For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

BOOSTRIX

Diphtheria, Tetanus and Pertussis (Acellular Component) Vaccine (Adsorbed, Reduced Antigens Content) Ph. Eur.

1. NAME OF THE MEDICINAL PRODUCT

Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed, reduced antigens content) Ph. Eur**.**

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Diphtheria toxoid[1]	not less than 2 International Units (IU) (2.5Lf)
Tetanus toxoid[1]	not less than 20 International Units (IU) (5 Lf)

Bordetella pertussis antigens:

Pertussis toxoid[1]	8 micrograms
Filamentous Haemagglutinin[1]	8 micrograms
Pertactin[1]	2.5 micrograms

[1] adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.3 milligrams Al^{3+}
and aluminium phosphate ($AlPO_4$)	0.2 milligrams Al^{3+}

For the full list of excipients, see section *6.1 List of Excipients*.

3. PHARMACEUTICAL FORM

Suspension for injection.

BOOSTRIX is a turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

BOOSTRIX is indicated for booster vaccination against diphtheria, tetanus and pertussis in individuals aged 4 years and above who have previously completed primary vaccination with DPT.

The administration of *BOOSTRIX* should be based on official recommendations.

4.2 Posology and method of administration

Posology

A single 0.5 ml dose of the vaccine is recommended.

BOOSTRIX may be administered from the age of 4 years onwards.

BOOSTRIX should be administered in accordance with official recommendations and/or local practice regarding the use of vaccines with reduced content of diphtheria, tetanus and pertussis antigens.

BOOSTRIX can be administered to pregnant women during the second or the third trimester in accordance with official recommendations (see sections *4.6 Pregnancy and lactation* and *5.1 Pharmacodynamic Properties*).

BOOSTRIX may also be administered to adolescents and adults with unknown vaccination status or incomplete vaccination against diphtheria, tetanus and pertussis as part of an immunisation series against diphtheria, tetanus and pertussis. Based on data in adults, two additional doses of a diphtheria and tetanus containing vaccine are recommended one and six months after the first dose to maximize the vaccine response against diphtheria and tetanus (see section *5.1 Pharmacodynamic Properties*).

BOOSTRIX can be used in the management of tetanus prone injuries in persons who have previously received a primary vaccination series of tetanus toxoid vaccine and for whom a booster against diphtheria and pertussis is indicated. Tetanus immunoglobulin should be administered concomitantly in accordance with official recommendations.

Repeat vaccination against diphtheria, tetanus and pertussis should be performed at intervals as per official recommendations (generally 10 years).

Paediatric population

The safety and efficacy of *BOOSTRIX* in children below 4 years of age have not been established.

Method of administration

BOOSTRIX is for deep intramuscular injection preferably in the deltoid region (see section *4.4 Special warnings and precautions for use*).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section *6.1 List of excipients*.

Hypersensitivity after previous administration of a diphtheria, tetanus or pertussis vaccines.

BOOSTRIX is contraindicated if the subject has experienced an encephalopathy of unknown aetiology occurring within 7 days following a previous vaccination with pertussis-containing vaccine. In these circumstances, pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria and tetanus vaccines .

BOOSTRIX should not be administered to subjects who have experienced transient thrombocytopenia or neurological complications (for convulsions or hypotonic-hyporesponsive episodes, see section *4.4 Special warnings and precautions for use*) following an earlier immunisation against diphtheria and/or tetanus.

As with other vaccines, administration of *BOOSTRIX* should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

4.4 Special warnings and precautions for use

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

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

- Temperature of ≥ 40.0°C within 48 hours of vaccination, not due to another identifiable cause.

- Collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting ≥ 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.

As for any vaccination, the risk-benefit of immunising with *BOOSTRIX* or deferring this vaccination should be weighed carefully in a child suffering from a new onset or progression of a severe neurological disorder.

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

BOOSTRIX should be administered with caution to subjects with thrombocytopenia (see section *4.3 Contraindications*) or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

BOOSTRIX should in no circumstances be administered intravascularly .

A history or a family history of convulsions and a family history of an adverse event following DTP vaccination do not constitute contraindications.

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

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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

4.5 Interaction with other medicinal products and other forms of interaction

Use with other vaccines or immunoglobulins

BOOSTRIX may be administered concomitantly with human papilloma virus vaccine with no clinically relevant interference with antibody response to any of the components of either vaccine.

