Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed)

HEXASIIL

1 NAME OF THE MEDICINAL PRODUCT

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed).
HEXASIIL, suspension for injection in vial presentation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains

Diphtheria Toxoid	⩾ 30 IU
Tetanus Toxoid	⩾ 40 IU
B. pertussis (whole cell)	⩾ 4 IU
HBsAg (rDNA)	15 mcg
Inactivated polio vaccine (Salk strains grown on vero cells)	
Type - 1 (Mahoney strain)	40 DU
Type - 2 (MEF-1 strain)	8 DU
Type - 3 (Saukett strain)	32 DU
Hib (PRP)	10 mcg
conjugated to TT (carrier protein)	19 to 33 mcg
Adsorbed on Aluminium Phosphate, Al^{+++}	⩽ 1.25 mg
2-Phenoxyethanol	0.5 %

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in single dose vial and multi dose vial presentation.

HEXASIIL is a pinkish to yellowish turbid liquid in which the Aluminium Phosphate adjuvant tends to settle down slowly on storage.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

HEXASIIL is indicated for active immunization of infants, at or above the age of 6 weeks against Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis and invasive diseases caused by *Haemophilus influenzae* Type b for 3 dose regimen (6,10 & 14 Weeks) for primary vaccination and booster dose at the age of 12-24 months.

4.2 Posology and method of administration

Posology

Primary vaccination:
For active immunization of infants, it is recommended that 3 doses of 0.5 ml to be administered with an interval of at least four weeks between doses starting at six weeks of age.
In countries, where peri-natal transmission of hepatitis B virus (HBV) is common, the first dose of Hepatitis B should be given as soon as possible after birth. In this case, the **HEXASIIL** can be used to complete the primary series from 6 weeks of age.

Booster vaccination:
A booster dose of DTP, Hib and IPV should be given preferably during the second year of life (≥ 6 months after last primary dose). Booster doses should be given in accordance with the official recommendations.
Booster dose may be provided to children having received primary vaccination of **HEXASIIL** or any other DTP containing vaccine and Poliomyelitis Vaccine (OPV and/or IPV).

Method of Administration

The **HEXASIIL** liquid vaccine vial should be shaken before use to homogenize the suspension. **HEXASIIL** should be administered intramuscularly. The recommended injection sites are generally the antero-lateral aspect of the upper thigh in infants and toddlers. Do not administer by intravascular, intradermal or subcutaneous injection.
A sterile syringe and sterile needle must be used for the injection. Any other injection if co-administered with **HEXASIIL** should be given at a different site.

Once opened, multi-dose vials should be kept between +2°C and +8°C. Multi-dose vials of **HEXASIIL** from which one or more doses of vaccine have been removed during an immunisation session may be used in subsequent immunisation sessions for upto a maximum of 28 days, provided that all of the following conditions are met (as described in the WHO policy statement: Handling of multi dose vaccine vials after opening, WHO/IVB/14.07):

- The vaccine is currently prequalified by WHO;
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO;
- The expiry date of the vaccine has not passed;
- The vaccine vial has been, and will continue to be, stored at WHO - or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

The vaccine should be visually inspected for any foreign particulate matter and /or variation of physical aspect prior to administration. In event of either being observed discard the vaccine.

4.3 Contraindications

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.
Hypersensitivity to the active substances, to any of the excipients listed in section 6.1. *List of excipients.*
The vaccination with **HEXASIIL** is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine (whole cell or acellular pertussis vaccines).
In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, polio and Hib vaccines.
Uncontrolled neurologic disorder or uncontrolled epilepsy: Pertussis vaccine should not be administered to individuals with these conditions until the treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk.
Generally, vaccination must be postponed in cases of acute moderate or severe febrile illness. The presence of a minor infection and/or low-grade fever does not constitute a contraindication.

