HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VAXELIS safely and effectively. See full prescribing information for VAXELIS.

VAXELIS® (Diphtheria and Tetanus Toxoids and Acellular Pertussis, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine) injectable suspension, for intramuscular use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

VAXELIS is a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b. VAXELIS is approved for use as a 3-dose series in children from 6 weeks through 4 years of age (prior to the 5th birthday). (1)

----------DOSAGE AND ADMINISTRATION----------

The 3-dose immunization series consists of a 0.5 mL intramuscular injection, administered at 2, 4, and 6 months of age. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injectable suspension (0.5 mL dose) available in prefilled syringes. (3)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) to a previous dose of VAXELIS, any ingredient of VAXELIS, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, or *Haemophilus influenzae* type b vaccine. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Carefully consider benefits and risks before administering VAXELIS to persons with a history of:
  - fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
  - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following VAXELIS. (5.3)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including VAXELIS, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.5)
- Urine antigen detection may not have definitive diagnostic value in suspected *H. influenzae* type b disease following vaccination with VAXELIS. (5.7) (7.1)

----------ADVERSE REACTIONS----------

The solicited adverse reactions following any dose were irritability (≥55%), crying (≥45%), injection site pain (≥44%), somnolence (≥40%), injection site erythema (≥25%), decreased appetite (≥23%), fever ≥38.0°C (≥19%), injection site swelling (≥18%), and vomiting (≥9%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Vaccines US Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VAXELIS® is a vaccine indicated for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* (*H. influenzae*) type b. VAXELIS is approved for use as a 3-dose series in children 6 weeks through 4 years of age (prior to the 5th birthday).

2 DOSAGE AND ADMINISTRATION

For intramuscular use.

2.1 Vaccination Schedule

VAXELIS is to be administered as a 3-dose series at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age. Three doses of VAXELIS constitute a primary immunization course against diphtheria, tetanus, *H. influenzae* type b invasive disease and poliomyelitis.

VAXELIS may be used to complete the hepatitis B immunization series.

A 3-dose series of VAXELIS does not constitute a primary immunization series against pertussis; an additional dose of pertussis-containing vaccine is needed to complete the primary series. [See *Pertussis Vaccination Following VAXELIS.*]

Pertussis Vaccination following VAXELIS

VAXELIS, Pentacel® [(Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine): DTaP-IPV/Hib], Quadracel® [(Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine): DTaP-IPV] and DAPTACEL® [(Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed): DTaP] contain the same pertussis antigens manufactured by the same process. Children who have received a 3-dose series of VAXELIS should complete the primary and pertussis vaccination series with Pentacel, Quadracel or DAPTACEL according to the respective prescribing information in the approved package inserts. [See *ADVERSE REACTIONS (6.1) AND CLINICAL STUDIES (14).]*

Administration of VAXELIS following previous doses of other DTaP-containing Vaccines

VAXELIS may be used to complete the first 3 doses of the 5-dose DTaP series in infants and children who have received 1 or 2 doses of Pentacel or DAPTACEL and are also scheduled to receive the other antigens in VAXELIS. Data are not available on the safety and immunogenicity of such mixed sequences.

Data are not available on the safety and effectiveness of using VAXELIS following 1 or 2 doses of a DTaP vaccine from a different manufacturer.

Administration of VAXELIS following previous doses of any Hepatitis B Vaccine

A 3-dose series of VAXELIS may be administered to infants born to HBsAg-negative mothers, and who have received a dose of any hepatitis B vaccine, prior to or at 1 month of age. [See *ADVERSE REACTIONS (6.1) AND CLINICAL STUDIES (14)*.]

VAXELIS may be used to complete the hepatitis B vaccination series following 1 or 2 doses of other hepatitis B vaccines, in infants and children born of HBsAg-negative mothers and who are also scheduled to receive the other antigens in VAXELIS. However, data are not available on the safety and effectiveness of VAXELIS in such infants and children.