Concomitant administration of *BOOSTRIX* with other vaccines or with immunoglobulins has not been studied.

It is unlikely that co-administration will result in interference with the immune responses.

According to generally accepted vaccine practices and recommendations, if concomitant administration of *BOOSTRIX* with other vaccines or immunoglobulins is considered necessary, the products should be given at separate sites.

Use with immunosuppressive treatment

As with other vaccines, patients receiving immunosuppressive therapy may not achieve an adequate response.

4.6 Pregnancy and lactation

Fertility

No human data from prospective clinical studies are available. Animal studies do not indicate direct or indirect harmful effects on female fertility (see section *5.3 Preclinical safety data*).

Pregnancy

BOOSTRIX can be used during the second or third trimester of pregnancy in accordance with official recommendations.

For data relating to the prevention of pertussis disease in infants born to women vaccinated during pregnancy, see section *5.1 Pharmacodynamic Properties.*

Safety data from a randomised controlled clinical trial (341 pregnancy outcomes) and from a prospective observational study (793 pregnancy outcomes), where *BOOSTRIX* was administered to pregnant women during the third trimester, have shown no vaccine related adverse effect on pregnancy or on the health of the foetus/newborn child.

Safety data from prospective clinical studies on the use of *BOOSTRIX or BOOSTRIX POLIO* during the first and second trimester of pregnancy are not available.

Data from passive surveillance where pregnant women were exposed to *BOOSTRIX* or to *BOOSTRIX POLIO* (dTpa-IPV vaccine) in the 3rd or 2nd trimester have shown no vaccine-related adverse effect on pregnancy or on the health of the foetus/newborn child.

As with other inactivated vaccines, it is not expected that vaccination with *BOOSTRIX* harms the foetus at any trimester of pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section *5.3 Preclinical safety data*).

Lactation

The effect of administration of *BOOSTRIX* during lactation has not been assessed. Nevertheless, as *BOOSTRIX* contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering *BOOSTRIX* to breastfeeding women should carefully be evaluated by the health-care providers.

4.7 Effects on Ability to Drive and Use Machines

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable Effects

Summary of the safety profile

The safety profile presented below is based on data from clinical trials where *BOOSTRIX* was administered to 839 children (from 4 to 8 years of age) and 1931 adults, adolescents and children (from 10 to 76 years of age) (Table 1).

The most common events occurring after *BOOSTRIX* administration in both groups were local injection site reactions (pain, redness and swelling) reported by 23.7 – 80.6% of subjects in each trial. These usually had their onset within the first 48 hours after vaccination. All resolved without sequelae.

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency:

Very common: (≥1/10)
Common: (≥ 1/100 to < 1/10)
Uncommon: (≥ 1/1,000 to < 1/100)
Rare: (≥ 1/10,000 to < 1/1,000)
Very rare: (< 1/10,000)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Clinical trials

Table 1: Adverse reactions reported in clinical trials with *BOOSTRIX*

System Organ Class	***Frequency***	***Adverse reactions***	
		Subjects aged 4 - 8 years (N=839)	***Subjects aged 10 - 76 years (N = 1931)***
Infections and infestations	Uncommon	upper respiratory tract infection	upper respiratory tract infection, pharyngitis
Blood and lymphatic system disorders	Uncommon		lymphadenopathy
Metabolism and nutrition disorders	Common	anorexia	
Psychiatric disorders	Very common	irritability	
Nervous system disorders	Very common	somnolence	headache
	Common	headache	dizziness
	Uncommon	disturbances in attention	syncope
Eye disorders	Uncommon	conjunctivitis	
Respiratory, thoracic and mediastinal disorders	Uncommon		cough