4.4 Special warnings and special precautions for use

WARNINGS

As with any vaccine, a protective immune response may not be elicited in all vaccinees. **HEXASIIL** will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. It does not prevent Hepatitis caused by other agents different from HBV (as virus A, C and E) but it is considered effective in preventing Hepatitis caused by the delta agent. Hib vaccine does not protect against disease due to other types of *Haemophilus influenzae* nor against meningitis caused by other organisms. Due to the long incubation period of Hepatitis B (up to 6 months or more), cases where prior exposure to Hepatitis B virus has taken place, vaccination may not be effective.
Vaccination should be preceded by a review of medical history (in particular previous vaccinations and possible adverse events). In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of **HEXASIIL** must be carefully considered.
If any of the following events occur in temporal relation to receipt of **HEXASIIL**, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

- Temperature 40.5°C (105°F) or more within 48 hours of a dose unexplained by another cause. Collapse or shock-like state (hypotonic-hypo responsive episode) within 48 hours.
- Persistent, inconsolable crying lasting 3 hours or more occurring within 48 hours.
- Convulsions with or without fever occurring within three days.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.
HEXASIIL should not be given to children with any coagulation disorder, including thrombocytopenia that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.
Infants and children with a history of convulsions in first-degree family members (i.e. siblings and parents) when administered DTP containing vaccine have an increased risk for neurologic events and permanent neurologic damage when compared with infants without such history. Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestation of the underlying neurologic disorder within two or three days following vaccination.
The administration of **HEXASIIL** vaccine to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

PRECAUTION

As with the use of all vaccines, the vaccinee should remain under observation for not less than 30 minutes for possibility of occurrence of immediate or early allergic reactions. Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

IMMUNE DEFICIENCY

Individuals infected with the human immuno-deficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with combined vaccine according to standard schedules. Immunosuppressed children may not obtain expected immunological response.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with other vaccines **HEXASIIL** can be administered concomitantly with a pneumococcal polysaccharide conjugate vaccine, measles, mumps, rubella (MMR) containing vaccines, oral polio vaccine, rotavirus vaccines, a meningococcal conjugate vaccine, as it is unlikely to result in an interference with the immune responses. The **HEXASIIL** can be given safely and effectively at the same time as BCG, Yellow Fever vaccines and Vitamin A supplementation.
If co-administration with another vaccine is considered, immunisation should be carried out on separate injection sites. **HEXASIIL** must not be mixed with any other vaccines or other parenterally administered medicinal products.
As with other intramuscular injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal or tendon injections with corticosteroids should not be immunosuppressive.

4.6 Fertility, pregnancy and lactation

This vaccine is not intended for administration to women of child-bearing age, thus human data on use during pregnancy or lactation are not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Overall summary of the safety profile

The safety profile presented below is based on data from pivotal clinical trial (SII-wHEXA/IN-02) conducted in India where **HEXASIIL** was administered to 110 toddlers and 884 infants. The majority of the reactions observed following vaccination were of mild or moderate severity and were of short duration.

Tabulated summary of adverse reactions

Adverse events are organized by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse events are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to < 1/1000) and very rare (< 1/10,000).
The following drug-related adverse reactions were reported in clinical studies.

Table 1 : Summary of adverse reactions reported in clinical studies

System Organ Class	Frequency	Adverse Reactions
Metabolism and nutrition disorders	Very Common	Decreased appetite
Nervous system disorders	Very Common	Somnolence
Gastrointestinal disorders	Very Common	Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
General disorders and administration site conditions	Very Common	Injection site erythema
	Very Common	Injection site pain
	Very Common	Injection site swelling
	Uncommon	Nodule
	Very Common	Crying
	Very Common	Irritability
	Very Common	Pyrexia

4.9 Overdose

No cases of overdose were reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pharmaco-therapeutic group: Bacterial and viral vaccines combined,
ATC code J07CA09.

Immunogenicity:

The immunogenicity of **HEXASIIL** has been evaluated in a pivotal, multicentric, randomized, controlled clinical trial (SII-wHEXA/IN-02). After 3-dose primary vaccination schedule in infants, robust immune response was achieved for all antigens and non-inferiority was demonstrated against licensed vaccine.
The results of these clinical studies are summarized in the table below.

