SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vaxelis suspension for injection in pre-filled syringe
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated), and Haemophilus type b conjugate vaccine (adsorbed).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 mL) contains:

Diphtheria Toxoid[1]	not less than 20 IU
Tetanus Toxoid[1]	not less than 40 IU
Bordetella pertussis antigens[1]	
Pertussis Toxoid (PT)	20 micrograms
Filamentous Haemagglutinin (FHA)	20 micrograms
Pertactin (PRN)	3 micrograms
Fimbriae Types 2 and 3 (FIM)	5 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (Inactivated)[4]	
Type 1 (Mahoney)	40 D antigen units[5]
Type 2 (MEF-1)	8 D antigen units[5]
Type 3 (Saukett)	32 D antigen units[5]
Haemophilus influenzae type b polysaccharide	
(Polyribosylribitol Phosphate)	3 micrograms
Conjugated to meningococcal protein[2]	50 micrograms

[1] adsorbed on aluminium phosphate (0.17 mg Al^{3+})
[2] adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al^{3+})
[3] produced in yeast (*Saccharomyces cerevisiae*) cells by recombinant DNA technology
[4] produced in Vero cells
[5] or equivalent antigenic quantity determined by a suitable immunochemical method.

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin, polymyxin B, and bovine serum albumin which are used during the manufacturing process (see section 4.3).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection.
Uniform, cloudy, white to off-white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaxelis (DTaP-HB-IPV-Hib) is indicated 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).

The use of Vaxelis should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination:

The primary vaccination schedule consists of two or three doses, with an interval of at least 1 month between doses, and may be given from 6 weeks of age, in accordance with the official recommendations.

Where a dose of hepatitis B vaccine is given at birth, Vaxelis can be used for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used. Vaxelis can be used for a mixed hexavalent/pentavalent/hexavalent combined vaccine immunisation schedule.

Booster vaccination:

After a 2-dose or a 3-dose primary series vaccination with Vaxelis, a booster dose should be given at least 6 months after the last priming dose. Booster dose should be given in

accordance with the official recommendations. As a minimum, a dose of Hib vaccine must be administered.

Other paediatric population

The safety and efficacy of Vaxelis in infants less than 6 weeks of age have not been established. No data are available.

No data are available in older children (see sections 4.8 and 5.1).

Method of administration

Vaxelis should only be administered by intramuscular (IM) injection. The recommended injection sites are the anterolateral area of the thigh (preferred site for infants under one year of age) or the deltoid muscle of the upper arm.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

History of an anaphylactic reaction after a previous administration of Vaxelis or a vaccine containing the same components or constituents.

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to trace residuals (glutaraldehyde, formaldehyde, neomycin, streptomycin, polymyxin B, and bovine serum albumin).

Encephalopathy of unknown aetiology, occurring within 7 days following prior vaccination with a pertussis containing vaccine. In these circumstances, pertussis vaccination should be discontinued, and the vaccination course should be continued with diphtheria, tetanus, hepatitis B, poliomyelitis, and Hib vaccines.

Uncontrolled neurologic disorder or uncontrolled epilepsy: pertussis vaccination should not be administered until treatment for the condition has been established, the condition has stabilised, and the benefit clearly outweighs the risk.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Protection

Vaxelis will not prevent disease caused by pathogens other than Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, hepatitis B virus, poliovirus or Haemophilus influenzae type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Vaxelis will not protect against hepatitis infection caused by other agents such as hepatitis A, hepatitis C and hepatitis E or by other liver pathogens.

Because of the long incubation period of hepatitis B, it is possible for unrecognised hepatitis B infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B infection in such cases.

Vaxelis does not protect against disease caused by Haemophilus influenzae other than type b or by other microorganisms that cause invasive disease such as meningitis or sepsis, including N. meningitidis.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Prior to immunisation

Vaccination should be preceded by a review of the individual's medical history (in particular, previous vaccinations and possible adverse reactions).

As with all injectable vaccines, appropriate medical treatment and supervision should be readily available for immediate use in case of a rare anaphylactic reaction following the administration of the vaccine (see section 4.3).

As with other vaccines, administration of Vaxelis should be postponed in children suffering from moderate to severe acute disease, with or without fever. The presence of a minor illness and /or low-grade fever does not constitute a contraindication.

