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ADIS DRUG EVALUATION

DTaP5-HB-IPV-Hib Vaccine (Vaxelis®): A Review of its Use in Primary and Booster Vaccination

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Abstract Vaxelis® is a fully liquid, ready-to-use, hexavalent vaccine approved in the EU for primary and booster vaccination in infants and toddlers from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib). It contains diphtheria and tetanus toxoids, five acellular pertussis antigens, recombinant hepatitis B virus surface antigen produced in the yeast, *Saccharomyces cerevisiae*, inactivated poliovirus, and the Hib polysaccharide (polyribosylribitol phosphate) conjugated to the outer membrane protein complex of *Neisseria meningitidis*. In pivotal clinical studies, Vaxelis® was highly immunogenic for all its component toxoids/antigens when administered by three different schedules. Primary endpoints of seroprotection or vaccine response rates with Vaxelis® met the predefined acceptability criteria and were noninferior to those with comparator vaccines (Infanrix® hexa or Pentacel® plus Recombivax HB®). Limited data indicate that immune responses to Vaxelis® in preterm infants were generally similar to those seen in the overall population. Vaxelis® can be coadministered with a number of common childhood vaccines. In clinical studies, Vaxelis® was generally well tolerated with a tolerability profile similar to that of the comparator vaccines. Available clinical data indicate that Vaxelis® is a new hexavalent vaccine option for immunization against several serious childhood infectious diseases.

Vaxelis®: clinical considerations in primary and booster vaccination

Pediatric hexavalent vaccine, approved in the EU for primary and booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by *Haemophilus influenzae* type b (Hib)

Produces acceptable seroprotection or vaccine responses after primary and/or booster vaccinations

Noninferior to Infanrix® hexa or Pentacel® plus Recombivax HB® in terms of seroprotection or vaccine response

Generally well tolerated

First hexavalent, fully liquid vaccine to contain five pertussis antigens and the Hib antigen conjugated to the meningococcus outer membrane protein complex

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1 Introduction

Most European countries recommend vaccination of infants against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive diseases caused by *Haemophilus influenzae* type b (Hib) [1]. Combination vaccines against these diseases have become the cornerstone of pediatric

immunization programs [2, 3], because they simplify complex immunization schedules, minimize the number of injections and associated complications, reduce cost, decrease the risk of noncompliance, and provide better vaccination coverage [4, 5].

A combination of diphtheria and tetanus toxoids, and acellular pertussis antigens (DTaP) is combined with inactivated poliovirus (IPV) and antigens for hepatitis B and/or Hib to produce pentavalent and hexavalent vaccines. A hexavalent vaccine (Hexavac™) was withdrawn from the market because of suboptimal long-term immunogenicity against hepatitis B [6]. Currently available hexavalent vaccines in the EU include Hexaxim® (Hexacima® or Hexyon® in the EU) [7], Infanrix® hexa [6], and the most recently approved Vaxelis® [diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and haemophilus type b conjugate vaccine (adsorbed)] [8].

Vaxelis® contains the following components: diphtheria toxoid (D); tetanus toxoid (T); five acellular pertussis antigens [pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)]; recombinant hepatitis B virus surface antigen (HBsAg) produced in the yeast *Saccharomyces cerevisiae*; IPV (type 1, 2, and 3; Maoney, MEF-1, and Saukett strains, respectively) produced in Vero cells; and, the Hib capsular polysaccharide polyribosylribitol phosphate (PRP), conjugated to the outer membrane protein complex (OMPC) of *Neisseria meningitidis* (PRP-OMPC) [8].

While Vaxelis® contains five pertussis antigens, Hexaxim® and Infanrix® hexa contain two and three pertussis antigens, respectively (Table 1). Furthermore, the PRP in Vaxelis® is conjugated to OMPC, whereas it is conjugated to T (PRP-T) in the other two vaccines. Of note, the OMPC carrier is associated with more rapid immunogenicity against Hib after primary vaccination than the T carrier [9]. Thus, Vaxelis® is the first fully liquid hexavalent vaccine to contain five pertussis antigens and PRP-OMPC. Other notable differences between Vaxelis® and Hexaxim® include the yeast from which HBsAg is derived (*S. cerevisiae* vs. *Hansenula polymorpha*) and the aluminum salt content (0.32 vs. 0.6 mg) [8, 10].

This article narratively reviews the immunogenicity and reactogenicity of Vaxelis® as primary and booster vaccination in clinical studies in infants aged ≥6 weeks, as approved in the EU. Supportive data from US clinical studies are also discussed.

2 Immunogenicity of Vaxelis®

2.1 Early-Phase Studies

Initial phase 1 [11] and phase 2a [12, 13] studies evaluated the immunogenicity of hexavalent vaccine formulations containing PRP-T 12 μg or PRP-OMPC 3 or 6 μg, and HBsAg 10 or 15 μg in infants. The PRP-T-containing formulation did not meet the predefined acceptability criterion for PRP response rate after a three-dose primary series [12, 13], although it did meet this criterion after a booster dose in infants primed with the same or a pentavalent vaccine [11–13]. On the other hand, all PRP-OMPC-containing formulations met the acceptability criterion for all antigens after the primary series [12, 13]. Furthermore, a formulation containing the lowest concentration of PRP-OMPC and HBsAg (3 and 10 μg, respectively) was associated with a better tolerability profile, and hence, selected for further clinical development [9].

In a phase 2b trial ($n = 460$) conducted in Canada (study 004), Vaxelis® produced a robust antibody response after a three-dose primary series at 2, 4, and 6 months of age [14] and after a booster dose at 15 months of age [15]. Seroprotection or seroconversion rates were acceptable for all but FHA antigen after the primary series and for all antigens after the booster dose [14, 15]. These results

Table 1 Composition per one dose (0.5 mL) of Vaxelis® and other hexavalent or comparator vaccines

Vaccines	D (IU)	T (IU)	PT (μg)	FHA (μg)	PRN (μg)	FIM (μg)	IPVI (DAU)	IPV2 (DAU)	IPV3 (DAU)	PRP [conjugate, μg] (μg)	HBsAg (μg)
Vaxelis® [8]	≥20	≥40	20	20	3	5	40	8	32	3 [OMPC, 50]	10
Hexaxim® [10]	≥20	≥40	25	25	–	–	40	8	32	12 [T, 22–36]	10
Infanrix® hexa [26]	≥30	≥40	25	25	8	–	40	8	32	10 [T, 20–40]	10
Pentacel® [27]	≥20	≥40	20	20	3	5	40	8	32	10 [T, 24]	–
Daptacel® [28]	≥20	≥40	10	5	3	5	–	–	–	–	–
Recombivax HB® [29]	–	–	–	–	–	–	–	–	–	–	10
Pedvax HIB® [30]	–	–	–	–	–	–	–	–	–	7.5 [OMPC, 125]	–
Act-HIB® [31]	–	–	–	–	–	–	–	–	–	10 [T, 18–30]	–

DAU D antigen units, *D* diphtheria toxoid, *FHA* filamentous haemagglutinin, *FIM* fimbriae types 2 and 3, *HBsAg* recombinant hepatitis B virus surface antigen, *IPV1/2/3* inactivated poliovirus types 1/2/3, *IU* international unit, *OMPC* outer membrane protein complex of *Neisseria meningitidis*, *PRN* pertactin, *PRP* polyribosylribitol phosphate, *PT* pertussis toxoid, *T* tetanus toxoid, – not present

supported the initiation of the phase 3 clinical trial program for Vaxelis®.

