

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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
<i>Bordetella pertussis</i> 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
<i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate)	3 micrograms
Conjugated to meningococcal protein ²	50 micrograms

¹ adsorbed on aluminium phosphate (0.17 mg Al³⁺)

² adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al³⁺)

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 and polymyxin B 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, and polymyxin B).

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

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 $\geq 40.5^{\circ}\text{C}$ 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.

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).

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 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.

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 age.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

a- 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 ($\geq 38^{\circ}\text{C}$), 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 $\geq 38.0^{\circ}\text{C}$ was reported in 54.3% of children, compared to 33.1% to 40.7% of children during the primary series. Fever $\geq 39.5^{\circ}\text{C}$ 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 ($< 39.5^{\circ}\text{C}$) and transient (duration of ≤ 2 days).

b- Tabulated list of adverse reactions

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

Very common	($\geq 1/10$)
Common	($\geq 1/100$ to $< 1/10$)
Uncommon	($\geq 1/1,000$ to $< 1/100$)
Rare	($\geq 1/10,000$ to $< 1/1,000$)
Very rare	($< 1/10,000$)

Table 1: List of Adverse Reactions

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	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

c- 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, dyspnea, erythema multiforme), anaphylactic reaction (such as urticaria, angioedema, edema, face edema, shock).

Nervous system disorders

Convulsion, febrile convulsion.

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.

d- 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 national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 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 ($\geq 1:8$ dilution)		93.8	100.0	100.0
Anti-Polio type 2 ($\geq 1:8$ dilution)		98.0	99.8	100.0
Anti-Polio type 3 ($\geq 1:8$ dilution)		92.9	100.0	100.0
Anti-HBs Ag (≥ 10 IU/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 μ g/mL)		96.6	98.4	98.1

^aVaccine response: If pre-Dose 1 antibody concentration < lower limit of quantification (LLOQ), then the post-vaccination series antibody concentration was \geq LLOQ; if pre-Dose 1 antibody concentration \geq LLOQ, then the post-vaccination series antibody concentration was \geq pre-Dose 1 levels. LLOQ = 4EU/mL are for anti-PT, anti-PRN and anti-FIM; and LLOQ = 3EU/mL for anti-FHA

^bN=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)	
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 ($\geq 1:8$ dilution)		99.3	99.8
Anti-Polio type 2 ($\geq 1:8$ dilution)		99.8	100.0
Anti-Polio type 3 ($\geq 1:8$ dilution)		99.5	100.0
Anti-HBs Ag (≥ 10 mIU/mL) ^b		98.1	99.6
Anti-PRP	(≥ 0.15 μ g/mL)	99.6	99.5
	(≥ 1.0 μ g/mL)	89.9	95.0

^a Vaccine response: If pre-Dose 1 antibody concentration < LLOQ, then post-booster antibody concentration should be \geq LLOQ; If pre-Dose 1 antibody concentration \geq LLOQ, then the post-booster antibody concentration should be \geq pre-Dose 1 levels. LLOQ = 4EU/mL are for anti-PT, anti-PRN and anti-FIM; and LLOQ = 3EU/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 remain 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

Long-term persistence of antibody to hepatitis B surface antigen

The persistence of antibody to hepatitis B surface antigen (anti-HBsAg) was measured in children 4 or 5 years of age who had received Vaxelis either at 2, 4 and 11-12 months or at 2, 3, 4 and 12 months of age. The proportion of children seroprotected (anti-HBsAg \geq 10 mIU/mL) after those vaccination schedules was 98.1% and 99.6%, respectively, and decreased to 65.7% and 70.2% approximately 4 years later. Considerable study data suggest that individuals who have ever had a seroprotective response to hepatitis B vaccination will have a memory response that is protective against clinical disease if exposed to the hepatitis B virus.

Long-term 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. After approximately 4 years, the percentages of children with anti-pertussis antibodies above LLOQ were as follows: anti-PT 58.4%, anti-FHA 80.9%, anti-PRN 66.1% and anti-FIM 94.3%.

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 container 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 and other handling

Instructions for Use

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)

EU/1/15/1079/001
EU/1/15/1079/002
EU/1/15/1079/003
EU/1/15/1079/004
EU/1/15/1079/005
EU/1/15/1079/006

EU/1/15/1079/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 February 2016

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Merck Sharp and Dohme Corporation
770 Sumneytown Pike
West Point, PA 19486.
United States

Sanofi Pasteur SA
1541 Avenue Marcel Mérieux
69280 Marcy l'Etoile
France

Sanofi Pasteur Limited
1755 Steeles Avenue West Toronto
Ontario M2R 3T4
Canada

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for pre-filled syringe without needle, with one separate needle, with two separate needles. Pack of 1 or 10.