System Organ Class	*Frequency*	*Adverse reactions*	
		Subjects aged 4 - 8 years (N=839)	***Subjects aged 10 - 76 years (N = 1931)***
Gastrointestinal disorders	Common	diarrhoea, vomiting, gastrointestinal disorders	nausea, gastrointestinal disorders
	Uncommon		diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	rash	hyperhidrosis, pruritus, rash
Musculoskeletal and connective tissue disorders	Uncommon		arthralgia, myalgia, joint stiffness, musculoskeletal stiffness
General disorders and administration site conditions	Very common	injection site reactions (such as redness and/or swelling), injection site pain, fatigue	injection site reactions (such as redness and/or swelling), malaise, fatigue, injection site pain
	Common	pyrexia (fever ≥ 37.5°C including fever > 39.0°C), extensive swelling of vaccinated limb (sometimes involving the adjacent joint)	pyrexia (fever ≥ 37.5°C), injection site reactions (such as injection site mass and injection site abscess sterile)
	Uncommon	other injection site reactions (such as induration), pain	pyrexia (fever > 39.0°C), influenza like illness, pain

Reactogenicity after repeat dose

Data on 146 subjects suggest that there might be a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedule in adults (>40 years of age).

Data suggest that in subjects primed with DTP in childhood a booster dose might give an increase of local reactogenicity.

Post-marketing surveillance

Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.

Table 2: Adverse reactions reported with *BOOSTRIX* during post-marketing surveillance

System Organ Class	*Frequency*	*Adverse reactions*
Immune system disorders	unknown	Allergic reactions, including anaphylactic and anaphylactoid reactions
Nervous system disorders	unknown	Hypotonic-hyporesponsiveness episodes, convulsions (with or without fever)
Skin and subcutaneous tissue disorders	unknown	Urticaria, angioedema
General disorders and administration site conditions	unknown	Asthenia

Following administration of tetanus toxoid containing vaccines, there have been very rare reports of adverse reactions on the central or peripheral nervous systems, including ascending paralysis or even respiratory paralysis (e.g. Guillain-Barré syndrome).

4.9 Overdose

Cases of overdose have been reported during post-marketing surveillance. Adverse events following overdosage, when reported, were similar to those reported with normal vaccine administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Bacterial vaccines, pertussis vaccines; ATC code: J07AJ52.

Immune response

Approximately one month following booster vaccination with *BOOSTRIX*, the following seroprotection / seropositivity rates were observed (Table 3):

Table 3: Immune response in children, adolescents and adults

Antigen	Response[(1)]	Adults and adolescents from the age of 10 years onwards ATP[(2)] N=1694 (% vaccinees)	Children from the age of 4 years onwards ATP[(2)] N=415 (% vaccinees)
Diphtheria	≥ 0.1 IU/ml	97.2%	99.8%
Tetanus	≥ 0.1 IU/ml	99.0%	100.0%
Pertussis:			
- Pertussis toxoid	≥ 5 EL.U/ml	97.8%	99.0%
- Filamentous haemagglutinin		99.9%	100.0%
- Pertactin		99.4%	99.8%

(1) Response: where, at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/ml was considered as seroprotection and a concentration of antibodies against pertussis ≥ 5 EL.U/ml was considered as seropositivity.

(2) ATP: According to protocol – includes all eligible subjects, who had received a single booster dose of *BOOSTRIX,* for whom immunogenicity data was available for at least one antigen at the specified time-point.

N: the minimum number of subjects with available data for each antigen.

In adolescents and adults, comparative trials have demonstrated that one month post-vaccination, diphtheria antibody titres are similar to adult-type Td vaccines with the same antigen content as *BOOSTRIX*; lower tetanus antibody titres were seen as compared to adult-type Td vaccines.

As with other adult-type Td vaccines, *BOOSTRIX* induces higher titres of both anti-D and anti-T antibodies in children and adolescents as compared to adults.

Persistence of the immune response

Three to 3.5 years, 5 to 6 years and 10 years following a first vaccination with *BOOSTRIX*, the following seroprotection/seropositivity rates were observed in subjects vaccinated according to protocol (ATP[1]) (Table 4):

