Infanrix *hexa*

Version GDSv20-IPIv15

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Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), polio (inactivated) (IPV), and *Haemophilus influenzae* type b (absorbed) vaccine

Powder and suspension for suspension for injection

Qualitative and Quantitative Composition

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid1	not less than 30 international units (IU)
Tetanus toxoid1	not less than 40 international units (IU)
Bordetella pertussis antigens	
Pertussis toxoid (PT)1	25 micrograms
Filamentous hemagglutinin (FHA)1	25 micrograms
Pertactin (PRN)1	8 micrograms
Hepatitis B (HB) surface antigen2, 3	10 micrograms
Inactivated polio virus (IPV)	
type 1 (Mahoney strain)4	40 antigenic units D
type 2 (strain MEF-1)4	8 antigenic units D
type 3 (Saukett strain)4	32 antigenic units D
Haemophilus influenzae polysaccharide type b (polyribosylribitol phosphate, PRP)3	10 micrograms
Conjugated to tetanus toxoid as carrier protein, approx.	25 micrograms

1 adsorbed in aluminum hydroxide, hydrated (Al(OH)3), 0.5 milligrams Al3+
2produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology
3adsorbed on aluminum phosphate (AlPO4), 0.32 milligrams Al3+
4 propagated in VERO cells

The DTaP-HBV-IPV component presents as a cloudy white suspension. After storage, a white deposit and a transparent supernatant can be observed, which is normal.

The Hib component occurs as a white powder.

For excipients, see *List of excipients*.

Clinical Information

Directions

INFANRIX HEXA is indicated for primary and booster vaccination in infants and children against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

The use of ***INFANRIX HEXA*** should comply with official recommendations.

Dosage and Administration

Dosage

The primary vaccination schedule consists of two or three doses (from 0.5 ml) to be administered according to official recommendations (see *Pharmacodynamics* for regimens evaluated in clinical trials). ***INFANRIX HEXA*** may be considered for booster if the antigen composition is consistent with official recommendations.

Primary vaccination	Booster vaccination	General considerations
Full-term infants		
3 servings	A booster dose may be given.	There should be an interval of at least 1 month between primary doses. When a booster dose is given, it should be given at least 6 months after the last primary dose, preferably before 18 months of age.
2 servings	A booster dose may be given.	There should be an interval of at least 1 month between primary doses. When a booster dose is given, it should be given at least 6 months after the last primary dose, and preferably between 11 and 13 months of age.
Preterm infants born after 24 weeks' gestation		
3 servings	A booster dose should be given.	There should be an interval of at least 1 month between primary doses. When a booster dose is given, it should be given at least 6 months after the last primary dose, preferably before 18 months of age.

The PAI (Expanded Programme on Immunization) schedule (at 6, 10, 14 weeks of age) can only be used if a dose of hepatitis B vaccine has been administered at birth.

When a dose of hepatitis B vaccine is given at birth, ***INFANRIX HEXA*** may be used as a replacement for supplemental doses of hepatitis B vaccine starting at 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

Locally established immunoprophylactic measures against hepatitis B should be maintained.

Other antigen combinations have been studied in clinical trials after primary vaccination with ***INFANRIX*** hexa, and may be used as booster doses in: diphtheria, tetanus, acellular pertussis (DTaP); diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b (DTaP+Hib); diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTaP-IPV+Hib); and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTaP-HBV-IPV+Hib).

Method of Administration

INFANRIX HEXA should be injected deep intramuscularly.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Qualitative and quantitative composition* and *List of excipients*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio, or *Haemophilus influenzae* type b (Hib) vaccine.

INFANRIX HEXA is contraindicated if the child has developed an encephalopathy of unknown etiology within 7 days of previous vaccination with a pertussis vaccine. Under these circumstances, pertussis vaccination should be discontinued and the vaccination series should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and *Haemophilus influenzae* type b (Hib) vaccines.

Warnings and Precautions

As with other vaccines, ***INFANRIX HEXA*** should be postponed in persons suffering from severe acute febrile illness. The presence of a mild infection is not a contraindication.

Vaccination should be preceded by a review of the history (in particular with respect to previous vaccinations and the possible occurrence of adverse events), and by a clinical examination.

An immunoprotective response may not be obtained in all vaccinated persons (see *section Pharmacodynamics*).