Administration of VAXELIS following previous doses of Inactivated Polio Vaccine (IPV)

VAXELIS may be administered to infants and children who have received 1 or 2 doses of IPV and are also scheduled to receive the other antigens in VAXELIS. However, data are not available on the safety and effectiveness of VAXELIS in such infants and children.

Administration of VAXELIS following previous doses of Haemophilus b Conjugate Vaccines

VAXELIS may be administered to infants and children who have received 1 or 2 doses of *H. influenzae* type b Conjugate Vaccine and are also scheduled to receive the other antigens in VAXELIS. However, data are not available on the safety and effectiveness of VAXELIS in such infants and children.

2.2 Administration

Just before use, shake the syringe until a uniform, white, cloudy suspension results.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exist, the product should not be administered.

Administer a single 0.5 mL dose of VAXELIS intramuscularly.

In infants younger than 1 year, the anterolateral aspect of the thigh is the preferred site of injection. The vaccine should not be injected into the gluteal area.

VAXELIS should not be combined through reconstitution or mixed with any other vaccine. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

VAXELIS is an injectable suspension available in 0.5 mL prefilled syringes.
[See *HOW SUPPLIED/STORAGE AND HANDLING (16)*.]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer VAXELIS to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to a previous dose of VAXELIS, any ingredient of VAXELIS, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine, hepatitis B vaccine, or *H. influenzae* type b vaccine [See *DESCRIPTION (11)*.]

4.2 Encephalopathy

Do not administer VAXELIS to anyone with a history of encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of a previous dose of a pertussis containing vaccine, that is not attributable to another identifiable cause.

4.3 Progressive Neurologic Disorder

Do not administer VAXELIS to anyone with a history of progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Adverse Reactions Following Prior Pertussis Vaccination

If any of the following events occur after administration of a pertussis vaccine, the decision to administer VAXELIS should be based on careful consideration of potential benefits and possible risks.

- Temperature of ≥40.5°C (≥105°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode [HHE]) within 48 hours.
- Persistent, inconsolable crying lasting ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

5.3 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following VAXELIS. (1)

5.4 Altered Immunocompetence

If VAXELIS is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.5 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including VAXELIS, to an infant born prematurely should be based on consideration of the infant's medical status and the potential benefits and possible risks of vaccination.

5.6 Limitations of Vaccine Effectiveness

Vaccination with VAXELIS may not protect all individuals.

5.7 Interference with Laboratory Tests

Urine antigen detection may not have definitive diagnostic value in suspected *H. influenzae* type b disease following vaccination with VAXELIS. [See *DRUG INTERACTIONS (7.1).*]

6 ADVERSE REACTIONS

Rates of adverse reactions varied by number of doses of VAXELIS received. The solicited adverse reactions 0-5 days following any dose were irritability (≥55%), crying (≥45%), injection site pain (≥44%), somnolence (≥40%), injection site erythema (≥25%), decreased appetite (≥23%), fever ≥38.0°C (≥19%), injection site swelling (≥18%), and vomiting (≥9%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to vaccine use and for approximating rates of those events.

The safety of VAXELIS was evaluated in 6 clinical studies, in which a total of 5,251 infants 43 to 99 days of age at enrollment received at least 1 dose of VAXELIS. Two of these (study 005 and 006) were controlled clinical studies conducted in the US, in which a total of 3,380 infants 46 to 89 days of age at enrollment received at least 1 dose of VAXELIS. The vaccination schedules of VAXELIS, Control vaccines, and concomitantly administered vaccines used in these studies are provided in Table 1. At 15 months of age, participants in Study 005 received a dose of DAPTACEL and a *H. influenzae* type b conjugate vaccine, whereas participants in Study 006 received a dose of Pentacel. In a non-US study, 294 children received a dose of VAXELIS at 15 months of age.