Table 4: Persistence of immune response in children, adolescents and adults

Antigen	Response [2]	Adults and adolescents from the age of 10 years onwards (% vaccinees)						Children from the age of 4 years onwards (% vaccinees)	
		3-3.5 years persistence		5 years persistence		10 years persistence		3-3.5 years persistence	5 to 6 years persistence
		Adult[3] (N=309)	Adolescent[3] (N=261)	Adult[3] (N=232)	Adolescent[3] (N=250)	Adult[3] (N=158)	Adolescent[3] (N=74)	(N=118)	(N=68)
Diphtheria	≥ 0.1 IU/ml	71.2%	91.6%	84.1%	86.8%	64.6%	82.4%	97.5 %	94.2 %
	≥ 0.016 IU/ml[4]	97.4%	100%	94.4%	99.2%	89.9%	98.6%	100 %	Not determined
Tetanus	≥ 0.1 IU/ml	94.8%	100%	96.2%	100%	95.0%	97.3%	98.4 %	98.5 %
Pertussis									
Pertussis toxoid	≥ 5 EL.U/ml	90.6%	81.6%	89.5%	76.8%	85.6%	61.3%	58.7 %	51.5 %
Filamentous Haemagglutinin		100%	100%	100%	100%	99.4%	100%	100 %	100 %
Pertactin		94.8%	99.2%	95.0%	98.1%	95.0%	96.0%	99.2 %	100 %

(1) ATP: According to protocol –includes all eligible subjects who had received a single booster dose of *BOOSTRIX* for whom immunogenicity data was available for at least one antigen at the specified time-point.

(2) Response: Where, at the specified time point, a concentration of antibodies against diphtheria and tetanus ≥ 0.1 IU/ml was considered as seroprotection and, a concentration of antibodies against pertussis ≥ 5 EL.U/ml was considered as seropositivity.

(3) The terms 'adult' and 'adolescent' reflect the ages at which subjects received their first vaccination with *BOOSTRIX*.

(4) Percentage of subjects with antibody concentrations associated with protection against disease (≥ 0.1 IU/ml by ELISA assay or ≥ 0.016 IU/ml by an *in-vitro* Vero-cell neutralisation assay).

N = the minimum number of subjects with available data for each antigen.

Efficacy in protecting against pertussis

The pertussis antigens contained in *BOOSTRIX* are an integral part of the paediatric acellular pertussis combination vaccine (*INFANRIX*), for which efficacy after primary vaccination has been demonstrated in a household contact efficacy study. The antibody titres to all three pertussis components following vaccination with *BOOSTRIX* are higher than those observed during the household contact efficacy trial. Based on these comparisons, *BOOSTRIX* would provide protection against pertussis, however the degree and duration of protection afforded by the vaccine are undetermined.

Passive protection against pertussis in infants (below 3 months of age) born to mothers vaccinated during pregnancy

In a randomised, cross-over, placebo-controlled study, higher pertussis antibody concentrations were demonstrated at delivery in the cord blood of babies born to mothers vaccinated with *BOOSTRIX* (dTpa group; N=291) versus placebo (control group; N=292) at 27-36 weeks of pregnancy. The cord blood geometric mean concentrations of antibodies against the pertussis antigens PT, FHA and PRN were 46.9, 366.1 and 301.8 IU/ml in the dTpa group, and 5.5, 22.7 and 14.6 IU/ml in the control group. This corresponds to antibody titres that are 8, 16 and 21 times higher in the cord blood of babies born to vaccinated mothers versus controls. These antibody titres may provide passive protection against pertussis as shown by observational effectiveness studies.

Immunogenicity in infants and toddlers born to mothers vaccinated during pregnancy

The immunogenicity of *INFANRIX HEXA* (diphtheria, tetanus, pertussis, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccine) in infants and toddlers born to healthy mothers vaccinated with *BOOSTRIX* at 27-36 weeks of pregnancy was evaluated in two clinical studies.

INFANRIX HEXA was co-administered with a 13-valent pneumococcal conjugate vaccine to infants for primary vaccination (n=268); and to the same infants/toddlers from 11 to 18 months as booster dose (n=229).

Post-primary and post-booster vaccination, immunological data did not show clinically relevant interference of maternal vaccination with *BOOSTRIX* on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b or pneumococcal antigens.

Lower antibody concentrations against pertussis antigens post-primary (PT, FHA and PRN) and post-booster (PT, FHA) vaccination were observed in infants and toddlers born to mothers vaccinated with *BOOSTRIX* during pregnancy. The fold-increases of anti-pertussis antibody concentrations from the pre-booster to the 1-month post-booster time point were in the same range for infants and toddlers born to mothers vaccinated with *BOOSTRIX* or with placebo, demonstrating effective priming of the immune system. In the absence of correlates of protection for pertussis, the clinical relevance of these observations remains to be fully understood. However, current epidemiological data on pertussis disease following the implementation of dTpa maternal immunisation do not suggest any clinical relevance of this immune interference.