INFANRIX HEXA does not prevent infections caused by other pathogenic microorganisms other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, polio virus or *Haemophilus influenzae* type b. However, it is to be expected that hepatitis D can be prevented by immunization, since hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

If any of the following events are known to occur in time with a pertussis vaccine, the decision to administer new doses of pertussis vaccine should be carefully considered:

- Temperature 40≥.0 ºC in the first 48 hours after vaccination, not due to another identifiable cause;
- collapse or shock-like state (hyporeactive hypotonic episode) within 48 hours of vaccination;
- inconsolable, persistent crying of 3 hours duration, occurring within 48 hours of vaccination;≥
- seizures with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of whooping cough, where the potential benefits outweigh the possible risks.

In children with progressive neurological problems, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy, it is preferable to delay pertussis immunization (Pa, acellular, or Pw, whole cell) until the disease has been corrected or stabilized. However, the decision to administer pertussis vaccine should be made on a case-by-case basis after carefully determining the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should be available at all times in the rare event of an anaphylactic reaction following administration of the vaccine.

INFANRIX HEXA should be administered with caution in people with thrombocytopenia or bleeding disorders, as bleeding may occur in these patients following intramuscular administration.

The vaccine should not be administered intravascularly or intradermally.

History of febrile seizures, family history of seizures, or sudden infant death syndrome (SIDS) are not contraindications to vaccination with ***INFANRIX*** hexa. Vaccinated persons with a history of febrile seizures should be closely monitored, as such an adverse event may occur within 2 to 3 days of vaccination.

Clinical trial data indicate that when INFANRIX HEXA is coadministered with pneumococcal conjugate vaccine, the febrile reaction rate is higher compared to that occurring after administration of ***INFANRIX HEXA*** alone.

Higher rates of seizures (with or without fever) and hypotonic hyporesponsive episode (HHE) have been observed with concomitant administration of ***INFANRIX HEXA*** and Prevenar 13 (see *ADVERSE REACTIONS*).

Antipyretic treatment should be initiated in accordance with local treatment guidelines.

Syncope (fainting) may occur after, or even before, any vaccination as a psychogenic response to needle injection. It is important that procedures are established to prevent fainting injuries.

Special Populations

Human immunodeficiency virus (HIV) infection is not considered a contraindication. After vaccination of immunosuppressed patients, the expected immune response may not be obtained.

Clinical data indicate that ***INFANRIX HEXA*** can be administered to preterm infants, however, as expected in this population, a lower immune response has been observed for some antigens (see *Adverse reactions* and *Pharmacodynamics*).

When administering the primary vaccination series to preterm infants ≤ 28 weeks' gestation and especially those with a prior history of respiratory immaturity, both the potential risk of apnoea and the need for respiratory monitoring for 48 to 72 hours should be considered. As the benefit of vaccination is high in these infants, vaccination should not be prevented or delayed.

Interference with Laboratory Analysis

Since Hib capsular polysaccharide antigen is excreted in the urine, a positive urine result can be obtained within 1 to 2 weeks after vaccination. Other tests should be performed to confirm Hib infection during this period.

Interactions

INFANRIX HEXA can be administered concomitantly with pneumococcal conjugate, meningococcal (Men) C conjugate, MenACWY conjugate, MenB, rotavirus, measles, rubella and varicella vaccines. The data have not demonstrated clinically relevant interference in the antibody response to each of the individual antigens.

When ***INFANRIX HEXA*** is coadministered with MenB and pneumococcal conjugate vaccines, inconsistent results were presented in studies for responses to inactivated poliovirus type 2 and pneumococcal conjugate serotype 6B antigen, but these data do not suggest significant clinical interference.

Clinical trial data suggest that when INFANRIX HEXA is coadministered with pneumococcal conjugate vaccine, the febrile reaction rate is higher compared to that occurring after administration of ***INFANRIX HEXA*** alone (see *WARNINGS AND PRECAUTIONS* FOR GUIDANCE ON PNEUMOCOCCAL CONJUGATE VACCINES).

Data from clinical studies indicate increased frequency of fever, injection site pain, loss of appetite, irritability when ***INFANRIX HEXA*** is coadministered with MenB vaccine and 7-valent pneumococcal conjugate vaccine.

As with other vaccines, it is expected that in patients treated with immunosuppressive therapy an adequate response may not be achieved.