Across the 2 studies conducted in the US, among all randomized participants (3,392 in the VAXELIS group and 889 in the Control group), 52.6% were male and 47.4% were female. The race distribution was as follows: 71.7% were White, 11.0% were Black, 4.5% were American Indian or Alaska Native, 3.5% were Asian, and 9.3% were of other racial groups. Most participants (81.8%) were of non-Hispanic or Latino ethnicity. The racial/ethnic distribution of participants who received VAXELIS and Control vaccines was similar.

Table 1: Clinical Safety Studies with VAXELIS in the US: Vaccination Schedules

Study	Vaccine	Concomitantly Administered Vaccines
005*	VAXELIS at 2, 4, 6 months and DAPTACEL + PedvaxHIB® at 15 months	RotaTeq® at 2, 4, and 6 months Prevnar 13® at 2, 4, 6, and 15 months
	Control group vaccines: Pentacel at 2, 4, 6 months and RECOMBIVAX HB® at 2 and 6 months DAPTACEL+ ActHIB® at 15 months	RotaTeq at 2, 4, and 6 months Prevnar 13 at 2, 4, 6, and 15 months
006*	VAXELIS at 2, 4, 6 months and Pentacel at 15 months	RotaTeq at 2, 4, and 6 months Prevnar 13 at 2, 4, 6, and 15 months
	Control group vaccines: Pentacel at 2, 4, 6, and 15 months RECOMBIVAX HB at 2 and 6 months	RotaTeq at 2, 4, and 6 months Prevnar 13 at 2, 4, 6, and 15 months

Prevnar 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent)
PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]
RECOMBIVAX HB (Hepatitis B Vaccine [Recombinant])
* The first dose of Hepatitis B vaccine was administered prior to study initiation (prior to or at 1 month of age).

Solicited Adverse Reactions

Information on solicited adverse events was recorded daily by parents or guardians on vaccination report cards. The incidence and severity of solicited injection site and systemic adverse reactions (i.e., vaccine-related adverse events) that occurred within 5 days following each dose of VAXELIS or Control vaccines at 2, 4, and 6 months of age in studies 005 and 006 are shown in Table 2.

Table 2: Percentage of Infants with Solicited Adverse Reactions Occurring within 5 days Following VAXELIS or Control Vaccines Administered Concomitantly at Separate Sites with Prevnar 13 and RotaTeq in Studies 005 and 006

		VAXELIS + Prevnar 13 + RotaTeq			Pentacel + RECOMBIVAX HB + Prevnar 13 + RotaTeq		
		Dose 1 (N=3,370) (%)	Dose 2 (N=3,221) (%)	Dose 3 (N=3,134) (%)	Dose 1 (N=880) (%)	Dose 2 (N=849) (%)	Dose 3 (N=825) (%)
Injection Site Adverse Reactions		**VAXELIS site**			**Pentacel or RECOMBIVAX HB site**		
Injection site erythema	Any	25.8	31.8	31.8	25.0	25.8	30.9
	≥2.5 cm	0.9	1.0	1.3	1.1	1.1	1.2
	>5.0 cm	0.0	0.1	0.2	0.3	0.2	0.1
Injection site pain*	Any	53.3	49.0	44.9	55.8	43.7	44.4
	Moderate or severe	16.3	14.1	12.5	19.1	11.3	10.8
	Severe	2.8	2.5	2.0	3.2	1.9	1.3
Injection site swelling	Any	18.9	22.8	23.4	20.8	20.4	22.9
	≥2.5 cm	2.5	1.6	1.7	2.7	1.3	0.8
	>5.0 cm	0.2	0.2	0.2	0.3	0.1	0.0
Systemic Adverse Reactions							
Fever	≥38°C	19.2	29.0	29.3	14.6	18.0	17.8
	≥38.5°C	5.3	11.5	13.2	3.4	6.5	8.1
	≥39.5°C	0.2	0.7	1.5	0.1	0.2	0.9
Crying	Any	52.0	49.5	45.1	50.6	47.0	40.6
	>1 hour	18.6	19.8	16.7	20.6	16.8	14.1
	>3 hours	3.6	3.8	3.4	4.4	4.0	2.9
Decreased Appetite[†]	Any	28.9	24.2	23.2	25.8	20.5	20.1
	Moderate or severe	7.0	5.5	4.8	6.8	3.9	5.0
	Severe	0.5	0.5	0.5	0.6	0.2	0.0
Irritability[‡]	Any	61.8	58.9	55.2	61.7	56.3	51.6
	Moderate or severe	24.6	23.4	20.1	25.7	19.2	16.8
	Severe	2.5	3.8	2.9	2.2	2.7	2.2