Table 2 : Seroprotection/Seroconversion rates one month after primary vaccination with 3 doses of HEXASIIL

Antibody (Cut-off)	Post Dose 3 after Primary vaccination at 6-10-14 Weeks			Post Booster vaccination during the second year of life		
	N	n	(%)	N	n	(%)
Anti-Diphtheria (≥ 0.1 IU/ml)	804	801	**99.6**	109	108	**99.1**
Anti-Tetanus (≥ 0.1 IU/ml)	804	804	**100.0**	109	109	**100.0**
Anti-Bordetella Pertussis (> 24 U/mL)	804	603	**75.0**	109	103	**94.5**
Anti-Pertussis Toxin (Seroconversion*)	804	648	**80.6**	109	84	**77.1**
Anti-HBsAg (≥ 10 mIU/ml)	804	787	**97.9**	110	110	**100.0**
Anti-PRP (≥ 0.15 µg/ml)	804	799	**99.4**	109	109	**100.0**
Anti-Polio Type 1 (≥ 8 (1/dilution))	796	795	**99.9**	110	110	**100.0**
Anti-Polio Type 2 (≥ 8 (1/dilution))	796	791	**99.4**	110	108	**98.2**
Anti-Polio Type 3 (≥ 8 (1/dilution))	796	795	**99.9**	110	110	**100.0**

N = Number of available subjects for each of the antigen,
n = Number of subjects achieving seroprotection/seroconversion.
* In subjects with no quantifiable antibody - below the LLOQ - prior to vaccination, seroconversion was defined as achieving a quantifiable antibody level post-vaccination. In subjects with quantifiable antibody prior to vaccination, seroconversion was defined by a 4-fold-increase in antibody titres from pre- to post-vaccination.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of acute and repeat dose toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aadsorbed on Aluminium Phosphate Al^{+++}, 2-Phenoxyethanol, Sodium Chloride (Normal saline), Acetic Acid (Glacial) and Sodium hydroxide are used for pH adjustment.

6.2 Incompatibilities

The vaccine is not to be mixed with other vaccines or other parenterally administered drugs.

6.3 Shelf-life

Unopened vial :
Shelf-life is 24 months.

Opened multidose vial :
After first opening, the vaccine can be used for up to 28 days, provided it is stored between +2°C to +8°C.

6.4 Special precautions for storage

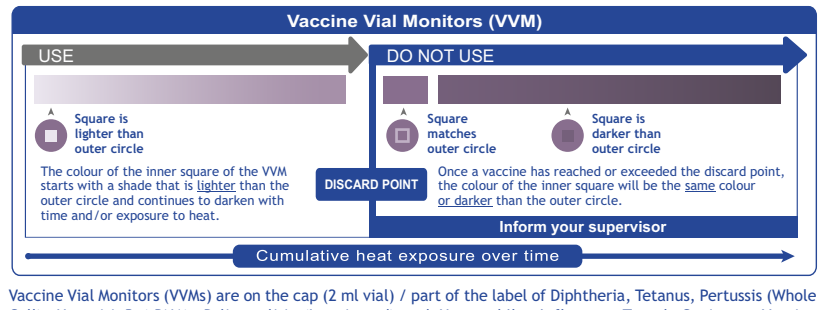
Store in a refrigerator (+2°C to +8°C). Do not freeze. Discard vaccine if frozen.
Before use, the vaccine should be shaken in order to obtain a homogenous pinkish to yellowish turbid liquid.
Keep the vaccine in the outer carton in order to protect from light.
Do not use this vaccine after the expiry date which is stated on the carton and label.
The Vaccine should be visually inspected for any foreign particulate matter and /or variation of physical aspect prior to administration. In event of either being observed discard the vaccine.

6.5 Nature and contents of container

Single dose presentation :
1 dose vial of 0.5 ml

Multi-dose presentation :
10 dose vial of 5 ml

THE VACCINE VIAL MONITOR (VVM) (Optional)



Vaccine Vial Monitors (VVMs) are on the cap (2 ml vial) / part of the label of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) supplied through Serum Institute of India Pvt. Ltd. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.
The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the outer circle or of a darker colour than the outer circle, then the vial should be discarded.

6.6 Special precautions for disposal

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

Revision date: September 2022

Manufactured by:
SERUM INSTITUTE OF INDIA PVT. LTD.
212/2, Hadapsar, Pune 411 028, INDIA

Protection from birth onwards.

