

## INFANRIX HEXA

**Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine**

### QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid <sup>1</sup>	not less than 30 International Units (IU)
Tetanus toxoid <sup>1</sup>	not less than 40 International Units (IU)
<i>Bordetella pertussis</i> antigens	
Pertussis toxoid (PT) <sup>1</sup>	25 micrograms
Filamentous Haemagglutinin (FHA) <sup>1</sup>	25 micrograms
Pertactin (PRN) <sup>1</sup>	8 micrograms
Hepatitis B surface antigen (HBs) <sup>2,3</sup>	10 micrograms
Poliovirus (inactivated) (IPV)	
type 1 (Mahoney strain) <sup>4</sup>	40 D-antigen unit
type 2 (MEF-1 strain) <sup>4</sup>	8 D-antigen unit
type 3 (Saukett strain) <sup>4</sup>	32 D-antigen unit
<i>Haemophilus influenzae</i> type b polysaccharide (polyribosylribitol phosphate, PRP) <sup>3</sup>	10 micrograms
conjugated to tetanus toxoid as carrier protein	approximately 25 micrograms

<sup>1</sup>adsorbed on aluminium hydroxide, hydrated (Al(OH)<sub>3</sub>) 0.5 milligrams Al<sup>3+</sup>

<sup>2</sup>produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

<sup>3</sup>adsorbed on aluminium phosphate (AlPO<sub>4</sub>) 0.32 milligrams Al<sup>3+</sup>

<sup>4</sup>propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal observation.

The Hib component is presented as a white powder.

For excipients, see *List of Excipients*.

### PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

### CLINICAL PARTICULARS

#### Indications

Infanrix hexa is indicated for primary and booster vaccination of infants and toddlers against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

## Dosage and Administration

### Posology

The primary vaccination schedule consists of three doses (of 0.5 ml) which should be administered according to official recommendations (see *Pharmacodynamics* for schedules evaluated in clinical trials). Infanrix hexa can be considered for the booster if the antigen composition is in accordance with the official recommendations.

Primary vaccination	Booster vaccination	General considerations
<b>Full-term infants</b>		
3-dose	A booster dose must be given.	<ul style="list-style-type: none"> <li>• There should be an interval of at least 1 month between primary doses.</li> <li>• When giving a booster dose, this should be at least 6 months after the last priming dose and preferably before 18 months of age.</li> </ul>
<b>Preterm infants born after at least 24 weeks of gestational age</b>		
3-dose	A booster dose must be given.	<ul style="list-style-type: none"> <li>• There should be an interval of at least 1 month between primary doses.</li> <li>• When giving a booster dose, this should be at least 6 months after the last priming dose and preferably before 18 months of age.</li> </ul>

The vaccine may be used to complete a vaccination course initiated with Infanrix-IPV+Hib vaccine.

During the development of the vaccine, the following primary vaccination schedules which are compatible with a policy of administering hepatitis B vaccine at birth were studied in full-term infants: at 2, 3, 4 months of age; at 2, 4, 6 months of age; at 1.5, 3, 5 months of age and at 6, 10, 14 weeks of age.

Additionally, in a study in full-term infants undertaken in Singapore, Infanrix hexa was given as part of a 3, 4, 5 month schedule with Infanrix-IPV+Hib. The Infanrix-IPV+Hib was administered at months 3 and 4 and Infanrix hexa given at month 5. As part of this study, monovalent Hepatitis B vaccine was given at 0 and 1 month in accord with Singapore's hepatitis B immunisation policy.

Immunogenicity data for preterm infants was solely obtained in trials that studied 2-4-6 months schedule for primary vaccination. Safety data for preterm infants was also

obtained in study Rota-54 that included a greater variety of schedules, i.e. in France (2-3-4 months), Poland (2-3/4-5 months), Spain and Portugal (2-4-6 months).

The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement 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.

Locally established immunoprophylactic measures against hepatitis B should be maintained.

### **Method of administration**

Infanrix hexa is for deep intramuscular injection.