Pregnancy and Lactation

No data are available on the safety of ***INFANRIX HEXA*** when used during pregnancy or lactation as the vaccine is not for use in adults.

Adverse Reactions

Clinical Trial Data

The safety profile given below is based on data from more than 16,000 patients.

As observed for DTaP vaccines or DTaP-containing combinations, an increase in local reactogenicity and fever following booster vaccination with ***INFANRIX HEXA*** has been reported relative to the primary cycle.

Reported adverse reactions are indicated according to the following frequency:

Very common 1/10 ≥
Frequent 1/100 and <1/10 ≥
Uncommon1/1000 and <1/100 ≥
Rare1/10000 and <1/1000 ≥
Very rare<1/10000

Systemic group	Frequency	Adverse reactions
Infections and infestations	Uncommon	Upper respiratory infection
Metabolism and nutrition disorders	Very common	Loss of appetite
Psychiatric disorders	Very common	Irritability, abnormal crying, restlessness
	Frequent	Nervousness
Nervous system disorders	Muy frequent	Sleepiness
	Very rare	Seizures (with or without fever)***
Respiratory, thoracic and mediastinal disorders	Uncommon	Cough*
	Rare	Bronchitis
Gastrointestinal disorders	Frequent	Vomiting, diarrhea
Skin and subcutaneous tissue disorders	Frequent	Pruritus*
	Rare	Rash
	Very rare	Dermatitis, hives*
General disorders and administration site disorders	Very common	Pain, redness, local swelling at the injection site (≤ 50 mm), fever 38 °C≥
	Frequent	Local swelling at injection site (> 50 mm)**, fever >39.5 °C, injection site reactions, including induration
	Uncommon	Diffuse swelling of the injected limb, sometimes involving the adjacent joint**, fatigue

* Observed only with other GSK vaccines containing DTaP.
** Children who received acellular pertussis vaccines are more likely to experience inflammatory reactions after booster dose administration compared with children who received whole-cell vaccines at primary vaccination. These reactions resolve, on average, within 4 days.
Analysis of postmarketing reporting rates suggests a potential increased risk of seizures (with or without fever) and HHE when comparing groups that have reported the use of INFANRIX HEXA and Prevnar 13/Prevenar 13 with those that have reported the use of ***INFANRIX HEXA*** alone.

Post-marketing data

The following medication-related adverse reactions have been reported during the pharmacovigilance period.

Systemic group	Frequency	Adverse reactions
Blood and lymphatic system disorders	Rare	Lymphadenopathy, thrombocytopenia
Immune system disorders	Rare	Allergic reactions (including anaphylactic and anaphylactoid reactions)
Nervous system disorders	Rare	Collapse or shock-like state (hyporeactive hypotonic episode)***
Respiratory, thoracic and mediastinal disorders	Rare	Apnoe*[see Warnings and precautions for apnoea in preterm infants (≤ 28 weeks' gestation)]
Skin and subcutaneous tissue disorders	Rare	Angioneurotic edema*
General disorders and administration site disorders	Rare	Extensive inflammation reactions, inflammation of the entire injected limb**, vesicles at the injection site

*Observed only with other GSK vaccines containing DTaP.
** Children who received acellular pertussis vaccines during primary vaccination are more likely to have inflammatory reactions after booster dose administration compared to children who received whole-cell vaccines during primary vaccination. These reactions resolve, on average, within 4 days.
Analysis of postmarketing rates suggests a potential increased risk of seizures (with or without fever) and HEH when comparing groups that have reported the use of INFANRIX HEXA and Prevnar 13/Prevenar 13 with those that have reported the use of ***INFANRIX HEXA*** alone.

Safety in preterm infants

INFANRIX HEXA has been administered to more than 1000 preterm infants (born after a gestation period of 24 to 36 weeks) in primary vaccination studies and to more than 200 preterm infants as a booster dose in the second year of life. In comparative studies, similar rates of symptoms have been observed in both preterm and term infants .

Safety in infants and young children born to mothers vaccinated with dTpa during pregnancy

In clinical studies, Infanrix hexa was administered to more than 500 individuals born to mothers vaccinated with dTpa or a placebo during pregnancy. The safety profile of Infanrix hexa was similar regardless of exposure/non-exposure to dTpa during pregnancy.