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).

DTaP-HB-IPV-Hib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml):

Diphtheria Toxoid	≥ 20 IU
Tetanus Toxoid	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis Toxoid/Filamentous Haemagglutinin/ Fimbriae types 2 and 3/Pertactin)	20/20/5/3 µg
Hepatitis B surface antigen	10 µg
Poliovirus (Inactivated) Types 1/2/3	40/8/32 DU
<i>Haemophilus influenzae</i> type b polysaccharide conjugated to meningococcal protein	3 µg 50 µg

3. LIST OF EXCIPIENTS

Excipients:

Sodium phosphate

Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

1 pre-filled syringe (0.5 ml) without needle

10 pre-filled syringes (0.5 ml) without needle

1 pre-filled syringe (0.5 ml) with 1 needle

10 pre-filled syringes (0.5 ml) with 10 needles

1 pre-filled syringe (0.5 ml) with 2 needles

10 pre-filled syringes (0.5 ml) with 20 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.

Shake before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vaccine in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1079/001
EU/1/15/1079/002
EU/1/15/1079/003
EU/1/15/1079/004
EU/1/15/1079/005
EU/1/15/1079/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for prefilled syringes without needle. Pack of 10 (**without blue box**). Component of a multipack.

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).

DTaP-HB-IPV-Hib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) :

Diphtheria Toxoid	≥ 20 IU
Tetanus Toxoid	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis Toxoid/Filamentous Haemagglutinin/ Fimbriae types 2 and 3/Pertactin)	20/20/5/3 μ g
Hepatitis B surface antigen	10 μ g
Poliovirus (Inactivated) Types 1/2/3	40/8/32 DU
<i>Haemophilus influenzae</i> type b polysaccharide conjugated to meningococcal protein	3 μ g 50 μ g

3. LIST OF EXCIPIENTS

Excipients:

Sodium phosphate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

10 pre-filled syringes (0.5 ml) without needle

Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

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EXP: {MM/YYYY}

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Store in a refrigerator. Do not freeze.
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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1079/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton for multipack containing 5 packs of 10 pre-filled syringes without needle. Multipack of **50 (with blue box)**.

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).

DTaP-HB-IPV-Hib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) :

Diphtheria Toxoid	≥ 20 IU
Tetanus Toxoid	≥ 40 IU
<i>Bordetella pertussis</i> antigens (Pertussis Toxoid/Filamentous Haemagglutinin/ Fimbriae types 2 and 3/Pertactin)	20/20/5/3 µg
Hepatitis B surface antigen	10 µg
Poliovirus (Inactivated) Types 1/2/3	40/8/32 DU
<i>Haemophilus influenzae</i> type b polysaccharide conjugated to meningococcal protein	3 µg 50 µg

3. LIST OF EXCIPIENTS

Excipients:

Sodium phosphate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection

Multipack: 50 (5 packs of 10) pre-filled syringes (0.5 mL) without needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Keep the vaccine in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1079/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Label – Prefilled Syringe}

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vaxelis injection

IM

DTaP-HB-IPV-Hib

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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).

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before your child is vaccinated with this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for your child only. Do not pass it on to others.
- If your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vaxelis is and what it is used for
2. What you need to know before Vaxelis is given to your child
3. How to use Vaxelis
4. Possible side effects
5. How to store Vaxelis
6. Contents of the pack and other information

1. What is Vaxelis and what it is used for

Vaxelis is a vaccine, which helps to protect your child against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and serious diseases caused by *Haemophilus influenzae* type b. Vaxelis is given to children from the age of six weeks.

The vaccine works by causing the body to produce its own protection (antibodies) against the bacteria and viruses that cause the following diseases:

- Diphtheria: a bacterial infection that usually first affects the throat, causing pain and swelling which can lead to suffocation. The bacteria also make a toxin (poison) that can damage the heart, kidneys and nerves.
- Tetanus (often called lock jaw): caused by the tetanus bacteria entering a deep wound. The bacteria make a toxin (poison) that causes spasms of the muscles, leading to inability to breathe and the possibility of suffocation.
- Pertussis (often called whooping cough): a highly infectious illness that affects the airways. It causes severe coughing that may lead to problems with breathing. The coughing often has a “whooping” sound. The cough may last for one to two months or longer. Whooping cough can also cause ear infections, chest infections (bronchitis) which may last a long time, lung infections (pneumonia), fits, brain damage and even death.
- Hepatitis B: caused by the hepatitis B virus. It causes the liver to become swollen (inflamed). In some people, the virus can stay in the body for a long time, and can eventually lead to serious liver problems, including liver cancer.
- Poliomyelitis (often just called polio): caused by viruses that affect the nerves. It can lead to paralysis or muscle weakness most commonly of the legs. Paralysis of the muscles that control breathing and swallowing can be fatal.
- *Haemophilus influenzae* type b infections (often just called Hib infections): serious bacterial infections causing meningitis (inflammation of the outer covering of the brain), which can lead to brain damage, deafness, epilepsy, or partial blindness. Infection can also cause inflammation and swelling of the throat, leading to difficulties in swallowing and breathing, and infection can

affect other parts of the body such as the blood, lungs, skin, bones, and joints.

Important information about the protection provided

- Vaxelis will only help to prevent these diseases caused by the bacteria and viruses targeted by the vaccine. Vaxelis does not protect your child against diseases caused by other bacteria and viruses that may cause similar symptoms.
- The vaccine does not contain any live bacteria or viruses and it cannot cause any of the infectious diseases against which it protects.
- As with any vaccine, Vaxelis may not protect 100% of children who receive the vaccine.

2. What you need to know before Vaxelis is given to your child

To make sure that Vaxelis is suitable for your child, it is important to talk to your doctor or nurse if any of the points below apply to your child. If there is anything you do not understand, ask your doctor, pharmacist or nurse to explain.

Do not use Vaxelis if your child:

- has had shortness of breath or swelling of the face (anaphylactic reaction) after administration of a previous dose of Vaxelis.
- is allergic (hypersensitive)
 - to Vaxelis vaccine or any diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines,
 - to any ingredients listed in section 6,
 - to neomycin, streptomycin or polymyxin B (antibiotics), glutaraldehyde or formaldehyde, as these substances are used during the manufacturing process.
- has suffered from a severe reaction affecting the brain (encephalopathy) within 7 days of a prior dose of a pertussis vaccine (acellular or whole cell pertussis).
- has an uncontrolled condition or severe illness affecting the brain and nervous system (uncontrolled neurologic disorder) or uncontrolled epilepsy.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before vaccination if your child:

- has a moderate to severe acute disease, with or without fever (e.g. sore throat, cough, cold or flu). Vaccination with Vaxelis may need to be delayed until your child is better.
- has had any of the following events after receiving a vaccine against pertussis (whooping cough), as the decision to give further doses of pertussis containing vaccine will need to be carefully considered:
 - had a fever of 40.5°C or above within 48 hours not due to another identifiable cause.
 - became floppy, unresponsive or unconscious after the previous vaccination, within 48 hours of vaccination.
 - cried continuously and could not be comforted for more than 3 hours within 48 hours of vaccination.
 - had a fit (convulsions) with or without fever, within 3 days of vaccination.
- previously had Guillain-Barré syndrome (temporary loss of feeling and movement) after being given a vaccine containing tetanus toxoid (an inactivated form of tetanus toxin). Your doctor will decide whether to give Vaxelis to your child.
- is receiving a treatment (such as steroids, chemotherapy or radiotherapy) or has a disease that suppresses or weakens the body's ability to fight infections. It is recommended to postpone vaccination until the end of such treatment or disease. However, children with long standing problems with their immune system such as HIV infection (AIDS) may still be given Vaxelis but the protection may not be as good as in children with a healthy immune system.
- suffers from any undiagnosed illness of the brain or epilepsy which is not controlled. Your doctor or nurse will assess the potential benefit offered by vaccination, once the condition is stabilized.

- suffers from fits during a fever, or there is family history of fits occurring during a fever.
- has any problems with bleeding for a long time after minor cuts, or bruises easily. Your doctor will advise you whether your child should receive Vaxelis.
- was born very prematurely (at or before 28 weeks of gestation). In these infants, longer gaps than normal between breaths may occur for 2 to 3 days after vaccination.

Other medicines or vaccines and Vaxelis

Tell your doctor or nurse if your child is taking or has recently taken or might take any other medicines or vaccines.

Vaxelis can be given at the same time as other vaccines such as pneumococcal vaccines, measles-mumps-rubella-varicella (MMRV) vaccines, rotavirus vaccines or meningococcal C vaccines.