If any of the following events have occurred after administration of a pertussis-containing vaccine, the decision to administer further doses of a pertussis-containing vaccine should be carefully considered:

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

There may be some circumstances, such as high incidence of pertussis, when the potential benefits outweigh possible risks.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give any vaccine containing tetanus toxoid, including Vaxelis, should be based on careful consideration of the potential benefits and possible risks.

A history of febrile convulsions, a family history of convulsions, or Sudden Infant Death Syndrome (SIDS) do not constitute a contraindication for the use of Vaxelis. Individuals with a history of febrile convulsions should be closely followed up as febrile convulsions may occur within 2 to 3 days post vaccination.

Do not administer by intravascular, intradermal or subcutaneous injection.

Special populations

Premature infants

Limited data from 111 pre-term newborn infants in clinical trials indicate that Vaxelis can be given to premature infants. The immune responses to Vaxelis in these infants were generally similar to those of the overall study population. However, a lower immune response may be observed, and the level of clinical protection is unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born ≤28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Genetic Polymorphism
Immune responses to the vaccine have not been studied in the context of genetic polymorphism.

Immunocompromised children
The immunogenicity of the vaccine may be reduced by immunosuppressive treatment or immunodeficiency. It is recommended to postpone vaccination until the end of such treatment or disease. Nevertheless, vaccination of individuals with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited.

Blood disorders
As with all injectable vaccines, the vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

Interference with laboratory testing
Since the Hib capsular polysaccharide antigen is excreted in the urine, a false positive urine test can be observed using sensitive tests, for at least 30 days following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vaxelis may be administered simultaneously with pneumococcal polysaccharide conjugate vaccines, rotavirus vaccines, measles, mumps, rubella (MMR) and varicella containing vaccines and meningococcal C conjugate vaccines.
Data from a clinical study indicate that, when Vaxelis is co-administered with pneumococcal conjugate vaccine (PCV13), the rate of fever is higher following the booster dose in the second year of life compared to the primary series. Almost all fevers were mild or moderate (<39.5°C) and transient (duration of ≤2 days) (see section 4.8).

Co-administration of Vaxelis with other injectable vaccines must be carried out at separate injection sites and, preferably, separate limbs.

Vaxelis should not be mixed with any other vaccine or other parenterally administered medicinal products.

Immunosuppressive therapy may interfere with the development of expected immune response (see section 4.4).

4.6 Fertility, pregnancy and lactation

This vaccine is not intended for administration to women of child-bearing potential.

4.7 Effects on ability to drive and use machines

Vaxelis is indicated for infants and toddlers; therefore, no studies have been conducted to assess its effect on the ability to drive or use machines. It is expected that the vaccine will have negligible or no effects in this regard.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions after Vaxelis administration were irritability, crying, somnolence, injection site reactions (pain, erythema, swelling), pyrexia (≥38°C), decreased appetite, and vomiting.

The safety of Vaxelis in children over 15 months of age has not been studied in clinical trials.

In a clinical study where Vaxelis was administered concomitantly with Prevenar 13 (PCV13) as a booster dose of both vaccines, fever ≥38.0°C was reported in 52.5% of children, compared to 33.1% to 40.7% of children during the primary series. Fever ≥39.5°C was observed in 3.7% of children (post-booster) and 0.2% to 0.8% of children (post-primary) receiving Vaxelis with PCV13 (see sections 4.4 and 4.5). Almost all fevers after primary and booster doses were mild or moderate (<39.5°C) and transient (duration of ≤2 days).

Tabulated list of adverse reactions

The following convention has been used for the classification of adverse reactions:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Table 1: List of Adverse Reactions

MedDRA System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Uncommon	Rhinitis
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Uncommon	Increased appetite
Psychiatric disorders	Uncommon	Sleep disorders including insomnia, restlessness
Nervous system disorders	Very Common	Somnolence
	Uncommon	Hypotonia
Vascular disorders	Uncommon	Pallor
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough
Gastrointestinal disorders	Very Common	Vomiting
	Common	Diarrhoea
	Uncommon	Abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	Rash, hyperhidrosis
General disorders and administration site conditions	Very Common	Crying, irritability
		Injection site erythema, injection site pain, injection site swelling
		Pyrexia
	Common	Injection site bruising, injection site induration, injection site nodule
	Uncommon	Injection site rash, injection site warmth, fatigue

Post-Marketing Surveillance

The following adverse events have been reported during post-marketing use. Because these events were reported from a population of uncertain size, it is generally not possible to reliably estimate their frequency or to establish, a causal relationship to the vaccine.