		VAXELIS + Prevnar 13 + RotaTeq			Pentacel + RECOMBIVAX HB + Prevnar 13 + RotaTeq		
		Dose 1 (N=3,370) (%)	Dose 2 (N=3,221) (%)	Dose 3 (N=3,134) (%)	Dose 1 (N=880) (%)	Dose 2 (N=849) (%)	Dose 3 (N=825) (%)
Somnolence§	Any	56.3	47.8	40.8	55.2	44.1	38.8
	Moderate or severe	15.0	11.5	8.5	14.5	9.4	8.2
	Severe	1.5	1.1	1.0	1.7	0.6	1.1
Vomiting¶	Any	13.1	11.5	9.5	11.3	9.7	6.9
	Moderate or severe	3.5	2.6	2.1	2.8	3.1	1.0
	Severe	0.4	0.2	0.1	0.5	0.6	0.1

N = Number of vaccinated participants with safety follow-up.

* Moderate: cries and protests when injection site is touched; Severe: cries when injected limb is moved or the movement of the injected limb is reduced.
† Moderate: missed 1 or 2 feeds/meals completely; Severe: refuses ≥3 feeds or refuses most feeds.
‡ Moderate: requiring increased attention; Severe: inconsolable.
§ Moderate: not interested in surroundings or did not wake up for a meal; Severe: Sleeping most of the time or difficult to wake up.
¶ Moderate: 2-5 episodes per 24 hours; Severe: ≥6 episodes per 24 hours or requiring parenteral hydration.
A subject with the same adverse reactions at both the Pentacel and RECOMBIVAX HB injection site, was counted once and was classified according to the highest intensity grading.
Fever is based upon actual temperatures recorded with no adjustments due to the measurement route. Following Doses 1-3 combined, the proportion of temperature measurements that were taken by rectal, axillary, or other routes were 91.7%, 8.1%, and 0% respectively, for VAXELIS group, and 90.3%, 9.7%, and 0%, respectively, for Pentacel + RECOMBIVAX HB vaccines group.

Non-fatal Serious Adverse Events

Across Studies 005 and 006, within 30 days following any infant dose vaccination, 68 participants (2.0%) who received VAXELIS and concomitant vaccines versus 19 participants (2.2%) who received Control and concomitant vaccines experienced a serious adverse event. Of these, a vaccine-related SAE was reported for no participants in the Control vaccines group and for 4 participants (0.1%) in the VAXELIS group:

- 3 of these 4 experienced pyrexia 1 to 2 days following the first study vaccinations; and
- 1 of these 4 experienced an apparent life-threatening event (vomiting followed by pallor and lethargy) on the day of the first study vaccinations, and again 2 days later.

Deaths

In the 2 US studies, death was reported in 6 participants (0.2%) who received VAXELIS and in 1 participant (0.1%) who received Pentacel + RECOMBIVAX HB vaccines; none were assessed as vaccine related. Causes of death among infants who received VAXELIS were sepsis, 2 cases of Sudden Infant Death Syndrome, asphyxia, unknown cause, and hydrocephalus (occurring 2, 10 and 49, 42, 44 days, and 11 months post-vaccination, respectively). Across all 6 clinical studies, there were no deaths assessed as related to VAXELIS.