200XXXXX/0

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed)

1 NAME OF THE MEDICINAL PRODUCT

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed).
Suspension for injection in vial presentation.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.5 ml contains

Diphtheria Toxoid	⩾ 30 IU
Tetanus Toxoid	⩾ 40 IU
B. pertussis (whole cell)	⩾ 4 IU
HBsAg (rDNA)	15 mcg
Inactivated polio vaccine (Salk strains grown on vero cells)	
Type - 1 (Mahoney strain)	40 DU
Type - 2 (MEF-1 strain)	8 DU
Type - 3 (Saukett strain)	32 DU
Hib (PRP)	10 mcg
conjugated to TT (carrier protein)	19 to 33 mcg
Adsorbed on Aluminium Phosphate, Al^{+++}	⩽ 1.25 mg
2-Phenoxyethanol	0.5 %

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in single dose vial and multi dose vial presentation Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) is a pinkish to yellowish turbid liquid in which the Aluminium Phosphate adjuvant tends to settle down slowly on storage.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) is indicated for active immunization of infants, at or above the age of 6 weeks against Diphtheria, Tetanus, Pertussis, Hepatitis B, Poliomyelitis and invasive diseases caused by *Haemophilus influenzae* Type b for 3 dose regimen (6,10 & 14 Weeks) for primary vaccination and booster dose at the age of 12-24 months.

4.2 Posology and method of administration

Posology

Primary vaccination:
For active immunization of infants, it is recommended that 3 doses of 0.5 ml to be administered with an interval of at least four weeks between doses starting at six weeks of age.
In countries, where peri-natal transmission of hepatitis B virus (HBV) is common, the first dose of Hepatitis B should be given as soon as possible after birth. In this case, the Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) can be used to complete the primary series from 6 weeks of age.

Booster vaccination:
A booster dose of DTP, Hib and IPV should be given preferably during the second year of life (≥ 6 months after last primary dose). Booster doses should be given in accordance with the official recommendations.
Booster dose may be provided to children having received primary vaccination of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) or any other DTP containing vaccine and Poliomyelitis Vaccine (OPV and/or IPV).

Method of Administration

The Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) liquid vaccine vial should be shaken before use to homogenize the suspension. Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) should be administered intramuscularly.
The recommended injection sites are generally the antero-lateral aspect of the upper thigh in infants and toddlers.
Do not administer by intravascular, intradermal or subcutaneous injection.
A sterile syringe and sterile needle must be used for the injection. Any other injection if co-administered with Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) should be given at a different site.

Once opened, multi-dose vials should be kept between +2°C and +8°C. Multi-dose vials of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) from which one or more doses of vaccine have been removed during an immunisation session may be used in subsequent immunisation sessions for upto a maximum of 28 days, provided that all of the following conditions are met(as described in the WHO policy statement: Handling of multi dose vaccine vials after opening, WHO/IVB/14.07):

- The vaccine is currently prequalified by WHO;
- The vaccine is approved for use for up to 28 days after opening the vial, as determined by WHO;
- The expiry date of the vaccine has not passed;
- The vaccine vial has been, and will continue to be, stored at WHO - or manufacturer recommended temperatures; furthermore, the vaccine vial monitor, if one is attached, is visible on the vaccine label and is not past its discard point, and the vaccine has not been damaged by freezing.

The vaccine should be visually inspected for any foreign particulate matter and /or variation of physical aspect prior to administration. In event of either being observed discard the vaccine.

4.3 Contraindications

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.
Hypersensitivity to the active substances, to any of the excipients listed in section 6.1. *List of excipients.*
The vaccination with Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) is contraindicated if the infant has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine (whole cell or acellular pertussis vaccines).
In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, polio and Hib vaccines.
Uncontrolled neurologic disorder or uncontrolled epilepsy: Pertussis vaccine should not be administered to individuals with these conditions until the treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk.
Generally, vaccination must be postponed in cases of acute moderate or severe febrile illness. The presence of a minor infection and/or low-grade fever does not constitute a contraindication.

4.4 Special warnings and special precautions for use

WARNINGS

As with any vaccine, a protective immune response may not be elicited in all vaccinees. Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis,* hepatitis B virus, poliovirus or *Haemophilus influenzae* Type b. It does not prevent Hepatitis caused by other agents different from HBV (as virus A, C and E) but it is considered effective in preventing Hepatitis caused by the delta agent. Hib vaccine does not protect against disease due to other types of *Haemophilus influenzae* nor against meningitis caused by other organisms. Due to the long incubation period of Hepatitis B (up to 6 months or more), cases where prior exposure to Hepatitis B virus has taken place, vaccination may not be effective.
Vaccination should be preceded by a review of medical history (in particular previous vaccinations and possible adverse events). In persons who have a history of serious or severe reaction within 48 hours of a previous injection with a vaccine containing similar components, administration of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) must be carefully considered.
If any of the following events occur in temporal relation to receipt of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed), the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered.