2.2 Phase 3 Pivotal Studies

Vaxelis® as a primary and booster vaccination elicited robust immunogenic responses against all its component toxoids/antigens in healthy infants in four pivotal phase 3 studies, regardless of vaccination schedules. These studies were conducted in the EU (studies 007 [16] and 008 [17]) and in the USA (studies 005 [18] and 006 [19]). Additional data from the US studies are available in the US ClinicalTrials.gov registry [20, 21] and the European public assessment report for Vaxelis® [9].

All studies were randomized, and were double-blind (studies 007 and 008), partial double-blind (study 006) or open-label (study 005). The EU studies compared Vaxelis® with Infanrix® hexa, administered as a three- or two-dose primary series and a booster dose. The US studies compared Vaxelis® with a pentavalent (Pentacel®) plus a hepatitis B vaccine (Recombivax HB®, known as HBVaxPRO® in the EU), administered as a three-dose primary series, followed by a booster dose with a DTaP plus Hib vaccine or Pentacel®. In all studies, test vaccines were coadministered with other childhood vaccines. The qualitative and quantitative composition of test vaccines are shown in Table 1. Vaccination schedules and coadministered vaccines are shown in Tables 2 and 3.

The pivotal studies enrolled healthy infants aged 46–89 days (including preterm infants), without a personal or maternal history of HBsAg seropositivity [16–19]. Eligible infants in the US studies had received hepatitis B vaccination at birth as part of the standard-of-care [18, 19] and those in the EU studies were naïve to test vaccines [16, 17]. Exclusion criteria included previous use of, or expected to use, immunosuppressive agents or systemic steroids, and febrile illness or rectal temperature of ≥38.0 °C within 24 h before enrolment [16–19].

The immunogenicity of the test and coadministered vaccines was assessed in terms of geometric mean concentrations (GMCs) or geometric mean titers (GMTs) of serum antibodies against their component toxoids/antigens and seroprotection or vaccine response rates [16–19]. The seroprotection rate was generally defined as the proportion of subjects achieving the antibody thresholds of ≥0.1 IU/mL against D and T, ≥0.15 and ≥1.0 µg/mL for PRP (correlates of short-and long-term seroprotection, respectively), ≥10 mIU/mL for HBsAg and ≥8 dil^{-1} against IPV type 1, 2, and 3 antigens. Studies 007 and 008 used a lower threshold for D and T (≥0.01 IU/mL) and the lowest threshold for PRP (≥0.15 µg/mL) for assessing the seroprotection rate after the primary series [16, 17].

In the absence of generally accepted seroprotective threshold levels for pertussis antigens, vaccine response rates to these antigens was assessed, defined as the proportion of subjects achieving the following threshold: if prevaccination antibody concentration (Ab) was <4 × lower limit of quantification (LLoQ), then the postvaccination Ab was ≥4 × LLoQ, and if prevaccination Ab was ≥4 × LLoQ, then the postvaccination Ab was ≥prevaccination Ab (studies 007 [16], 005 [18] and 006 [19]); if prevaccination Ab was lower than LLoQ, then the postvaccination Ab was ≥LLoQ, and if prevaccination Ab was ≥LLoQ, then the postvaccination Ab was ≥prevaccination Ab (study 008 [17]).

Blood samples for immunogenicity analyses were drawn before the first dose and ≈1 month after the final dose for primary vaccination, and prior to and ≈1 month after the booster dose [16–19]. The coprimary endpoints were acceptability and/or noninferiority (using 5–10% margin) of seroprotection or vaccine response rates (studies 007, 008, and 005), and noninferiority of GMCs based on a Vaxelis® to comparator ratio of ≥0.67). Acceptability criteria were met if the lower limit of the two-sided 95% confidence interval (CI) for seroprotection or vaccine response rates was greater than predefined lower limits (75−90%, depending on the expected rates) [16–19]. The primary objective of study 006 was to determine the consistency of the immunogenicity between three lots of Vaxelis®; post-primary series GMC/GMT data showed that immune responses against each antigen were consistent across the lots [19].

2.2.1 *Response to Pertussis Antigens*

As Primary Vaccination Two- or three-dose primary series vaccination with Vaxelis® elicited strong immunogenic responses against PT and FIM, but slightly weaker responses against FHA and PRN [16–21]. Vaccine response rates in Vaxelis® recipients were 98.1−99.4% against PT, 89.7−97.2% against FIM, 87.3−89.0% against FHA, and 79.4−86.7% against PRN (Table 2).

Based on 95% CIs, vaccine response rates were similar between Vaxelis® and Infanrix® hexa recipients for PT, but lower with Vaxelis® for FHA and PRN (Table 2) [16, 17]. These results were consistent with GMC values, which were higher for PT and lower for FHA and PRN in the Vaxelis® group, compared with the Infanrix® hexa group. Vaxelis® elicited robust immunogenicity against FIM, which is not present in Infanrix® hexa (Table 2) [16, 17]

Vaxelis® was noninferior to Pentacel® plus Recombivax HB® in terms of vaccine response rates for all pertussis antigens and in terms of GMCs of antibodies against PT, PRN, and FIM, whereas the noninferiority criteria was not

Table 2 Immunogenicity of Vaxelis® against pertussis antigens in healthy infants in pivotal clinical trials