### **Contraindications**

Hypersensitivity to the active substances or to any of the excipients or residues such as formaldehyde, neomycin and polymyxin (see *Qualitative and quantitative composition* and *List of Excipients*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances, pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

### **Warnings and Precautions**

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamics*).

Infanrix hexa 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.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of  $\geq 40.0^{\circ}\text{C}$  within 48 hours of vaccination, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting  $\geq 3$  hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

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

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunisation until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Do not administer the vaccine intravascularly or intradermally.

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Data from clinical studies indicate that, when Infanrix hexa is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurring following the administration of Infanrix hexa alone.

Increased reporting rates of convulsion (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see *Adverse Reactions*).

Antipyretic treatment should be initiated according to local treatment guidelines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

### Special populations

Human Immunodeficiency Virus (HIV) infection is not considered as a contraindication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

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

The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunization series to very preterm infants (born  $\leq$  28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in these infants, vaccination should not be withheld or delayed.

### Interference with laboratory testing

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

## **Interactions**

Infanrix hexa can be given concomitantly with pneumococcal conjugate, MenC) conjugate, MenACWY conjugate, rotavirus, measles, mumps, rubella and varicella vaccines. Data have shown no clinically relevant interference in the antibody response to each of the individual antigens.

Data from clinical studies indicate that, when Infanrix hexa is co-administered with pneumococcal conjugate vaccine, the rate of febrile reactions is higher compared to that occurred following the administration of Infanrix hexa alone (see *Warnings and Precautions* for guidance on pneumococcal conjugate vaccines).

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

## Pregnancy and Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy or lactation is not available.

## Adverse Reactions

- Clinical Trial Data:**

The safety profile presented below is based on data from more than 16,000 subjects and events considered as having at least a reasonable possibility of being causally linked to vaccination are presented.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency  
 Very common:  $\geq 1/10$ , Common:  $\geq 1/100$  to  $< 1/10$ , Uncommon:  $\geq 1/1000$  to  $< 1/100$ ,  
 Rare:  $\geq 1/10000$  to  $< 1/1000$ , Very rare:  $< 1/10000$

System Organ Class	Frequency	Adverse events
Infections and infestations	Uncommon	upper respiratory tract infection
Metabolism and nutrition disorders	Very common	appetite lost
Psychiatric disorders	Very common	irritability, crying abnormal, restlessness
	Common	nervousness
Nervous system disorders	Very common	drowsiness
	Uncommon	somnolence
	Very rare	convulsions (with or without fever)***
Respiratory, thoracic and mediastinal disorders	Uncommon	cough*
	Rare	bronchitis
Gastrointestinal disorders	Common	vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common	pruritus*
	Rare	rash
	Very rare	dermatitis, urticaria*

General disorders and administration site conditions	Very common	pain, redness, local swelling at injection site ( $\leq 50$ mm), fever $\geq 38^{\circ}\text{C}$ , fatigue
	Common	local swelling at the injection site ( $> 50\text{mm}$ )**, fever $> 39.5^{\circ}\text{C}$ , injection site reactions, including induration
	Uncommon	diffuse swelling of the injected limb, sometimes involving the adjacent joint**

\* Observed only with other GSK DTPa-containing vaccines

\*\* Children primed with acellular pertussis vaccines are more likely to experience swelling after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

\*\*\* Analysis of postmarketing reporting rates suggest a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of *Infanrix hexa* with *Prevnar 13/Prevenar 13* to those which reported use of *Infanrix hexa* alone.

- Post Marketing Data:**

The following drug-related adverse reactions were reported during post-marketing surveillance.

System Organ Class	Frequency	Adverse events
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 (hypotonic hyporesponsive episode)***
Respiratory, thoracic and mediastinal disorders	Rare	Apnoea* [see <i>Warnings and Precautions</i> for apnoea in preterm infants ( $\leq 28$ weeks of gestation)]
Skin and subcutaneous tissue disorders	Rare	Angioneurotic oedema*
General disorders and administration site conditions	Rare	Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

\* observed only with other GSK DTPa-containing vaccines

\*\* Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

\*\*\* Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with *Prevnar 13/ Prevenar 13* to those which reported use of Infanrix hexa alone.