6.2 Postmarketing Experience

The following adverse events have been reported during post-marketing use of VAXELIS or other vaccines containing the antigens of VAXELIS. These adverse events are included based on a suspected causal connection to VAXELIS or the components of DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), IPOL® (Poliovirus Vaccine Inactivated), COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine]. (COMVAX is no longer licensed in the US.)

Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccination.

- ***Immune System Disorders***
  Hypersensitivity (such as rash, urticaria, dyspnea, erythema multiforme), anaphylactic reaction (such as urticaria, angioedema, edema, face edema, shock).
- ***General Disorders and Administration Site Conditions***
  Extensive swelling of injected limb (including swelling that involves adjacent joints).
- ***Nervous System***
  Seizure, febrile seizure, hypotonic-hyporesponsive episode (HHE).

7 DRUG INTERACTIONS

7.1 Interference with Laboratory Tests

Sensitive tests (e.g., Latex Agglutination kits) have detected vaccine-derived polyribosylribitol phosphate (PRP) in the urine of vaccinees for at least 30 days following vaccination with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]. (2) Therefore, urine antigen detection may not have definite diagnostic value in suspected *H. influenzae* type b disease following vaccination with VAXELIS. [See *WARNINGS AND PRECAUTIONS (5.7).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

VAXELIS is not approved for use in individuals 5 years of age and older. No human or animal data are available to assess vaccine-associated risks in pregnancy.

8.2 Lactation

VAXELIS is not approved for use in individuals 5 years of age and older. No human or animal data are available to assess the impact of VAXELIS on milk production, its presence in breast milk, or its effects on the breastfed infant.

8.4 Pediatric Use

The safety of VAXELIS has been established in the age group 6 weeks through 15 months, and the effectiveness of VAXELIS was established in the age group 6 weeks through 6 months on the basis of clinical studies. [See *ADVERSE REACTIONS (6.1) AND CLINICAL STUDIES (14).*]

The safety and effectiveness of VAXELIS in older children through 4 years of age are supported by evidence in younger children. The safety and effectiveness of VAXELIS in infants less than 6 weeks of age and in children and adolescents 5 through 17 years of age have not been established.

11 DESCRIPTION

VAXELIS (Diphtheria and Tetanus Toxoids and Acellular Pertussis, Inactivated Poliovirus, Haemophilus b Conjugate and Hepatitis B Vaccine) is a sterile injectable suspension for intramuscular use.

Each 0.5 mL dose is formulated to contain 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses [29 D-antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)], 3 mcg polyribosylribitol phosphate (PRP) of *H. influenzae* type b covalently bound to 50 mcg of the outer membrane protein complex (OMPC) of *Neisseria meningitidis* serogroup B, and 10 mcg hepatitis B surface antigen (HBsAg). Each 0.5 mL dose contains 319 mcg aluminum from aluminum salts used as adjuvants.

Other ingredients per 0.5 mL dose include <0.0056% polysorbate 80 and the following residuals from the manufacturing process: ≤14 mcg formaldehyde, ≤50 ng glutaraldehyde, ≤50 ng bovine serum albumin, <5 ng of neomycin, <200 ng streptomycin sulfate, <25 ng polymyxin B sulfate, ≤0.125 µg ammonium thiocyanate and ≤0.1 mcg yeast protein (maximum 1% relative to HBsAg protein).

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (3) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and diafiltered.

Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (4) Tetanus toxin is detoxified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown in Stainer-Scholte medium (5) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

The Type 1, Type 2, and Type 3 polioviruses are individually grown in Vero cells. The viral harvests are concentrated and purified, then inactivated with formaldehyde to produce

monovalent suspensions of each serotype. Specified quantities of monovalent suspensions of each serotype are mixed to produce the trivalent poliovirus concentrate.

The HBsAg antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The recombinant *Saccharomyces cerevisiae* is grown in a fermentation medium which consists of an extract of yeast, soy peptone, dextrose, amino acids, and mineral salts. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods which includes ion and hydrophobic chromatography, and diafiltration. The purified protein is treated in phosphate buffer with formaldehyde and then co-precipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate.