MedDRA System Organ Class	Frequency	Adverse Event
Nervous system disorders	Not known	Convulsions with or without fever, hypotonic-hyporesponsive episode (HHE) (see section 4.4)

Description of selected adverse reactions

The following adverse events have been reported with other vaccines containing the components or constituents of Vaxelis without regard to causality or frequency.

Immune system disorders
Hypersensitivity (such as rash, urticaria, dyspnoea, erythema multiforme), anaphylactic reaction (such as urticaria, angioedema, oedema, face oedema, shock).

General disorders and administration site conditions

Extensive swelling of the vaccinated limb from the injection site beyond one or both joints, has been reported in children. These reactions start within 24 to 72 hours after vaccination, may be associated with erythema, warmth, tenderness or pain at the injection site and resolve spontaneously within 3 to 5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine, with a greater risk following the 4th and 5th doses.

Premature infants

Apnoea in very premature infants (≤28 weeks of gestation) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Medicines and Healthcare products Regulatory Agency (MHRA), Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No cases of overdose have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Bacterial and viral vaccines combined, ATC code: J07CA09

Immunogenicity after primary series and booster doses

The primary vaccination schedules used in clinical studies were: 2, 4 months of age without hepatitis B vaccination at birth; 2, 3, 4 months of age without hepatitis B vaccination at birth; and 2, 4, 6 months of age with and without hepatitis B vaccination at birth. The booster dose in clinical studies was given at 11-12 months of age after a 2-dose primary series, at 12 months of age after a 3-dose primary series (2, 3, 4 months), and at 15 months of age after a 3-dose primary series (2, 4, 6 months). Results obtained for each component of the vaccine are summarised in Table 2 and Table 3.

Table 2: Seroprotection/Vaccine Response Rates One Month After the Primary Vaccination Series

Antibody Thresholds	**Two doses**	**Three doses**

		2, 4 months	2, 3, 4 months	2, 4, 6 months
		N = 319-609 %	N = 498-550 %	N = 2455-2696 %
Anti-diphtheria (≥ 0.01 IU/mL)		98.3	99.8	99.8
Anti-tetanus (≥ 0.01 IU/mL)		100.0	100.0	100.0
Anti-PT (vaccine response)[a]		98.1	99.4	98.9
Anti-FHA (vaccine response)[a]		89.0	89.0	88.1
Anti-PRN (vaccine response)[a]		80.3	86.7	84.0
Anti-FIM (vaccine response)[a]		93.3	97.2	90.0
Anti-Polio type 1 (≥ 1:8 dilution)		93.8	100.0	100.0
Anti-Polio type 2 (≥ 1:8 dilution)		98.0	99.8	100.0
Anti-Polio type 3 (≥ 1:8 dilution)		92.9	100.0	100.0
Anti-HBs Ag (≥ 10 mIU/mL)	With hepatitis B vaccination at birth	/	/	99.8
	Without hepatitis B vaccination at birth	98.1	97.8	97.8[b]
Anti-PRP (≥ 0.15 µg/mL)		96.6	98.4	98.1

[a]Vaccine response: If pre-dose 1 antibody concentration < lower limit of quantification (LLOQ), then the post-vaccination series antibody concentration was ≥ LLOQ; if pre-dose 1 antibody concentration ≥ LLOQ, then the post-vaccination series antibody concentration was ≥ pre-dose 1 levels.
LLOQ = 4 EU/mL are for anti-PT, anti-PRN and anti-FIM; and LLOQ = 3 EU/mL for anti-FHA

[b]N=89 subjects from a separate study

Table 3: Seroprotection/Vaccine Response Rates One Month After Booster Vaccination