Effectiveness in the protection against pertussis disease in infants born to women vaccinated during pregnancy.

BOOSTRIX or *BOOSTRIX POLIO* vaccine effectiveness (VE) was evaluated in three observational studies, in UK, Spain and Australia. The vaccine was used during the third trimester of pregnancy to protect infants below 3 months of age against pertussis disease, as part of a maternal vaccination programme.

Details of each study design and results are provided in Table 5.

Table 5: VE against pertussis disease for infants below 3 months of age born to mothers vaccinated during the third trimester of pregnancy with *BOOSTRIX* / *BOOSTRIX POLIO*:

Study location	Vaccine	Study design	Vaccination Effectiveness
UK	*BOOSTRIX POLIO*	Retrospective, screening method	88% (95% CI: 79, 93)
Spain	*BOOSTRIX*	Prospective, matched case-control	90.9% (95% CI: 56.6, 98.1)
Australia	*BOOSTRIX*	Prospective, matched case-control	69% (95% CI: 13, 89)

CI: confidence interval

If maternal vaccination occurs within two weeks before delivery, vaccine effectiveness in the infant may be lower than the figures in the table.

Immune response after a repeat dose of BOOSTRIX

The immunogenicity of *BOOSTRIX* administered 10 years after a previous booster dose with reduced-antigen content diphtheria, tetanus and acellular pertussis vaccine(s) has been evaluated. One month post vaccination, > 99 % of subjects were seroprotected against diphtheria and tetanus and seropositive against pertussis.

Immune response in subjects without prior or with unknown vaccination history

After administration of one dose of *BOOSTRIX* to 83 adolescents aged from 11 to 18 years, without previous pertussis vaccination and no vaccination against diphtheria and tetanus in the previous 5 years, all subjects were seroprotected against tetanus and diphtheria.

The seropositivity rate after one dose varied between 87% and 100% for the different pertussis antigens.

After administration of one dose of *BOOSTRIX* to 139 adults ≥ 40 years of age that had not received any diphtheria and tetanus containing vaccine in the past 20 years, more than 98.5% of adults were seropositive for all three pertussis antigens and 81.5% and 93.4% were seroprotected against diphtheria and tetanus respectively. After administration of two additional doses one and six months after the first dose, the seropositivity rate was 100% for all three pertussis antigens and the seroprotection rates for diphtheria and tetanus reached 99.3% and 100% respectively.

5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical Safety Data

Reproductive toxicology

Fertility

Non-clinical data obtained with *BOOSTRIX* reveal no specific hazard for humans based on conventional studies of female fertility in rats and rabbits.

Pregnancy

Non-clinical data obtained with *BOOSTRIX* reveal no specific hazard for humans based on conventional studies of embryo-foetal development in rats and rabbits, and also of parturition and postnatal toxicity in rats (up to the end of the lactation period).

Animal toxicology and/or pharmacology

Preclinical data reveal no special hazard for humans based on conventional studies of safety and of toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, water for injections.

For adjuvants, see section 2. *Qualitative and quantitative composition*.

6.2 Incompatibilities

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

6.3 Shelf Life

36 months.

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special Precautions for Storage

Store in a refrigerator (+2 to +8°C).

Upon removal from the refrigerator, the vaccine is stable for 8 hours at +21°C. Discard the vaccine if it was not used during this period. This information is intended to guide healthcare professionals in case of temporary temperature excursion only.

Do not freeze.

Store in the original package in order to protect from light.

Keep out of reach of children.

6.5 Nature and contents of Container

0.5 ml of suspension a in pre-filled syringe (Type I glass) with a stopper (butyl rubber), with or without a needle in pack sizes of 1, 10, 20, 25 or 50.

All presentations may not be marketed in the country.

6.6 Special precautions for disposal and other handling

Prior to use, the vaccine should be at room temperature, and well shaken in order to obtain a homogeneous turbid white suspension. Prior to administration, the vaccine should be visually inspected for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, do not administer the vaccine.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited.
Registered Office
Dr. Annie Besant Road, Worli
Mumbai 400 030, India

8. MARKETING AUTHORISATION NUMBER(S)

Import Permission No.: Import - 6056/05(B).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 3rd August, 2005.

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