Study	Vaccine (no. of subjects)	Time point	Vaccine response rate (% of sub)				Geometric mean concentrations (EU/mL; [before booster])			
			PT	FHA	PRN	FIM	PT	FHA	PRN	FIM
Primary series at 2, 3, and 4 months of age and booster dose at 12 months of age[a]										
007 [16]	Vaxelis® (611)	PS	99.4	89.0	86.7	97.2	129.6*	49.5	46.8	353.6
		BD	99.8[b,c]	97.2[b,c]	98.9[b,c]	99.6	[12.9] 196.8*	[8.6] 121.6	[11.5] 166.7	[46.0] 803.8
	Infanrix® hexa (606)	PS	98.6	96.7*	92.3*	–	83.7	96.8*	77.8*	–
		BD	98.5	99.8*	98.9	–	[13.5] 90.7	[22.8*] 196.5*	[12.1] 182.1	–
Primary series at 2 and 4 months of age and booster dose at 11−12 months of age[a]										
008 [17]	Vaxelis® (656)	PS	98.1	89.0	80.3	93.3	113.1*	44.5	37.8	231.7
		BD	99.1[b, c]	97.4[b,c]	96.9[b,c]	98.3	[11.2] 157.4*	[8.1] 120.8	[6.5] 104.3	[29.1] 553.6
	Infanrix® hexa (659)	PS	99.0	96.5*	91.6*	–	92.4	86.6*	78.3*	–
		BD	99.6	99.1	98.3	–	[15.4*] 110.0	[22.7*] 204.2*	[11.0*] 153.5*	–
Primary series at 2, 4, and 6 months of age[a] and booster dose at 12 months of age[d]										
005 [18, 20]	Vaxelis® (986)	PS	98.1[c]	87.3[c]	79.4[c]	90.2[c]	109.6[c]	46.6[c]	55.8[c]	235.9[c]
		BD	99.3[c]	94.4[c]	93.0[c]	97.3[c]	126.9[c]	87.5[c]	108.5[c]	657.3[c]
	Pentacel® + HBV[e] (487)	PS	98.5	92.1	82.1	86.2	85.4	72.3	66.8	184.4
		BD	97.4	93.1	93.5	91.2	90.8	87.5	139.7	415
006 [19, 21]	Vaxelis® (2406)[f]	PS	98.6[g]	87.4[g]	79.5[g]	89.7[g]	95.6[c]	46.5[c]	52.8[c]	255.3[c]
		BD	98.5[g]	95.3[g]	92.2[g]	93.0[g]	104.9[g]	99.0[g]	105.3[g]	426.4[g]
	Pentacel® + HBV[e] (402)	PS	97.9	92.1	76.2	86.9	79.9	69.1	51.5	169.0

EU ELISA units, *FHA* filamentous haemagglutinin, *FIM* fimbriae types 2 and 3, *HBV* hepatitis B vaccine, *BD* assessment ≈1 month after the booster dose, *PS* assessment ≈1 month after the final primary dose, *PRN* pertactin, *PT* pertussis toxoid, *sub* subjects

* 95% CIs did not overlap

[a] Coadministered vaccines: Prevenar 13® and RotaTeq® (and Rotarix® in a subset in study 008) with primary series; Prevenar 13® (studies 008, 005, and 006) or ProQuad® (study 007) with the booster dose

[b] Acceptability criteria met (coprimary endpoint)

[c] Noninferior to the comparator, except for PS geometric mean concentrations for FHA in studies 005 and 006 (coprimary endpoint)

[d] Daptacel® plus Pedvax HIB® and Daptacel® plus Act-HIB® (Vaxelis® and comparator groups; study 005), or Pentacel® (both groups; study 006)

[e] Recombivax HB®, administered at 2 and 6 months of age

[f] Subjects were randomized to one of three lots of Vaxelis® or to the comparator; data shown are for all lots combined

[g] Noninferior to the comparator, except for BD geometric mean concentrations for PRN in study 006 (secondary endpoint)

met for GMC of antibodies against FHA (Table 2; coprimary and/or secondary endpoints) [18–21].

As Booster Vaccination After a single booster dose of Vaxelis®, following a two- or three-dose primary series, vaccine response rates in studies 007 and 008 were ≥96.9% against all pertussis antigens and met the acceptability criteria (Table 2; coprimary endpoints) [16, 17]. Vaxelis® was noninferior to Infanrix® hexa with respect to post-booster vaccine response rates for PT, FHA, and PRN (Table 2; coprimary endpoints). Post-booster GMCs for PT were higher with Vaxelis® than with Infanrix® hexa. However, Vaxelis® recipients had lower pre- and post-booster GMCs for FHA (in studies 007 and 008) and PRN (in study 008) than Infanrix® hexa recipients (Table 2) [16, 17].

In study 005, after a booster dose with Daptacel® plus a Hib vaccine, vaccine response rates and GMCs for pertussis antigens in the Vaxelis® group were noninferior to those in the Pentacel® plus Recombivax HB® group (Table 2; coprimary endpoint) [18]. Similar results were seen in study 006 (which used Pentacel® as the booster dose), although the noninferiority criteria for Vaxelis® versus Pentacel® plus Recombivax HB® was not met for the GMCs of antibodies against PRN (Table 2; secondary endpoints) [19].

Table 3 Immunogenicity of Vaxelis® against diphtheria, tetanus, poliovirus, *Haemophilus influenzae* type b, and hepatitis B antigens in healthy infants in pivotal clinical trials

Study	Vaccines (no. of subjects)	Time point	Seroprotection rate (% of subjects)								Geometric mean concentrations/titers [before booster]						
			D	T	IPV1	IPV2	IPV3	PRP (μg/mL)		HBsAg	D	T	IPV1	IPV2	IPV3	PRP	HBsAg
								≥0.15	≥1.0		(IU/mL)	(IU/mL)	(dil^{-1})	(dil^{-1})	(dil^{-1})	(μg/mL)	(mIU/mL)
Primary series at 2, 3, and 4 months of age and booster dose at 12 months of age[a]																	
007 [16]	Vaxelis® (611)	PS	99.8[b,c]	100.0[b,c]	100.0[b,c]	99.8[b,c]	100.0[b,c]	98.4[b,c]	83.3*	97.8	0.1	0.7	176.5	153.9	346.5	3.9*	234.3
		BD	99.8[b]	100.0[b]	99.8[b]	100[b]	100.0[b]	99.5	95.0[b]	99.6[b,c]	4.7	8.2	3550.2	4561.2	3594.2	[1.2] 6.8	2984.3
	Infanrix® hexa (606)	PS	99.8	100.0	99.8	99.6	100.0	87.0	36.7	96.1	0.1	0.5	215.0	165.6	352.1	0.7	242.2
		BD	100.0	98.0	100.0	100.00	99.8	99.3	97.7	99.1	3.1	3.8	4310.0	5457.9	4542.1	[0.2] 21.4*	3369.1
Primary series at 2 and 4 months of age and booster dose at 11–12 months of age[a]																	
008 [17]	Vaxelis® (656)	PS	98.3	100.0	93.8	98.0	92.9	96.6*	72.9[†]	98.1	0.1	0.5	65.3	92.5	76.6	2.4*	225.5*
		BD	98.6[b,c]	99.8[b,c]	99.3[b,c]	99.8[b,c]	99.5[b,c]	99.6	89.9[b,c]	98.1[b,c]	2.0*	5.5*	1706.6	2027.7	1128.9	[0.9] 4.4	1986.3
	Infanrix® hexa (659)	PS	99.5	100.0	96.4	97.4	95.2	77.9	26.7	96.4	0.1	0.5	88.1*	89.0	105.3*	0.5	343.5
		BD	99.8	100.0	99.8	100.0	99.7	99.4	91.0	98.7	1.5	3.3	2538.0*	2483.3	1626.5*	[0.2] 7.8*	3244.7*
Primary series at 2, 4, and 6 months of age[a] and booster dose at 12 months of age[d]																	
005 [18, 20]	Vaxelis® (986)	PS	82.4[c]	99.9[c]	100.0[b,c]	100.0[b,c]	100.0[b,c]	97.3[c]	85.0[c]	99.4[c]						4.9[g]	
	Pentacel® + HBV[e] (487)	PS	86.3	99.5	98.2	99.8	99.8	92.4	75.4	98.6						3.1	
006 [19, 21]	Vaxelis® (2406)[f]	PS	85.4[g]	100.0[g]	100.0[g]	100.0[g]	100.0[g]	98.4[g]	87.5[g]	99.9[g]	0.4	1.6	579.8–684.7	1212.4–1359.8	825.3–901.7	5.6[c]	1196.0–1414.5
	Pentacel® + HBV[e] (402)	PS	87.7	98.7	99.4	100.0	99.7	96.2	79.5	99.0	0.4	0.9	270.0	846.1	784.2	3.4	609.1

