation time. Available data suggest that Hexyon® is a convenient, useful option for vaccination against childhood diseases caused by six major pathogens.

Data Selection Hexyon: 145 records identified	
Duplicates removed	25
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	37
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	33
Cited efficacy/tolerability articles	20
Cited articles not efficacy/tolerability	30

Search Strategy: EMBASE, MEDLINE and PubMed from 2013 to present. Previous Adis Drug Evaluation published in 2013 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Hexaxim, Hexyon, Hexacima, DTaP-IPV-HepB-Hib. Records were limited to those in English language. Searches last updated 15 July 2019.

Compliance with Ethical Standards

Conflicts of interest Yahiya Syed is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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