The purified PRP of *H. influenzae* type b (Haemophilus b, Ross strain) is conjugated to an OMPC of the B11 strain of *N. meningitidis* serogroup B. *H. influenzae* type b is grown in a fermentation medium which includes an extract of yeast, nicotinamide adenine dinucleotide, hemin chloride, soy peptone, dextrose, and mineral salts. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. *N. meningitidis* serogroup B is grown in a fermentation medium which includes an extract of yeast, amino acids and mineral salts. The OMPC is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration. PRP is conjugated to OMPC by chemical coupling and the PRP-OMPC is then adsorbed onto an amorphous aluminum hydroxyphosphate sulfate adjuvant.

The adsorbed diphtheria, tetanus, and acellular pertussis antigens are combined with aluminum phosphate (as adjuvant) and water for injection into an intermediate concentrate. The individual HBsAg and PRP-OMPC adjuvanted bulks are added followed by the trivalent poliovirus concentrate, to produce VAXELIS.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL of serum in the guinea pig potency test. The potency of the acellular pertussis antigens PT, FHA, and FIM is evaluated by the antibody response of immunized mice to detoxified forms as measured by enzyme-linked immunosorbent assay (ELISA). The potency of the acellular pertussis antigen PRN is measured by an *in vitro* PRN antigenicity ELISA. The potency of the inactivated poliovirus antigens is determined using an *in vitro* D-antigen ELISA for each serotype. The potency of the HBsAg component is measured relative to a standard by an *in vitro* immunoassay. The potency of the PRP-OMPC component is measured by quantitating the polysaccharide concentration using a high-performance liquid chromatography (HPLC) method.

VAXELIS does not contain a preservative. The syringe plunger stopper and syringe tip cap are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of

protection. Antitoxin levels of ≥0.1 IU/mL are generally regarded as protective. (6) Levels of 1.0 IU/mL have been associated with long-term protection. (7)

Tetanus

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of ≥0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (6) (8) A tetanus antitoxoid level ≥0.1 IU/mL as measured by the ELISA used in clinical studies of VAXELIS is considered protective.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative coccobacillus produces a variety of biologically active components, though their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

Poliomyelitis

Polioviruses, of which there are 3 serotypes (Types 1, 2, and 3), are enteroviruses. The presence of poliovirus type-specific neutralizing antibodies has been correlated with protection against poliomyelitis. (9)

Hepatitis B

Hepatitis B virus is one of several hepatitis viruses that cause systemic infection, with major pathology in the liver. Antibody concentrations of ≥10 mIU/mL against HBsAg correlate with protection against hepatitis B virus infection.

Haemophilus influenzae type b Invasive Disease

H. influenzae type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody has been shown to correlate with protection against invasive disease due to *H. influenzae* type b.

Based on data from passive antibody studies (10) and an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland, (11) a post-vaccination anti-PRP level of ≥0.15 mcg/mL is considered a minimal protective level. Data from an efficacy study with *H. influenzae* type b polysaccharide vaccine in Finland indicate that an anti-PRP level of ≥1.0 mcg/mL 3 weeks after vaccination predicts protection through a subsequent 1-year period. (11) (12) These levels have been used to evaluate the effectiveness of *H. influenzae* type b conjugate vaccines, including the PRP-OMPC component of VAXELIS.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VAXELIS has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Effectiveness of VAXELIS

The effectiveness of VAXELIS is based on the immunogenicity of the individual antigens compared to US licensed vaccines. Serological correlates of protection exist for diphtheria,

tetanus, hepatitis B, poliomyelitis, and invasive disease due to *H. influenzae* type b. The effectiveness against pertussis is based upon the pertussis immune responses following 3 doses of VAXELIS compared to 3 doses of Pentacel, as well as the pertussis immune responses following a subsequent dose of DAPTACEL in the same 2 groups of children. VAXELIS, Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by the same processes.