D diphtheria toxoid, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B vaccine, *IPV 1/2/3* inactivated poliovirus types 1/2/3, *BD* assessment ≈1 month after the booster dose, *PS* assessment ≈1 month after the final primary dose, *PRP* polyribosyl ribitol phosphate, *T* tetanus toxoid

* 95% CIs did not overlap, † superior vs. comparator

[a] Coadministered vaccines: Prevenar 13® and RotaTeq®(and Rotarix® in a subset in study 008) with primary series; Prevenar 13® (studies 008, 005, and 006) or ProQuad® (study 007) with the booster dose

[b] Acceptability criteria met (coprimary endpoint)

[c] Noninferior vs. comparator (coprimary endpoint)

[d] Daptacel® plus Pedvax HIB®and Daptacel® plus Act-HIB® (Vaxelis®and comparator groups; study 005), or Pentacel® (both groups; study 006)

[e] Recombivax HB® administered at 2 and 6 months of age

[f] Subjects were randomized to one of three lots of Vaxelis® or to the comparator; data shown are for all lots combined or as a range across lots

[g] Noninferior vs. comparator (secondary endpoint)

2.2.2 Response to Haemophilus Influenzae Type b Antigen

As Primary Vaccination After two- or three-dose primary series vaccination with Vaxelis®, seroprotection rates against PRP were 96.6−98.4% and 72.9−87.5% at anti-PRP antibody thresholds of ≥0.15 and ≥1.0 μg/mL, respectively (Table 3) [16–21]. At the ≥0.15 μg/mL level, the seroprotection rate with Vaxelis® was acceptable (co-primary endpoint; study 007) [16].

After the three-dose primary series in study 007, Vaxelis® was noninferior to Infanrix® hexa in terms of the seroprotection rate for PRP at the ≥0.15 μg/mL level (coprimary endpoint), and the rate was higher with Vaxelis® at the ≥1.0 μg/mL level (Table 3) [16]. Of note, with the two-dose primary series in study 008, Vaxelis® was superior ($p < 0.001$) to Infanrix® hexa in terms of PRP seroprotection rates assessed at post-primary (≥1.0 μg/mL) (Table 1) and pre-booster (≥0.15 μg/mL) time points (treatment differences, 46.2 and 43.3%, respectively) [17]. Similarly, post-primary vaccination GMCs for PRP were also higher in Vaxelis® than Infanrix® hexa recipients (Table 3) [16, 17].

After primary vaccination in studies 005 and 006, Vaxelis® was also noninferior to Pentacel® plus Recombivax HB® with respect to PRP seroprotection rates at both the ≥0.15 and ≥1.0 μg/mL level and anti-PRP antibody GMC values (Table 3; coprimary or secondary endpoints) [18–21].

As Booster Vaccination In studies 007 and 008, post-booster seroprotection rates against PRP were ≥99.5 and ≥89.9% at the ≥0.15 and ≥1.0 μg/mL thresholds, respectively, in Vaxelis® recipients (Table 3) [16, 17]. At the ≥1.0 μg/mL level, the rates met the acceptability criteria in both studies (coprimary endpoint; Table 3).

Vaxelis® was noninferior to Infanrix® hexa for seroprotection rates against PRP at the ≥1.0 μg/mL level (Table 3; coprimary endpoint; study 008) [17]. However, contrary to the post-primary vaccination GMC values, post-booster values were lower with Vaxelis® versus Infanrix® hexa in studies 007 and 008 (Table 3) [16, 17].

Post-booster data from the US studies suggest that anti-PRP responses in infants receiving Vaxelis® primary series vaccination can be boosted with a different Hib vaccine, containing either PRP-OMPC or PRP-T [9]. For example, in study 005, the post-booster PRP seroprotection rate at the ≥1.0 μg/mL level was ≈95% in infants who received Vaxelis® and Pedvax HIB® as the primary and booster Hib vaccines, respectively [9].

2.2.3 Response to Hepatitis B Virus Surface Antigens

As Primary Vaccination After two- or three-dose primary series vaccination with Vaxelis®, seroprotection rates against HBsAg were high regardless of whether infants had received hepatitis B vaccination at birth (≥99.4% in studies 005 and 006 [18, 21]) or not (≥97.8% in studies 007 and 008 [16, 17]) (Table 3). Seroprotection rates with Vaxelis® were similar (95% CIs overlapped) to those obtained with Infanrix® hexa [16, 17], and were noninferior to those with Pentacel® plus Recombivax HB® (coprimary [18] or secondary [21] endpoint). As would be expected, GMCs of antibodies against HBsAg were notably high in infants who had received hepatitis B vaccination at birth (study 006 [19]).

As Booster Vaccination In studies 007 and 008, post-booster seroprotection rates against HBsAg were ≥98.1% (Table 3) [16, 17]. In both studies, these rates met the acceptability criteria and were noninferior to those obtained with Infanrix® hexa (coprimary endpoint). Post-booster GMC values for anti-HBsAg antibodies were lower (numerically in study 007 or 95% CI did not overlap in study 008) in Vaxelis® than in Infanrix® hexa recipients (Table 3) [16, 17].

2.2.4 Response to Diphtheria, Tetanus, and Poliovirus Antigens

As Primary Vaccination Following two- or three-dose primary series vaccination with Vaxelis®, seroprotection rates were 82.4–99.8% against D, ≥99.9% against T, and 92.9–100% against IPV type 1, 2, and 3 (Table 3) [16–19]. Where assessed as coprimary endpoints, Vaxelis® met the acceptability criteria for seroprotection against all of these antigens (study 007 [16]) or against IPV type 1, 2, and 3 (study 005 [20]).