Antibody Thresholds		**Booster at 11-12 months, after primary doses at 2, 4, months**	**Booster at 12 months after primary doses at 2, 3, 4 months**
		N = 377-591 %	**N = 439-551 %**
Anti-diphtheria (≥ 0.1 IU/mL)		98.6	99.8
Anti-tetanus (≥ 0.1 IU/mL)		99.8	100.0
Anti-PT (vaccine response)[a]		99.1	99.8
Anti-FHA (vaccine response)[a]		97.4	97.2
Anti-PRN (vaccine response)[a]		96.9	99.3
Anti-FIM (vaccine response)[a]		98.3	99.6
Anti-Polio type 1 (≥ 1:8 dilution)		99.3	99.8
Anti-Polio type 2 (≥ 1:8 dilution)		99.8	100.0
Anti-Polio type 3 (≥ 1:8 dilution)		99.5	100.0
Anti-HBs Ag (≥ 10 mIU/mL)[b]		98.1	99.6
Anti-PRP	(≥ 0.15 µg/mL)	99.6	99.5
	(≥ 1.0 µg/mL)	89.9	95.0

[a]Vaccine response: If pre-dose 1 antibody concentration < LLOQ, then post-booster antibody concentration should be ≥ LLOQ; If pre-dose 1 antibody concentration ≥ LLOQ, then the post-booster antibody concentration should be ≥ pre-dose 1 levels. LLOQ = 4 EU/mL are for anti-PT, anti-PRN and anti-FIM; and LLOQ = 3 EU/mL for anti-FHA

[b]Did not receive hepatitis B vaccine at birth

Regarding PT and FIM, similar response rates and higher GMCs were observed both post-primary and post-booster in comparison to control vaccine. Lower FHA, PRN, IPV1 and IPV3 immune responses were observed after a 2-dose primary schedule (2, 4 months), although the clinical relevance of these data remains uncertain. Pertussis response rates were similar to the control vaccine for all pertussis antigens after the booster dose.

The immunogenicity of Vaxelis administered to children over 15 months of age has not been studied in clinical trials.

Persistence of the immune response

Hepatitis B immune memory

The persistence of immune responses was evaluated in children up to 8 years after primary vaccination with Vaxelis. The proportions of these children with anti-HBsAg ≥ 10 mIU/mL after having received Vaxelis either at 2, 4, and 11-12 months or at 2, 3, 4, and 12 months of age, respectively, were:

- 65.8% (119 of 181) and 70.2% (134 of 191), respectively, at 4 or 5 years of age;
- 40.9% (38 of 93) and 49.1% (55 of 112), respectively, at 8 or 9 years of age.

A hepatitis B vaccine challenge dose was given to children 8 or 9 years of age. Approximately 1 month after this challenge dose, the proportions with anti-HBsAg ≥ 10 mIU/mL were 100% (93 of 93) and 99.1% (108 of 109), respectively. These data demonstrate an anamnestic response after a challenge dose, indicating the persistence of hepatitis B immune memory in persons who previously received Vaxelis.

Persistence of antibodies to pertussis antigens

The persistence of pertussis antibodies was measured in children 4 or 5 years of age who had received Vaxelis at 2, 4, and 11-12 months of age. The percentages of these children with anti-pertussis antibodies ≥ the lower limit of quantification were: anti-PT 58.4%, anti-FHA 80.9%, anti-PRN 66.1% and anti-FIM 94.4%.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other vaccines or medicinal products.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

Stability data indicate that the vaccine is stable at temperatures up to 25°C for 150 hours. At the end of this period Vaxelis should be used or discarded. These data are intended to guide healthcare professionals in case of a

temporary temperature excursion only.

6.5 Nature and contents of container

0.5 mL suspension in pre-filled syringe (type I glass) with plunger stopper (butyl) and tip cap (butyl), without needle – pack size of 1 or 10.
0.5 mL suspension in pre-filled syringe (type I glass) with plunger stopper (butyl) and tip cap (butyl), without needle – multipack of 5 packs of 10.
0.5 mL suspension in pre-filled syringe (type I glass) with plunger stopper (butyl) and tip cap (butyl), with 1 separate needle – pack size of 1 or 10.
0.5 mL suspension in pre-filled syringe (type I glass) with plunger stopper (butyl) and tip cap (butyl), with 2 separate needles – pack size of 1 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for use: suspension for injection in pre-filled syringe

Prior to administration, the pre-filled syringe should be shaken gently in order to obtain a homogeneous, whitish, cloudy suspension.

The suspension should be visually inspected, prior to administration, for foreign particulate matter and/or variation of physical appearance. If either is observed, discard the pre-filled syringe.

The needle must be fitted firmly on to the pre-filled syringe, rotating it by a one-quarter turn.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MCM Vaccine B.V.
Robert Boyleweg 4
2333 CG Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 50692/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

08/06/2022