Your doctor or nurse will give these injections at different sites and will use different syringes and needles for each injection.

3. How Vaxelis is given

Vaxelis will be given to your child by a doctor or nurse trained in the use of vaccines and who are equipped to deal with any uncommon severe allergic reaction to the injection (see section 4 Possible side effects).

Your doctor or nurse will inject Vaxelis into your child's thigh (in infants from the age of 6 weeks) or arm (in children older than one year).

The recommended dose is as follows:

First course of vaccination (primary vaccination)

Your child will receive two or three injections given at least one month apart. Your doctor or nurse will tell you when your child should come back for their next injection as per the local vaccination program.

Additional injections (booster)

After the first course of injections, your child will receive a booster dose, in accordance with local recommendations, at least 6 months after the last dose of the first course. Your doctor will tell you when this dose should be given.

If your child misses a dose of Vaxelis

If your child misses a scheduled injection, it is important that you discuss with your doctor or nurse who will decide when to give the missed dose.

It is important to follow the instructions from the doctor or nurse so that your child completes the course of injections. If not, your child may not be fully protected against the diseases.

If you have any further questions on the use of this vaccine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Serious allergic reactions

If any of these symptoms occur after leaving the place where your child received his/her injection, you

must consult a doctor IMMEDIATELY:

- difficulty in breathing
- blueness of the tongue or lips
- a rash
- swelling of the face or throat
- low blood pressure causing dizziness or collapse.

When these signs or symptoms occur they usually develop quickly after the injection is given and while the child is still in the clinic or doctor's surgery.

Serious allergic reactions are a very rare possibility (may affect up to 1 in 10,000 people) after receiving any vaccine.

Other side effects

If your child experiences any of the following side effects, please tell your doctor, nurse or pharmacist.

- Very common side effects (may affect more than 1 in 10 people) are:
 - decreased appetite
 - irritability
 - crying
 - vomiting
 - sleepiness or drowsiness
 - fever (temperature 38°C or higher)
 - pain, redness, swelling at the injection site
- Common side effects (may affect up to 1 in 10 people) are:
 - diarrhoea
 - hard mass, lump (nodule) at the injection site
 - bruising at the injection site
- Uncommon side effects (may affect up to 1 in 100 people) are:
 - rash
 - warmth, rash at the injection site
 - increased appetite
 - stomach pain
 - excessive sweating
 - cough
 - nasal congestion and runny nose
 - paleness
 - sleep disorders including inability to get adequate sleep
 - restlessness
 - swollen glands in the neck, armpit or groin
 - feeling tired
 - floppy

Other side effects not listed above have been reported with other diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B or Hib containing vaccines:

- allergic reaction, serious allergic reaction (anaphylactic reaction)
- extensive swelling of the vaccinated limb
- Fits (convulsions) with or without fever
- episodes of shock-like state or paleness, floppy and unresponsive

Reporting of side effects

If your child gets any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vaxelis

Keep this vaccine out of the sight and reach of children.

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

Do not use this vaccine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Vaxelis contains

The active substances per dose (0.5 mL):

Diphtheria Toxoid ¹	not less than 20 IU
Tetanus Toxoid ¹	not less than 40 IU
<i>Bordetella pertussis</i> 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
<i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate)	3 micrograms
Conjugated to meningococcal protein ²	50 micrograms

¹ adsorbed on aluminium phosphate (0.17 mg Al³⁺)

² adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al³⁺)

³ produced in yeast (*Saccharomyces cerevisiae*) by recombinant DNA technology

⁴ produced in Vero cells

⁵ or equivalent antigenic quantity determined by a suitable immunochemical method.

Aluminium phosphate and amorphous aluminium hydroxyphosphate sulphate are included in the vaccine as adjuvants. Adjuvants are included to improve the immune response of vaccines.

The other ingredients are:

Sodium phosphate, water for injections

The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B.

What Vaxelis looks like and contents of the pack

The normal appearance of the vaccine is a uniform, cloudy, white to off-white suspension, which may settle down during storage.

Vaxelis is provided as a suspension for injection in pre-filled syringe.

Pack size of 1 or 10 pre-filled syringes, without attached needle, with 1 separate needle or with 2 separate needles.

Multipack of 5 packs of 10 pre-filled syringes with no needle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {month YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

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.

Vaxelis is for intramuscular injection only.

The recommended injection sites are the anterolateral aspect of the thigh or the deltoid region of the upper arm if there is adequate muscle mass. The anterolateral aspect of the thigh is the preferred site for infants under one year of age.