After a three-dose primary vaccination series (study 007), Vaxelis® was noninferior to Infanrix® hexa with respect to seroprotection rates against D, T, and IPV type 1, 2, and 3 (Table 3; coprimary endpoint) [16]. However, after a two-dose primary series (study 008), seroprotection rates against IPV type 1 and 3 appeared to be lower with Vaxelis® than with Infanrix® hexa [17]. GMCs of antibodies against IPV antigens in Vaxelis® recipients were lower numerically (for all types in study 007) or based on 95% CIs (for types 1 and 3 in study 008) versus Infanrix® hexa (Table 3) [16, 17].

Vaxelis® was noninferior to Pentacel® plus Recombivax HB® with respect to seroprotection rates against D, T and IPV type 1, 2, and 3 in studies 005 and 006 (Table 3; coprimary or secondary endpoints) [18, 20, 21]. In study 006, Vaxelis® produced numerically higher GMCs of antibodies against IPV than the comparator [19].

As Booster Vaccination Post-booster seroprotection rates were ≥98.6% against D, T, and IPV type 1, 2, and 3 in studies 007 and 008 (Table 3) [16, 17]. These rates met the acceptability criteria in both studies and were

noninferior to those obtained with Infanrix® hexa in study 008 (coprimary endpoints) [16, 17]. Numerically or based on 95% CIs, vaxelis® recipients had higher GMCs for D and T, and lower GMCs for IPVs versus Infanrix® hexa recipients (Table 3) [16, 17].

2.3 Pooled Analyses and Supportive Studies

Results of pooled analyses of clinical studies were consistent with those of individual studies, demonstrating high immunogenicity with Vaxelis® regardless of vaccination schedules (Fig. 1) [8]. The seroprotection or vaccine response rates 1 month after a two- or three-dose primary series administered at 2–6 months of age were 100% against T, ≥97% against D, HBsAg, and PRP, 93–100% against IPV, and 80–99% for pertussis antigens (based on the same threshold used in the EU studies; see Sect. 2.2); the rates 1 month after the booster dose were 90–100% against all antigens. Post-primary vaccine response or seroprotection rates for PRN, IPV1, and IPV3 were ≥5% lower after the two-dose than after the three-dose (2, 3, and 4 month) series (Fig. 1). The clinical relevance of these data is not clear. Nevertheless, post-booster rates were generally similar between the two schedules (Fig. 1b). Limited data from clinical studies indicate that immune responses to Vaxelis® in preterm infants were generally similar to those in the overall study population [8].

Immune responses to Vaxelis® seen in a randomized, open-label, phase 3 study ($n = 284$) conducted in the UK (PRI01C) were generally consistent with those of pivotal studies (abstract presentation [22]). Furthermore, an open-label, single-arm study ($n = 385$) conducted in Spain (PRI02C) found that mixed primary vaccination with Vaxelis® at 2 and 6 months of age, and Pediacel® (a pentavalent vaccine containing DTaP, IPV and PRP-T) at 4 months of age, produced acceptable seroprotection rates against HBsAg (98.9%) and PRP (≥0.15 µg/mL; 100.0%) at 1 month after the primary series [9].

3 Immunogenicity of Coadministered Vaccines

Vaxelis® and comparator groups did not differ in terms of immune responses to coadministered measles, mumps, rubella, and varicella zoster virus (ProQuad®), rotavirus (Rotarix®, RotaTeq®), and pneumococcal (Prevnar®, Prevnar 13®) or meningococcal serogroup C conjugate (MCC) vaccines [9, 14–19]

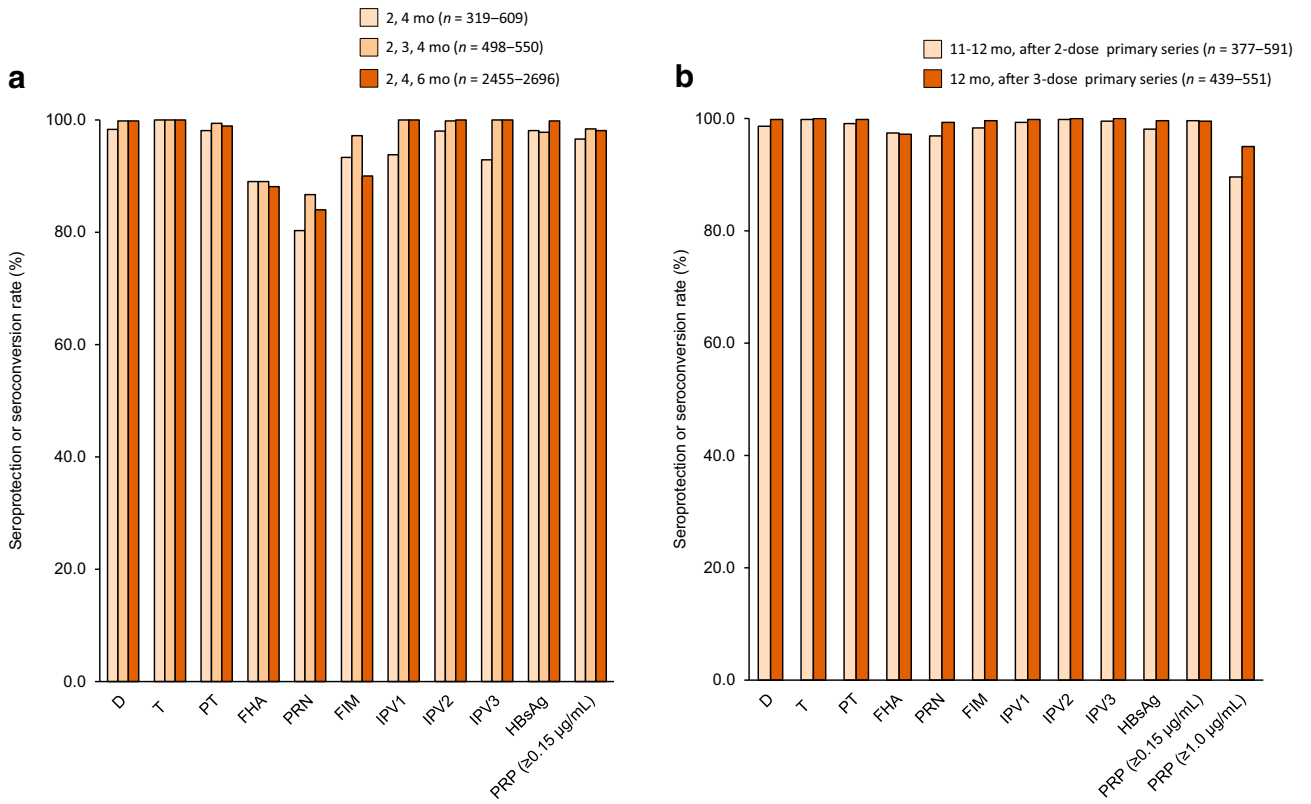

Fig. 1 Immunogenicity of Vaxelis® 1 month after **a** primary series vaccination and **b** a booster dose in healthy infants. Results from pooled analyses of clinical trials [8]. *D* diphtheria toxoid, *FHA* filamentous haemagglutinin, *FIM* fimbriae types 2 and 3, *HBsAg* hepatitis B surface antigen, *IPV1/2/3* inactivated poliovirus types 1/2/3, *mo* months, *PRN* pertactin, *PRP* polyribosyl ribitol phosphate, *PT* pertussis toxoid, *T* tetanus toxoid