- **Safety in perterm infants:**

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

- **Experience with hepatitis B vaccine:**

Paralysis, neuropathy, Guillain-Barré syndrome, encephalopathy, encephalitis, meningitis, allergic reactions mimicking serum sickness, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis and muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants and toddlers < 2 years old. The causal relationship to the vaccine has not been established.

## **PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamics**

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

#### *Immunogenicity*

The immunogenicity of Infanrix hexa has been evaluated in clinical studies from 6 weeks of age. The vaccine was assessed in 3-dose priming schedules, including the schedule for the Expanded Program on Immunisation, and as a booster dose. The result obtained in the clinical studies for each of the components are summarised in the tables below.

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

**Percentage of subjects with antibody titres  $\geq$  assay cut off one month after 3-dose primary and booster vaccination with Infanrix hexa**



Antibody (cut-off)	Post-dose 3				Post-dose 4 (Booster vaccination during the second year of life following a 3-dose primary course)
	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 study)	
	%	%	%	%	
<b>Anti-diphtheria</b> (0.1 IU/ml) †	100.0	99.8	99.7	99.2	99.9
<b>Anti-tetanus</b> (0.1 IU/ml) †	100.0	100.0	100.0	99.6	99.9
<b>Anti-PT</b> (5 EL.U/ml)	100.0	100.0	99.8	99.6	99.9
<b>Anti-FHA</b> (5 EL.U/ml)	100.0	100.0	100.0	100.0	99.9
<b>Anti-PRN</b> (5 EL.U/ml)	100.0	100.0	99.7	98.9	99.5
<b>Anti-HBs</b> (10 mIU/ml) †	99.5	98.9	98.0	98.5*	98.4
<b>Anti-Polio type 1</b> (1/8 dilution) †	100.0	99.9	99.7	99.6	99.9
<b>Anti-Polio type 2</b> (1/8 dilution) †	97.8	99.3	98.9	95.7	99.9
<b>Anti-Polio type 3</b> (1/8 dilution) †	100.0	99.7	99.7	99.6	99.9
<b>Anti-PRP</b> (0.15 µg/ml) †	96.4	96.6	96.8	97.4	99.7

N = number of subjects

\* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HB titres  $\geq$ 10 mIU/ml

† cut-off accepted as indicative of protection.

Serological correlates of protection have been established for diphtheria, tetanus, polio, Hepatitis B and Hib. For pertussis there is no serological correlate of protection. However, as the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix (DTPa), the protective efficacy of the two vaccines is expected to be equivalent.

*Efficacy in protecting against pertussis*

The protective efficacy of the pertussis component of Infanrix(DTPa) against WHO-defined typical pertussis ( $\geq 21$  days of paroxysmal cough) was demonstrated after 3-dose primary immunisation in the studies tabulated below:

<b>Study</b>	<b>Country</b>	<b>Schedule</b>	<b>Vaccine efficacy</b>	<b>Considerations</b>
Household contact study (prospective blinded)	Germany	3,4,5 months	88.7%	Based on data collected from secondary contacts in households where there was an index case with typical pertussis
Efficacy study (NIH sponsored)	Italy	2,4,6 months	84%	In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

*Immunogenicity in preterm infants*

The immunogenicity of Infanrix hexa was evaluated across three studies including approximately 300 preterm infants (born after a gestation period of 24 to 36 weeks) following a 3-dose primary vaccination course 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 poliovirus types 1 and 2; at least 90.9% had seroprotective antibody levels against the hepatitis B, PRP and poliovirus type 3 antigens; and all subjects were seropositive 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 against PT (at least 96.8%) and hepatitis B (at least 88.7%). The response to the booster dose in terms of fold increases in antibody concentrations (15- to 235-fold), indicate that preterm infants were adequately primed for all antigens of Infanrix hexa.