Experience with the Hepatitis B Vaccine

Paralysis, neuropathy, encephalopathy, encephalitis, meningitis, allergic reactions such as serum sickness, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and muscle weakness have been observed during the post-marketing surveillance period following administration of GlaxoSmithKline Biologicals hepatitis B vaccine in infants and children under 2 years of age. The causal relationship with the vaccine has not been established.

Pharmacological properties

Pharmacodynamics

Pharmacotherapeutic group: combined bacterial and viral vaccines, ATC code J07CA09.

Immunogenicity

The immunogenicity of ***INFANRIX HEXA*** has been evaluated in clinical trials from 6 weeks of age. The vaccine was evaluated in primary schedules of 2 and 3 doses, including the schedule for the Extended Program of Immunization, and as a booster dose. The results of these clinical trials are summarized below.

After a primary vaccination schedule of 3 doses, at least 95.7% of infants had developed levels of seroprotective or seropositive antibodies against each of the vaccine antigens. After booster vaccination (after dose 4), at least 98.4% of children had developed levels of seroprotective or seropositive antibodies against each of the vaccine antigens.

Percentage of patients with antibody titers ≥ trial cut-off value one month after primary vaccination of 3 doses and booster vaccination with *INFANRIX* hexa

Antibody (cut)	After 3 doses				After 4 doses (Booster vaccination during the second year of life after primary vaccination of 3 doses)
	2-3-4 months N = 196 (2 studies) %	2-4-6 months N = 1693 (6 studies) %	3-4-5 months N = 1055 (6 studies) %	6-10-14 weeks N = 265 (1 studio) %	N = 2009 (12 studies) %
Antidiphtheria (0.1 IU/ml) †	100.0	99.8	99.7	99.2	99.9
Antitetanus (0.1 IU/ml) †	100.0	100.0	100.0	99.6	99.9
Anti-PT (5 EL. U/ml)	100.0	100.0	99.8	99.6	99.9
Anti-FHA (5 EL. U/ml)	100.0	100.0	100.0	100.0	99.9
Anti-PRN (5 EL. U/ml)	100.0	100.0	99.7	98.9	99.5
Anti-HB (10 mIU/ml) †	99.5	98.9	98.0	98.5*	98.4
Antipolio type 1 1/8 dilution) †	100.0	99.9	99.7	99.6	99.9
Antipolio type 2 (1/8 dilution) †	97.8	99.3	98.9	95.7	99.9
Antipolio type 3 (1/8 dilution) †	100.0	99.7	99.7	99.6	99.9
Anti-PRP (0.15 g/ml) †µ	96.4	96.6	96.8	97.4	99.7

N = number of subjects
* In a subgroup of infants who had not received hepatitis B vaccine at birth, 77.7% of subjects exhibited anti-HB titers 10 mIU/ml≥
† Court accepted as indicative of protection

After complete vaccination according to a primary schedule of 2 doses and booster with ***INFANRIX*** hexa, at least 97.9% of subjects had developed levels of seroprotective or seropositive antibodies against each of the vaccine antigens.

Percentage of patients with antibody titers ≥ trial cut-off value one month after primary vaccination of 2 doses and booster with *INFANRIX* hexa

Antibody (cut)	After 3 doses (Vaccination at 2-4-12 months of age) N = 196 (1 study) %	After 3 doses (Vaccination at 3-5-11 months of age) N = 532 (3 studies) %
Antidiphtheria (0.1 IU/ml) †	100.0	100.0
Antitetanus (0.1 IU/ml) †	100.0	100.0
Anti-PT (5 EL. U/ml)	99.5	100.0
Anti-FHA (5 EL. U/ml)	100.0	100.0
Anti-PRN (5 EL. U/ml)	100.0	99.2
Anti-HB (10 mIU/ml) †	99.8	98.9
Antipolio type 1 (1/8 dilution) †	98.4	99.8
Antipolio type 2 (1/8 dilution) †	98.4	99.4
Antipolio type 3 (1/8 dilution) †	97.9	99.2
Anti-PRP (0.15 g/ml) †µ	100.0	99.6

N = number of subjects
† Court accepted as indicative of protection

Serological correlates of protection have been established for diphtheria, tetanus, polio, hepatitis B and Hib. There is no protective serological correlate for whooping cough. However, the immune response to pertussis antigens following administration of INFANRIX HEXA is equivalent to that of ***INFANRIX*** (DTaP), the protective efficacy of the two vaccines is expected to be equivalent.