- Temperature 40.5°C (105°F) or more within 48 hours of a dose unexplained by another cause. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
- Persistent, inconsolable crying lasting 3 hours or more occurring within 48 hours.
- Convulsions with or without fever occurring within three days.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.
Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) should not be given to children with any coagulation disorder, including thrombocytopenia that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.
Infants and children with a history of convulsions in first-degree family members (i.e. siblings and parents) when administered DTP containing vaccine have an increased risk for neurologic events and permanent neurologic damage when compared with infants without such history. Infants and children with recognized possible or potential underlying neurologic conditions seem to be at enhanced risk for the appearance of manifestation of the underlying neurologic disorder within two or three days following vaccination.
The administration of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) vaccine to children with proven or suspected underlying neurologic disorders that are not actively evolving must be decided on an individual basis.

PRECAUTION

As with the use of all vaccines, the vaccinee should remain under observation for not less than 30 minutes for possibility of occurrence of immediate or early allergic reactions. Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

IMMUNE DEFICIENCY

Individuals infected with the human immuno-deficiency virus (HIV), both asymptomatic and symptomatic, should be immunized with combined vaccine according to standard schedules. Immunosuppressed children may not obtain expected immunological response.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with other vaccines Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) can be administered concomitantly with a pneumococcal polysaccharide conjugate vaccine, measles, mumps, rubella (MMR) containing vaccines, oral polio vaccine, rotavirus vaccines, a meningococcal conjugate vaccine, as it is unlikely to result in an interference with the immune responses. The Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) can be given safely and effectively at the same time as BCG, Yellow Fever vaccines and Vitamin A supplementation.
If co-administration with another vaccine is considered, immunisation should be carried out on separate injection sites. Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) must not be mixed with any other vaccines or other parenterally administered medicinal products.
As with other intramuscular injections, use with caution in patients on anticoagulant therapy. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses) may reduce the immune response to vaccines. Short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal or tendon injections with corticosteroids should not be immunosuppressive.

4.6 Fertility, pregnancy and lactation

This vaccine is not intended for administration to women of child-bearing age, thus human data on use during pregnancy or lactation are not available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Overall summary of the safety profile

The safety profile presented below is based on data from pivotal clinical trial (SII-wHEXA/IN-02) conducted in India where Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) was administered to 110 toddlers and 884 infants. The majority of the reactions observed following vaccination were of mild or moderate severity and were of short duration.

Tabulated summary of adverse reactions

Adverse events are organized by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse events are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to < 1/1000) and very rare (< 1/10,000).
The following drug-related adverse reactions were reported in clinical studies.

Table 1 : Summary of adverse reactions reported in clinical studies

System Organ Class	Frequency	Adverse Reactions
Metabolism and nutrition disorders	Very Common	Decreased appetite
Nervous system disorders	Very Common	Somnolence
Gastrointestinal disorders	Very Common	Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
General disorders and administration site conditions	Very Common	Injection site erythema
	Very Common	Injection site pain
	Very Common	Injection site swelling
	Uncommon	Nodule
	Very Common	Crying
	Very Common	Irritability
	Very Common	Pyrexia

4.9 Overdose

No cases of overdose were reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pharmaco-therapeutic group: Bacterial and viral vaccines combined,
ATC code J07CA09.

Immunogenicity:

The immunogenicity of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) has been evaluated in a pivotal, multicentric, randomized, controlled clinical trial (SII-wHEXA/IN-02). After 3-dose primary vaccination schedule in infants, robust immune response was achieved for all antigens and non-inferiority was demonstrated against licensed vaccine.
The results of these clinical studies are summarized in the table below.