14.2 Immunogenicity

In the US Study 005 (Table 1), infants were randomized to receive 3 doses of VAXELIS at 2, 4, and 6 months of age and DAPTACEL and PedvaxHIB at 15 months of age, or Control group vaccines (3 doses of Pentacel vaccine at 2, 4, and 6 months of age + RECOMBIVAX HB at 2 and 6 months of age and DAPTACEL and ActHIB at 15 months of age). All subjects received concomitant vaccines: RotaTeq at 2, 4 and 6 months and Prevnar 13 at 2, 4, 6, and 15 months of age. [See *ADVERSE REACTIONS (6.1)*.] All infants had received a dose of hepatitis B vaccine prior to study initiation, prior to or at one month of age. Among all randomized participants, 53.0% were male and 47.0% were female. Most (79.2%) participants were White, 14.1% were Black and 5.2% were multi-racial. Most (91.4%) participants were of non-Hispanic or non-Latin ethnicity.

Antibody responses to diphtheria, tetanus, pertussis (PT, FHA, PRN and FIM), poliovirus types 1, 2 and 3, hepatitis B and *H. influenzae* type b antigens were measured in sera obtained one month following the third dose of VAXELIS or Pentacel + RECOMBIVAX HB vaccines. VAXELIS was non-inferior to Pentacel + RECOMBIVAX HB administered concomitantly at separate sites, as demonstrated by the proportions of participants achieving seroprotective levels of antibodies to diphtheria, tetanus, poliovirus, hepatitis B and PRP antigens, and pertussis vaccine response rates and GMCs (except FHA), following 3 doses of the vaccine. See Table 3.

To complete the 4-dose pertussis primary vaccination series, participants in both groups received DAPTACEL at 15 months of age and were evaluated for immune responses to pertussis antigens one month later. The non-inferiority criteria for vaccine response rates and GMCs for all pertussis antigens were met following the fourth dose.

Table 3: Antibody Responses One Month Following Dose 3 of VAXELIS or Control Vaccines Administered Concomitantly with Prevnar 13 and RotaTeq in Study 005

	VAXELIS + Prevnar 13 + RotaTeq (N=688 - 810)	Pentacel + RECOMBIVAX HB + Prevnar 13 + RotaTeq (N=353 - 400)
Anti-Diphtheria Toxoid		
% ≥0.1 IU/mL	82.4*	86.3
Anti-Tetanus Toxoid		
% ≥0.1 IU/mL	99.9†	99.5
Anti-PT		
% vaccine response‡	98.1*	98.5
GMC	109.6§	85.4
Anti-FHA		
% vaccine response‡	87.3*	92.0
GMC	46.6¶	72.3
Anti-PRN		
% vaccine response‡	79.3*	82.0
GMC	55.8§	66.8
Anti-FIM		
% vaccine response‡	90.2*	86.2
GMC	235.9§	184.4
Anti-Poliovirus Type 1		
% ≥1:8 dilution	100.0†	98.2
Anti-Poliovirus Type 2		
% ≥1:8 dilution	100.0†	99.7
Anti-Poliovirus Type 3		
% ≥1:8 dilution	100.0†	99.8
Anti-PRP		
% ≥0.15 μg/mL	97.3†	92.4
% ≥1.0 μg/mL	85.0*	75.3
Anti-HBsAg		
% ≥10 mIU/mL	99.4*	98.6

N = The number of participants with available data.

* Non-inferiority criterion met (lower bound of 2-sided 95% CI for the difference [VAXELIS group minus Control vaccines group] was >-10%).

† Non-inferiority criterion met (lower bound of 2-sided 95% CI for the difference [VAXELIS group minus Control vaccines group] was >-5%).

‡ Vaccine response = if pre-vaccination antibody concentration was <4 x lower limit of quantitation [LLOQ], then the post-vaccination antibody concentration was ≥4 x LLOQ; if pre-vaccination antibody concentration was ≥4 x LLOQ, then the post-vaccination antibody concentration was ≥pre-vaccination levels (pre-Dose 1).