Protective efficacy against whooping cough

The protective efficacy of the antipertussis component of ***INFANRIX*** (DTaP) was demonstrated under the WHO definition of typical pertussis (21 days of paroxysmal cough) following primary vaccination with 3 doses in the following tabulated studies:≥

I am a student	Country	Scheme	Vaccine efficacy	Considerations
Exposure study in the family environment	Germany	3, 4, 5 months	88.7 %	Based on data obtained for secondary contacts in households with an index case with typical pertussis

(prospectively blind)				
Efficacy Study (sponsored by the NIH)	Italy	2, 4, 6 months	84 %	In a follow-up study of the same cohort, efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis vaccine.

Immunogenicity in infants and young children born to mothers vaccinated with dTpa during pregnancy

Clinical data from more than 500 infants and toddlers showed no clinically relevant interference between maternal vaccination with Boostrix and infant or toddler response to diphtheria, tetanus, hepatitis B, inactivated polio viruses, *Haemophilus influenzae* type B, or pneumococcal antigens.. Although lower concentrations of antibodies against some pertussis antigens were observed after primary and booster vaccination, 92.1-98.1% of individuals born to vaccinated mothers showed a booster response against all pertussis antigens. Current epidemiological data on pertussis do not suggest any clinical relevance of this immune interference.

Immunogenicity in Premature Actuants

The immunogenicity of ***INFANRIX HEXA*** was evaluated in three studies involving approximately 300 preterm infants (born after a gestation period of 24 to 36 weeks) after primary vaccination of 3 doses at 2, 4 and 6 months of age. The immunogenicity of a booster dose at 18 to 24 months of age was evaluated in approximately 200 preterm infants.

One month after primary vaccination, at least 98.7% of subjects were seroprotected against diphtheria, tetanus, and polio types 1 and 2; at least 90.9% had levels of seroprotective antibodies against hepatitis B, PRP, and polio type 3 antigens; and all subjects were seroprotected for antibodies against FHA and PRN, while 94.9% were seropositive for anti-PT antibodies.

One month after the booster dose, at least 98.4% of subjects had seroprotective or seropositive antibody levels against each of the antigens, except PT (at least 96.8%) and hepatitis B (at least 88.7%). The response to the booster dose in terms of increasing the coefficient of antibody concentrations (from 15 to 235 times) indicates that preterm infants received adequate primary vaccination against all ***INFANRIX*** hexa antigens.

In a follow-up study, approximately 2.5 to 3 years after the booster dose, 85.3% of children were still seroprotected against hepatitis B and at least 95.7% were seroprotected against all three types of polio and PRP.

Persistence of the Immune Response

Persistence of immune response to a primary 3-dose regimen and booster with ***INFANRIX HEXA*** was evaluated in children 4 to 8 years of age. Protective immunity against the three types of polio and PRP was observed in at least 91.0% of children and against diphtheria and tetanus in at least 64.7% of children. At least 25.4% (anti-PT), 97.5% (anti-FHA) and 87.0% (anti-PRN) of the children were seropositive against pertussis components.

With respect to hepatitis B, seroprotective antibody concentrations after a primary 3-dose regimen and reinforcement with ***INFANRIX HEXA*** have been shown to persist in ≥ 85% of subjects between 4 and 5 years of age, in ≥ 72% of subjects between 7 and 8 years of age, in ≥ 60% of subjects between 12 and 13 years of age and in 53.7% of subjects between 14 and 15 years of age. In addition, after a primary 2-dose and booster schedule, hepatitis B seroprotective antibody concentrations persisted in ≥ 48% of subjects aged 11 to 12 years.

Immunological memory of hepatitis B was confirmed in children 4 to 15 years of age. These children had received ***INFANRIX HEXA*** as primary and booster vaccination in childhood, and when an additional dose of monovalent HBV vaccine was administered, protective immunity was observed in at least 93% of subjects.

Post-Market Experience

In Sweden, results from a long-term follow-up study demonstrated that acellular pertussis vaccines are effective in infants when administered according to the primary vaccination schedule at 3 and 5 months, with a booster dose given at approximately 12 months. However, data suggest that protection against whooping cough may decrease by age 7 to 8. This suggests that a second booster dose of pertussis vaccine is required in children 5 to 7 years of age previously vaccinated according to this schedule.