Table 2 : Seroprotection/Seroconversion rates one month after primary vaccination with 3 doses of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed)

Antibody (Cut-off)	Post Dose 3 after Primary vaccination at 6-10-14 Weeks			Post Booster vaccination during the second year of life		
	N	n	(%)	N	n	(%)
Anti-Diphtheria (≥ 0.1 IU/ml)	804	801	**99.6**	109	108	**99.1**
Anti-Tetanus (≥ 0.1 IU/ml)	804	804	**100.0**	109	109	**100.0**
Anti-Bordetella Pertussis (> 24 U/mL)	804	603	**75.0**	109	103	**94.5**
Anti-Pertussis Toxin (Seroconversion*)	804	648	**80.6**	109	84	**77.1**
Anti-HBsAg (≥ 10 mIU/ml)	804	787	**97.9**	110	110	**100.0**
Anti-PRP (≥ 0.15 µg/ml)	804	799	**99.4**	109	109	**100.0**
Anti-Polio Type 1 (≥ 8 (1/dilution))	796	795	**99.9**	110	110	**100.0**
Anti-Polio Type 2 (≥ 8 (1/dilution))	796	791	**99.4**	110	108	**98.2**
Anti-Polio Type 3 (≥ 8 (1/dilution))	796	795	**99.9**	110	110	**100.0**

N = Number of available subjects for each of the antigen,
n = Number of subjects achieving seroprotection/seroconversion.
* In subjects with no quantifiable antibody - below the LLOQ - prior to vaccination, seroconversion was defined as achieving a quantifiable antibody level post-vaccination. In subjects with quantifiable antibody prior to vaccination, seroconversion was defined by a 4-fold-increase in antibody titres from pre- to post-vaccination.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on a conventional study of acute and repeat dose toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aadsorbed on Aluminium Phosphate Al^{+++}, 2-Phenoxyethanol, Sodium Chloride (Normal saline), Acetic Acid (Glacial) and Sodium hydroxide are used for pH adjustment.

6.2 Incompatibilities

The vaccine is not to be mixed with other vaccines or other parenterally administered drugs.

6.3 Shelf-life

Unopened vial :
Shelf-life is 24 months.

Opened multidose vial :
After first opening, the vaccine can be used for up to 28 days, provided it is stored between +2°C to +8°C.

6.4 Special precautions for storage

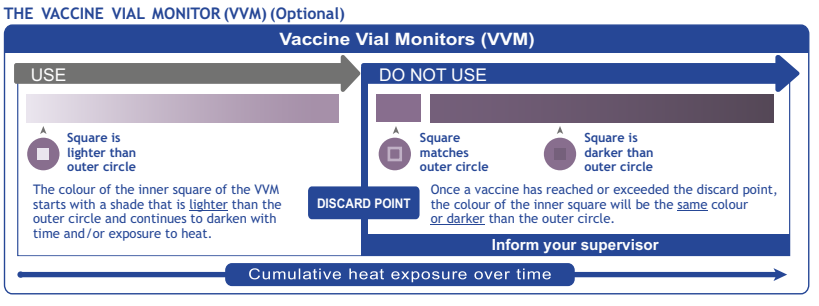
Store in a refrigerator (+2°C to +8°C). Do not freeze. Discard vaccine if frozen.
Before use, the vaccine should be shaken in order to obtain a homogenous pinkish to yellowish turbid liquid.
Keep the vaccine in the outer carton in order to protect from light.
Do not use this vaccine after the expiry date which is stated on the carton and label.
The Vaccine should be visually inspected for any foreign particulate matter and /or variation of physical aspect prior to administration. In event of either being observed discard the vaccine.

6.5 Nature and contents of container

Single dose presentation :
1 dose vial of 0.5 ml

Multi-dose presentation :
10 dose vial of 5 ml

THE VACCINE VIAL MONITOR (VVM) (Optional)



Vaccine Vial Monitors (VVMs) are on the cap (2 ml vial) / part of the label of Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis B (rDNA), Poliomyelitis (Inactivated) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) supplied through Serum Institute of India Pvt. Ltd. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.
The interpretation of the VVM is simple. Focus on the central square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the central square is the same colour as the outer circle or of a darker colour than the outer circle, then the vial should be discarded.

6.6 Special precautions for disposal

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

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Manufactured by:
SERUM INSTITUTE OF INDIA PVT. LTD.
212/2, Hadapsar, Pune 411 028, INDIA

Protection from birth onwards.

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