Following coadministration of Rotarix® (study 008 [17]) or RotaTeq® (study 005 [18]) with the primary series doses, post-primary vaccination GMCs of anti-rotavirus IgA antibodies in the Vaxelis® group were noninferior to those in the Infanrix® hexa (94.4 vs. 117.5 units/mL) [17] or Pentacel® plus Recombivax HB® (282.5 vs. 278.0 units/mL) [18] groups.

In study 006, post-primary GMCs of antibodies for 12 of 13 pneumococcal antigens of Prevenar 13® in the Vaxelis® group (0.5–4.7 μg/mL) were noninferior versus the Pentacel® plus Recombivax HB® group (0.5–4.9 μg/mL), but the noninferiority criterion was not met for the 6B antigen (1.0 vs. 1.2 μg/mL) [19]. However, response rates (the proportion of subjects achieving antipneumococcal antibody levels of ≥0.35 μg/mL) in the Vaxelis® group were noninferior to those in the comparator group for all antigens (66.3−99.3% vs. 68.1−99.0%) [19]. Likewise, following coadministration of Prevnar® with Vaxelis® or Pentacel® plus a hepatitis B vaccine (study 004), post-primary [14] and post-booster [15] GMCs of antipneumococcal antibodies were similar between the two groups.

When ProQuad® was coadministered with the booster dose of Vaxelis® (study 007), response rates to each of the antigens in ProQuad® met the predefined acceptability criterion and were noninferior to those when it was coadministered with Infanrix® hexa (96.2 vs. 96.4% against measles, 94.9 vs. 91.8% against mumps, 98.3 vs. 97.9% against rubella, and 97.6 vs. 97.7% against varicella) [16]. Response rates were defined as the proportion of children achieving antibody levels of ≥255 mIU/mL for measles, ≥10 Ab units/mL for mumps, ≥10 IU/mL for rubella, and ≥5 gp-EU/mL for varicella [16].

In PRI01C, an MCC vaccine coadministered with the Vaxelis® primary series produced acceptable seroprotection rates against its antigen, irrespective of whether it was conjugated to T (NeisVac-C®) or diphtheria CRM197 protein (Menjugate®) [9]. The seroprotection rates (percentage of subjects with a serum bactericidal titer of ≥8 dil^{-1}) were ≥99.1% with both MCC vaccines. However, NeisVac-C® produced approximately twofold higher post-primary vaccination GMTs (2024.7 vs. 1077.4 dil^{-1}; 95% CIs did not overlap) and pre-booster seroprotection rates (83.1 vs. 40.4%) than Menjugate® [9]. In this study, subjects received Vaxelis® at 2, 3, and 4 months of age and NeisVac-C® or Menjugate® at 3 and 4 months of age, with other concomitant and booster vaccines being the same in both groups [9].

The potential for immunologic interference between pneumococcal vaccines and Vaxelis® has not been formally studied. In study 004, the post-primary series GMCs of antibodies to D antigen was lower when Prevnar® was concomitantly administered with Vaxelis®, compared with when it was administered 1 month later (0.51 vs. 1.27 IU/mL; 95% CIs did not overlap), although these groups were not statistically powered to detect such differences [14].

4 Reactogenicity of Vaxelis®

Vaxelis® as a primary and booster or primary vaccination, coadministered with other approved childhood vaccines, was generally well tolerated in children aged up to ≈15 months participating in clinical studies discussed in Sect. 2. There were no major safety concerns with Vaxelis® [9]. Several pooled analyses are available, including for EU pivotal studies 007 and 008 (EU analysis) [9], US pivotal studies 005 and 006 (US analysis) [19], and studies 004 to 008 and PRI01C (overall analysis, which included Infanrix® hexa or Pentacel®-based vaccines as comparators) [9]. Statistical analyses are reported where available.

The main tolerability assessment of Vaxelis® included solicited injection-site (erythema, pain, swelling) and solicited systemic (crying, decreased appetite, irritability, pyrexia, somnolence, vomiting) adverse events occurring within 1–5 days of any dose of vaccine [9]. In a large pooled analysis ($n = 7557$), 85% of Vaxelis® recipients reported solicited injection-site reactions, with injection-site pain being the most common (71%). The majority of these reactions were mild or moderate and transient. Solicited systemic adverse events occurred in 95% of Vaxelis® recipients, with irritability being the most common (84%) [9].

The tolerability profile of Vaxelis® was broadly similar to that of comparator vaccines in terms of solicited adverse events in the EU [9] and US [23] analyses (Fig. 2). The incidence of severe injection-site erythema in Vaxelis® and Infanrix® hexa recipients was 4.9 and 3.2% (difference 1.7; 95% CI 0.2–3.3) and the incidence of severe injection-site swelling was 4.6 and 3.3% (1.3; −0.2 to 2.9) [9]. However, the combined incidences of these events were similar between the treatment groups, and the events were of short duration, and therefore of low clinical significance [9]. With respect to severe solicited systemic adverse events, most occurred in <4% of subjects who received Vaxelis® or either comparator vaccine, with the exceptions being crying (9–14% vs. 10% with either comparator) and irritability (8 vs. 6%) [9, 23].

The incidence of solicited pyrexia of any severity (temperature ≥38 °C) in Vaxelis® versus comparator groups was 56.8 versus 47.4% (difference 9.4; 95% CI for the difference 6.7−12.0) in the overall analysis [9]. Nevertheless, most pyrexia events were of mild (≥38 to <38.5 °C) to moderate (≥38.5 to <39.5 °C) intensity and of short duration (≤2 days), with severe events (≥39.5 °C) reported in 2.1 and 2.5% of children in the Vaxelis® and comparator groups, respectively [9].