§ Non-inferiority criterion met (lower bound of 2-sided 95% CI for the GMC ratio [VAXELIS group/Control vaccines group] was >0.67).

¶ Non-inferiority criterion not met for anti-FHA GMC (lower bound of 2-sided 95% CI for the GMC ratio [VAXELIS group/Control vaccines group was 0.59 which is below the non-inferiority criterion >0.67).

Study 006 (Table 1) was a lot consistency study conducted in the US, where infants were randomized to receive 3 doses of VAXELIS at 2, 4, and 6 months of age and Pentacel at 15 months of age (N=2,406), or control group vaccines (4 doses of Pentacel at 2, 4, 6, and 15 months of age + RECOMBIVAX HB at 2 and 6 months of age; N=402). All subjects received concomitant vaccines: RotaTeq at 2, 4 and 6 months and Prevnar 13 at 2, 4, 6, and 15 months of age. All infants had received a dose of hepatitis B vaccine prior to study initiation, from birth up to one month of age.

Antibody responses to diphtheria, tetanus, pertussis (PT, FHA, PRN and FIM), poliovirus types 1, 2 and 3, hepatitis B and *H. influenzae* type b antigens were measured in sera obtained one month following the third dose of VAXELIS or Pentacel + RECOMBIVAX HB. VAXELIS was non-inferior to Pentacel + RECOMBIVAX HB administered concomitantly at separate sites, as demonstrated by the proportions of participants achieving seroprotective levels of antibodies to diphtheria, tetanus, poliovirus, hepatitis B and PRP antigens, and pertussis vaccine response rates and GMCs, except for GMCs for FHA (lower bound of 2-sided 95% CI for GMC ratio [VAXELIS group/Control group vaccines] was 0.62, which was below the non-inferiority criterion >0.67).

To complete the 4-dose pertussis primary vaccination series, participants in both groups received Pentacel at 15 months of age and were evaluated for immune responses to pertussis antigens one month later. The non-inferiority criteria for antibody vaccine response rates and GMCs for all pertussis antigens were met following the fourth dose except for GMCs for PRN (lower bound of 2-sided 95% CI for GMC ratio [VAXELIS group/Control group vaccines] was 0.66, which was below the non-inferiority criterion >0.67).

14.3 Concomitantly Administered Vaccines

In Study 006 conducted in the US (Table 1), the immune responses to Prevnar 13 were measured one month after the third dose. Non-inferiority criteria were met for GMCs to 12 of the 13 serotype antigens in Prevnar 13 for participants who received VAXELIS relative to Control vaccines. For serotype 6B, the non-inferiority criterion was not met (lower bound of 2-sided 95% CI for GMC ratio [VAXELIS group/Control vaccines group] is 0.64, which is below the non-inferiority criterion >0.67).

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-dose, prefilled syringe with Luer lock connection and a tip cap, without needle, 0.5 mL (NDC 63361-243-88). Supplied as package of 10 (NDC 63361-243-15).

The syringe plunger stopper and syringe tip cap are not made with natural rubber latex.

16.2 Storage and Handling

VAXELIS should be stored at 2°C to 8°C (36°F to 46°F). **Do not freeze**. Product which has been exposed to freezing should not be used. Protect from light. Do not use after expiration date shown on the label. Discard unused portion.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the parent or guardian of the following:

- The potential benefits and risks of immunization with VAXELIS.
- The common adverse reactions that have occurred following administration of VAXELIS or other vaccines containing similar ingredients.
- Other adverse reactions can occur. Call healthcare provider with any adverse reactions of concern.

Provide the Vaccine Information Statements (VIS), which are required by the National Childhood Vaccine Injury Act of 1986.

Manufactured by:

Sanofi Vaccines Canada Ltd.
Toronto, Ontario, Canada

for:

MSP Vaccine Company

Swiftwater, PA 18370, USA

Distributed by:

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R12-0426 USA