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

### *Persistence of the immune response*

The persistence of the immune response to a 3-dose primary and booster schedule with Infanrix hexa was evaluated in children 4-8 years of age. Protective immunity against the three poliovirus types 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 children were seropositive against the pertussis components.

With regards to hepatitis B, protective immunity following a 3-dose primary and booster schedule with Infanrix hexa has been shown to persist in  $\geq 85\%$  of subjects 4-5 years of age, in  $\geq 72\%$  of subjects 7-8 years of age and in  $\geq 60\%$  of subjects 12-13 years of age.

Hepatitis B immunological memory was confirmed in children 4 to 13 years of age. These children had received Infanrix hexa as primary and booster vaccination in infancy, and when an additional dose of monovalent HBV vaccine was administered, protective immunity was induced in at least 96.8% of subjects.

### *Post marketing experience*

The effectiveness of the Hib component of Infanrix hexa was investigated via 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, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Results of ongoing routine national surveillance in Italy demonstrate that Infanrix hexa is effective in controlling Hib disease in infants when the vaccine is administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 11 months. Over a six year period starting in 2006, where Infanrix hexa was the principal Hib-containing vaccine in use with vaccination coverage exceeding 95%, Hib invasive disease continued to be well controlled, with four confirmed Hib cases reported in Italian children aged less than 5 years through passive surveillance.

## **PHARMACEUTICAL PARTICULARS**

### **List of Excipients**

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

Potassium chloride, disodium phosphate, monopotassium phosphate, polysorbate 20 and 80, glycine, formaldehyde, neomycin sulphate, polymyxin B sulphate are present as residues from the manufacturing process.

### **Incompatibilities**

Infanrix hexa should not be mixed with other vaccines in the same syringe.

### **Shelf Life**

The expiry date of the vaccine is indicated on the label and packaging. The date for last use corresponds to the last day of the month mentioned.

### **Special Precautions for Storage**

Infanrix hexa should be stored at 2°C - 8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

### **Nature and Contents of Container**

The DTPa-HBV-IPV component is presented in a pre-filled syringe (type 1 glass).

The Hib component is presented in a glass vial (type 1 glass).

Not all presentations are available in every country.

### **Instructions for Use/Handling**

#### **Vial and pre-filled syringe presentation**

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib

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

Infanrix hexa must be reconstituted by adding the entire contents of the pre-filled syringe to the vial containing the Hib powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature ( $25 \pm 3^{\circ}\text{C}$ ) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

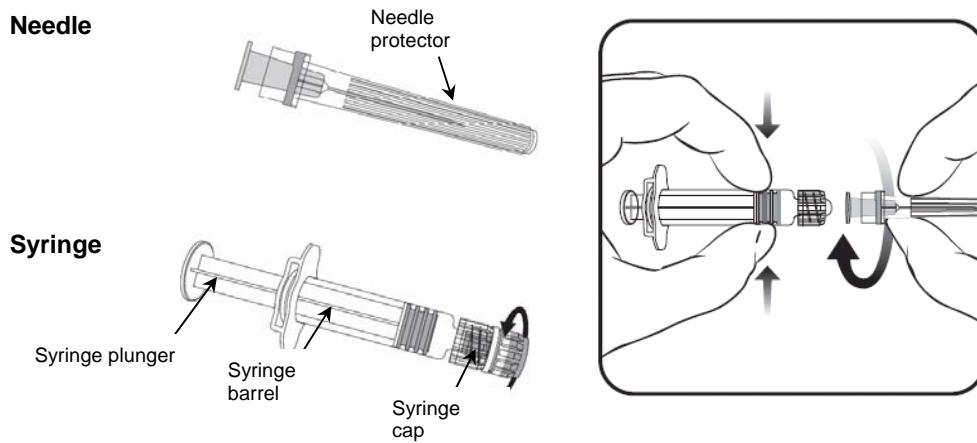
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature ( $21^{\circ}\text{C}$ ).

Withdraw the entire contents of the vial.

- **Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)**



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

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

**Manufacturer:**

GlaxoSmithKline Biologicals s.a., Rixensart, Belgium

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