In the EU analysis, the incidence of solicited pyrexia of any severity was similar between the Vaxelis® and Infanrix® hexa groups (72.7 vs. 70.1%; difference 2.5; 95% CI for the difference −1.0 to 6.1) [9]. In individual studies, the

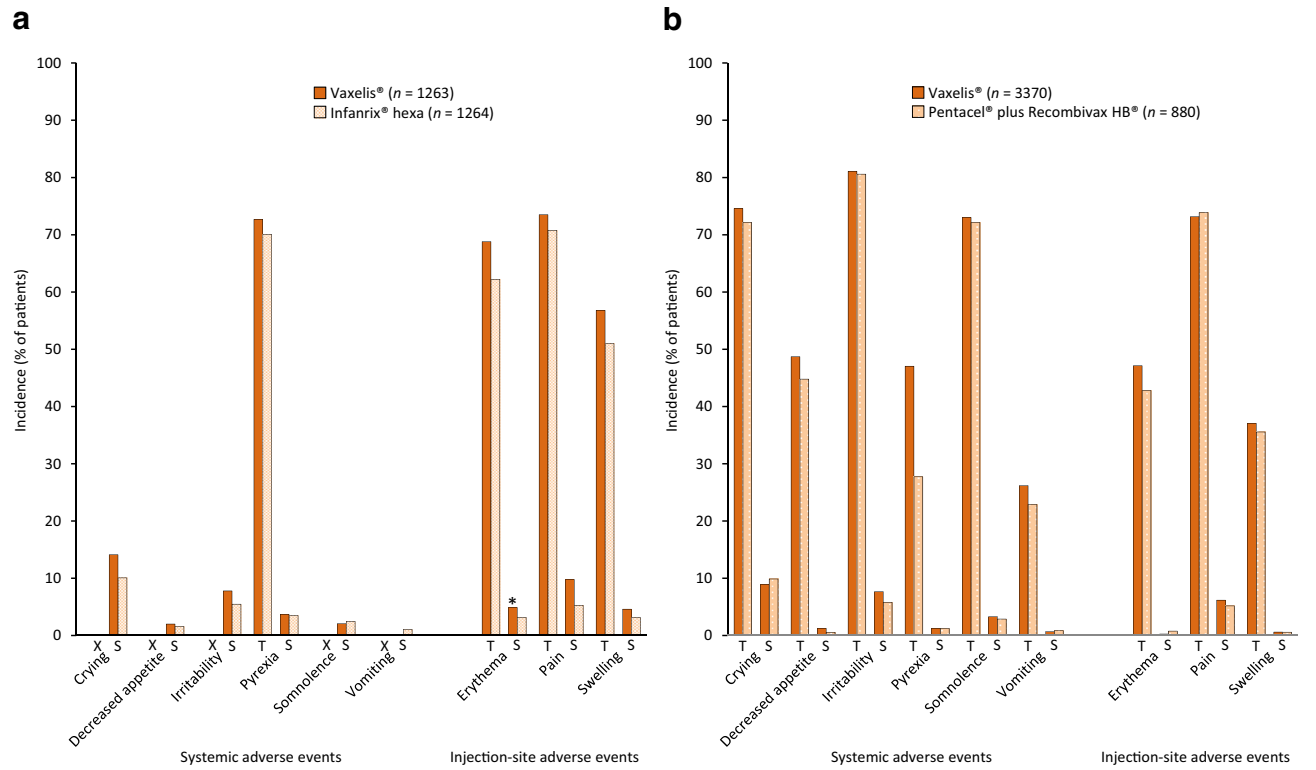

Fig. 2 Tolerability of Vaxelis® coadministered with other childhood vaccines in healthy infants in pivotal clinical studies. Pooled analyses of **a** studies 007 and 008 [9] **b** studies 005 and 006 (data estimated from graph; statistical analysis not available) [23]. *S* severe, *T* total, *X* data not available for T. *Significant vs. comparator based on 95 % CI

incidences of mild, moderate, and severe pyrexia (temperature assessed by all methods or by rectal measurement only from day 1 to 5 after any dose) did not differ significantly (based on 95% CI) between the groups [16, 17]. For example, the incidences in the Vaxelis® and Infanrix® hexa groups in study 007 for all temperature measurement methods were: mild 39.9 versus 34.7%; moderate 30.2 versus 35.2%; and severe 3.1 versus 4.0% [16]. In study 008, the incidence of pyrexia in Vaxelis® recipients appeared to be lower after the primary series (any 33.1–40.7%; severe 0.2–0.8%) than after the booster dose (54.3%; 3.7%) [9].

If elevated body temperature was felt to occur as part of an intercurrent illness, it was not counted as pyrexia, so objective measurements of temperature were recorded and reported separately [9]. It was assessed using the same severity rating scale as pyrexia. Across studies 004 to 008, the incidence of elevated temperature (≥38 °C, rectal) was significantly (*p*-value not reported) higher in the Vaxelis® than in the comparator groups (61.2 vs. 52.7%), driven by the US studies. However, the incidence of severe elevated temperature was low (≤3%) in both treatment groups [9]. In the EU studies, there was no significant difference between Vaxelis® and Infanrix® hexa groups in the incidence of no temperature elevation (26.6 vs. 29.7%), and mild (36.9 vs. 34.4%), moderate (32.7 vs. 32.5%), or severe (3.7 vs. 3.3%) temperature elevation, as assessed by all methods [9]. In the US studies, based on 95% CIs (*p*-values not reported), Vaxelis® was associated with a significantly lower incidence of no temperature elevation (50.9 vs. 64.4%) and a significantly higher incidence of mild (26.2 vs. 21.9%) or moderate (20.6 vs. 12.5%) temperature elevation, compared with Pentacel® plus Recombivax HB®; however, there was no significant difference between the groups for severe temperature elevation (2.3 vs. 1.2%) [19]. Where reported, Vaxelis® was not associated with an increase in fever-related medical events such as febrile convulsion or convulsion [17–19].

In the EU analysis, the incidence of unsolicited (occurring from day 1 to 15 after any vaccination dose) injection-site reactions did not differ significantly between the Vaxelis® and Infanrix® hexa groups [9]. The most common unsolicited systemic adverse events in the Vaxelis® and Infanrix® hexa groups were pyrexia (15.5 vs. 14.2%), diarrhea (13.8 vs. 12.1%), and rhinitis (8.8 vs. 10.0%), and the incidences of these events were not significantly different between the groups. In the overall analysis, the incidences of unsolicited elevated body temperature, diarrhea, and decreased appetite were significantly (based on 95% CIs) higher with Vaxelis® than with comparators. However, the differences were small and are not considered clinically relevant [9].