The effectiveness of the Hib component of ***INFANRIX HEXA*** has been investigated through an extensive post-marketing surveillance study conducted in Germany. Over a seven-year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, one of them being ***INFANRIX HEXA,*** was 89.6% for a complete primary series and 100% for a complete primary series plus a booster dose (regardless of the Hib vaccine used for primary vaccination).

INFANRIX HEXA has been the main Hib vaccine available in Italy since 2006. The vaccine is given at 3, 5 and 11 months of age, and coverage has exceeded 95%. Hib disease continued to be well controlled: there were no more than three confirmed cases of Hib reported annually between 2006 and 2011 in Italian children under 5 years of age.

Pharmaceutical Characteristics

List of Excipients

Lactose, sodium chloride (NaCl), Medium 199 (as a stabilizer containing amino acids, mineral salts and vitamins), water for injections.

As residues of the manufacturing process are present: potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulfate and polymyxin B sulfate.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Storage Precautions

Store in the refrigerator (2 °C-8 °C).

The DTaP-HBV-IPV suspension and the reconstituted vaccine should not be frozen. Discard if they have been frozen.

It must be protected from light.

During transport, the recommended storage conditions must be respected.

Stability data indicate that vaccine components are stable at temperatures up to 25 °C for 72 hours. These data are provided for the purpose of guiding healthcare professionals only in case of temporary fluctuations in temperatures.

The conditions of preservation are detailed in the packaging

Nature and Content of the Container

The DTaPD-HBV-IPV component is presented in a prefilled syringe (type I glass).

The Hib component is supplied in a glass vial (type I glass).

Not all presentations exist in all countries.

Incompatibilities

INFANRIX HEXA must not be mixed in the same syringe with other vaccines.

Instructions for Use/Handling

The DTaP-HBV-IPV suspension should be shaken well, to obtain a cloudy, homogeneous and white suspension. DTaP-HBV-IPV suspension and Hib powder should be visually examined for any foreign particles and/or variation in physical appearance. If any of these anomalies are appreciated, the vaccine should not be administered.

INFANRIX HEXA should be reconstituted by adding the entire contents of the prefilled syringe to the vial containing the Hib powder. The mixture should be stirred until the powder is completely dissolved in the suspension.

It is good clinical practice to inject a vaccine only when it has reached room temperature. In addition, a vial at room temperature ensures that the rubber seal has sufficient elasticity to minimize the shedding of rubber particles. To do this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the prefilled syringe and reconstituting the vaccine.

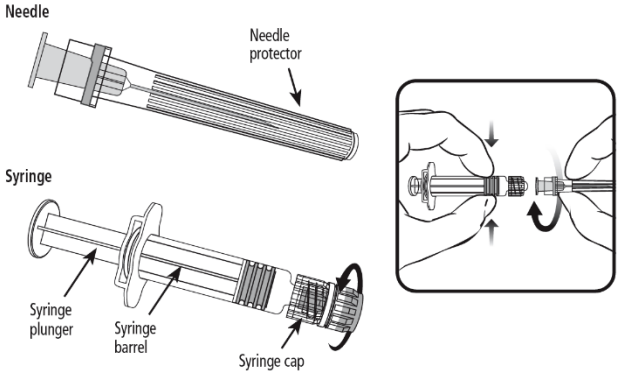
The reconstituted vaccine has a slightly cloudier suspension than the liquid component alone, which is normal.

The reconstituted vaccine should be examined visually for the absence of foreign particles and/or abnormal physical appearance. In case one or the other of these abnormalities is observed, do not administer the vaccine.

After reconstitution, the vaccine should be injected immediately. However, the vaccine can be stored for up to 8 hours at room temperature (21 °C).

Remove the entire contents of the vial.

Specific Instructions for the Prefilled Syringe, with Luer Lock Adapter (PRTC - Rigid Closure Plastic Capsule)



1. Holding the syringe **cylinder** with one hand (avoid holding the syringe plunger), unscrew the syringe closure capsule by turning it counterclockwise.
2. To attach the needle to the syringe, turn the needle clockwise into the syringe until it feels blocked (see figure).
3. Remove the needle guard, which can sometimes be a little tight.
4. Reconstitute the vaccine as described above

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

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