In the overall analysis ($n = 5234$ for the Vaxelis® group and $n = 2302$ for all comparator groups combined),

serious adverse events related to study vaccines, when coadministered with other vaccines (occurring after any vaccination dose), were reported in nine, four, and three subjects in the Vaxelis®, Infanrix® hexa, and Pentacel® groups, respectively [9]. In the Vaxelis® group, these events included febrile convulsion (one subject), idiopathic thrombocytopenic purpura (one), prolymphocytic leukemia (one), hypotonia (one), apparent life-threatening event (one), abdominal pain and crying (one), and pyrexia (three). None of the Vaxelis® recipients discontinued vaccination because of a vaccine-related serious adverse event in the pivotal studies [9].

Seven subjects died in the US pivotal studies (6 of 3370 in the Vaxelis® group and 1 of 880 in the comparator group) and none of these deaths were considered to be related to study vaccines [9]. There were no deaths in studies 004, 007, 008, and PRI01C. There were no clinically relevant tolerability issues with Vaxelis® in subgroups based on of race, ethnicity, gender, and preterm birth [9].

5 Dosage and Administration of Vaxelis®

Vaxelis® is available as a fully liquid 0.5 mL suspension (prefilled syringe) for intramuscular injection [8]. The recommended injection sites are the anterolateral area of the thigh (preferred site in infants) or the deltoid muscle of the upper arm. Primary series vaccination consists of two or three doses, with an interval of ≥1 month between doses, and may be given from 6 weeks of age. Vaxelis® can be used for a mixed primary series schedule of hexavalent–pentavalent–hexavalent vaccines. In children who have received a dose of hepatitis B vaccine at birth, Vaxelis® can be used for additional doses of this vaccine from the age of 6 weeks. A booster dose of Vaxelis® should be given ≥6 months after the last priming dose. All doses of Vaxelis® should be administered in accordance with the official recommendations [8]. Local prescribing information should be consulted for full details of administration, contraindications, warnings, and precautions.

6 Vaxelis®: Current Status

Vaxelis® is a hexavalent vaccine indicated in the EU for primary and booster vaccination of infants and toddlers from the age of 6 weeks against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive diseases caused by Hib [8]. Vaccination against these diseases is either mandatory or recommended in all EU countries [24]. In addition to Vaxelis®, two other hexavalent vaccines (Hexacima® or Hexyon® and Infanrix® hexa) are currently available in the EU. These vaccines differ from each other with respect to their qualitative and/or quantitative composition (Table 1).

The main randomized studies of Vaxelis® were conducted in the EU (Belgium, Finland, Germany, Italy, and Sweden) and the USA (Sect. 2.2). Since vaccination schedules vary across the EU countries [1], the EU studies were designed to represent a condensed vaccination schedule (three-dose primary series at 2, 3, and 4 months plus a booster dose at 12 months) and the most immunologically rigorous schedule (two-dose primary series at 2 and 4 months and a booster dose at 11–12 months) [1]. The US studies followed local immunization schedules (primary series at 2, 4, and 6 months and the booster dose at 15 months). Relevant approved vaccines were used as comparators (Infanrix® hexa in the EU and Pentacel® plus Recombivax HB® in the USA). In these studies, Vaxelis® was highly immunogenic for all its vaccine components, regardless of vaccination schedules. Where assessed as coprimary endpoints, Vaxelis® met the predefined criteria for acceptability and noninferiority versus comparators in terms of seroprotection or vaccine response rates against each of its antigen (Sect. 2.2). Vaxelis® showed good lot-to-lot consistency in immune responses (Sect. 2.2). Additional supportive studies showed that Vaxelis® can be coadministered with approved MCC vaccines and can be used for a mixed, three-dose, primary series schedule of hexavalent-pentavalent-hexavalent vaccines (Sect. 2.3).

There are some differences between the immunogenicity of Vaxelis® and comparators (Sect. 2.2). Compared with Infanrix® hexa, Vaxelis® produced lower vaccines response rates and GMC values for FHA (after the primary series and the booster dose) and for PRN (after the primary series). Likewise, Vaxelis® did not meet the noninferiority criteria versus Pentacel® plus Recombivax HB® in terms of post-primary GMC values for FHA (studies 005 and 006) and post-booster values for PRN (study 006). On the other hand, Vaxelis® produced higher GMC values for PT versus Infanrix® hexa after the primary series and after the booster dose. With regards to IPV, after the two-dose primary series, seroprotection rates for type 1 and 3 antigens were numerically lower with Vaxelis® than with Infanrix® hexa. The clinical relevance of the differences in pertussis and IPV immunogenicity data is currently not clear. Furthermore, Vaxelis® contains PRP-OMPC which is known to elicit a stronger early immunogenic response against Hib than the PRP-T antigen present in Infanrix® - hexa. Consistent with this, Vaxelis® generally displayed a stronger priming effect against PRP than Infanrix® hexa, although the boosting effect of Vaxelis® was generally similar to, or lower than, that of the comparator.

Vaxelis® was generally well tolerated in clinical studies in healthy infants aged ≤15 months (Sect. 4). The most common adverse reactions reported in Vaxelis® recipients included

decreased appetite, somnolence, vomiting, crying, irritability, pyrexia (≥38 °C), and injection-site reactions (erythema, pain, swelling). The tolerability profile of Vaxelis® was generally similar to that of the comparator vaccines.

While Vaxelis® is a fully liquid, ready-to-use vaccine, Infanrix® hexa requires reconstitution prior to administration. Fully liquid formulations offer some benefits. In an open-label study in 96 healthcare professionals in Belgium, a fully liquid vaccine was associated with a reduced mean vaccine preparation time (36 vs. 70.5 s) and immunization errors (10 vs. 47 on 192 preparations), compared with a non-fully liquid vaccine; furthermore, the majority (97.6%) of the professionals stated that they would prefer the fully liquid formulation in their daily practice [25].

In conclusion, Vaxelis® as primary and booster vaccination is highly immunogenic for all its components and is generally well tolerated in infants aged ≤15 months, regardless of vaccination schedules. It elicits acceptable seroprotection or vaccine response rates that are generally similar to those obtained with currently available vaccines. Data regarding the long-term persistence of immune response, immune memory, and vaccine effectiveness of Vaxelis® are awaited with interest. Meanwhile, Vaxelis® is an additional hexavalent vaccine option in the EU for the prevention of several infectious diseases caused by six pathogens. It offers the convenience of a fully liquid, ready-to-use vaccine.

Data Selection Vaxelis®: 222 records identified	
Duplicates removed	13
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	128
Excluded during initial selection (e.g. preclinical study; review; case report; not randomized trial)	29
Excluded by author (e.g. not randomized trials; review; duplicate data; small patient number; phase I/II trials)	22
Cited immunogenicity/reactogenicity articles	14
Cited articles not immunogenicity/reactogenicity	17
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Vaxelis, diphtheria, pertussis, tetanus, DTwP, DPT*, or DTP*, vaccine, hemophilus b, haemophilus b, Hib. Records were limited to those in English language. Searches last updated 06 December 2016.	

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Compliance with Ethical Standards

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