SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE:

BOOSTRIX

Diphtheria, tetanus and pertussis (acellular component) vaccine

(adsorbed, reduced antigen(s) content)

Suspension for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSTION:

1 dose (0,5 ml) contains:

Diphtheria toxoid[1]	< 2 International Units (IU) (2,5 Lf)
Tetanus toxoid[1]	< 20 International Units (IU) (5 Lf)
Bordetella pertussis antigens	
Pertussis toxoid[1]	8 µg
Filamentous Haemagglutinin[1]	8 µg
Pertactin[1]	2,5 µg
[1] adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0,3 mg Al^{3+}
and aluminium phosphate ($AlPO_4$)	0,2 mg Al^{3+}

For the full list of excipients, see section 6.1.

Sugar-free.

3. PHARMACEUTICAL FORM:

BOOSTRIX is a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

BOOSTRIX is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards (see section 4.2).
BOOSTRIX is also indicated for passive protection against pertussis in early infancy following maternal immunisation during pregnancy (see sections 4.2, 4.6 and 5.1).

The use of BOOSTRIX should be in accordance with official recommendations.

4.2 Posology and method of administration:

Posology

A single 0,5 ml dose of the vaccine is recommended.

BOOSTRIX can be given in accordance with the current local medical practices for booster vaccination with reduced-content combined diphtheria-tetanus vaccine, when a booster against pertussis is desired.

BOOSTRIX can be administered to pregnant women during the second or the third trimester in accordance with official recommendations (see sections 4.1, 4.6 and 5.1).

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 (see section 5.1). 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.

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

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. Tetanus immunoglobulin should be administered concomitantly in accordance with official recommendations.

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).

4.3 Contraindications:

BOOSTRIX should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines.

BOOSTRIX is contra-indicated if the subject 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 and tetanus vaccines.

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

4.4 Special warnings and precautions for use:

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.

BOOSTRIX should under no circumstances be administered intravenously.

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.

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.

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 careful consideration of the risks and benefits.

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 or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects. If in accordance with official recommendations, the vaccine may need to be administered subcutaneously to these subjects. With both routes of administration firm pressure should be applied to the injection site (without rubbing) for at least two minutes.
A history or a family history of convulsions and a family history of an adverse event following DTP vaccination do not constitute contra-indications.
Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication for diphtheria, tetanus and pertussis vaccination. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Extremely rare cases of collapse or shock-like state (hypotonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported in DTPa and DTPa combination vaccines.

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.

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

4.5 Interactions with other medicines and other forms of interactions:

Boostrix can be given concomitantly with any of the following monovalent or combination vaccines: unadjuvanted inactivated seasonal influenza vaccines, human papilloma virus vaccines, meningococcal serogroups A, C, W-135 and Y (MenACWY) conjugate vaccines and non-live herpes zoster vaccine. Data have shown no clinically relevant interference in the antibody response to each of the vaccine antigens.

Clinical data from co-administration of Boostrix with a trivalent inactivated influenza vaccine in subjects aged between 19 and 64 years demonstrated that the immune responses to the tetanus, diphtheria, pertussis toxoid (PT) and influenza antigens

were unaffected. Lower geometric mean concentrations (GMCs) were observed for the pertussis filamentous haemagglutinin (FHA) and pertactin (PRN) antigens; however, these data do not suggest clinically relevant interference. No differences were observed in a predefined exploratory cohort when the vaccines were given concomitantly or separately to subjects aged 65 years and older.

Clinical data from co-administration of Boostrix with non-live herpes zoster vaccine in subjects aged 50 years and older demonstrated that the immune responses to the tetanus, diphtheria, PT, FHA and herpes zoster antigens were unaffected. Lower GMCs were observed for the PRN antigen; however, these data do not suggest clinically relevant interference.

Clinical data from co-administration of Boostrix with MenACWY conjugate vaccines in subjects aged 9 to 25 years demonstrated that the immune responses to the tetanus, diphtheria and meningococcal antigens were unaffected. Lower GMCs were observed for the pertussis antigens; however, these data do not suggest clinically relevant interference.

Concomitant use with other inactivated vaccines and with immunoglobulin is unlikely to result in interference with the immune responses.
When considered necessary, BOOSTRIX can be administered simultaneously with other vaccines or immunoglobulins.

If BOOSTRIX is to be given at the same time as another injectable vaccine or immunoglobulin, the products should always be administered at different sites.
As with other vaccines, patients receiving immunosuppressive therapy or patients with immunodeficiency may not achieve an adequate response. In these patients, when tetanus vaccine is needed for tetanus prone wound, plain tetanus vaccine will be used.

4.6 Fertility, pregnancy and lactation:

Fertility: No human data available. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility.

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).

Safety data from a randomized 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 during the first and second trimester of pregnancy are not available.

Data from post-marketing surveillance where pregnant women were exposed to BOOSTRIX or to dTpa-IPV vaccine in the second or the third 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.

Lactation: The safety of BOOSTRIX when administered to breastfeeding women has not been evaluated.

It is unknown whether BOOSTRIX is excreted in human breast milk.

BOOSTRIX should only be used during breastfeeding when the possible advantages outweigh the potential risks.

4.7 Effects on the ability to drive and use machines:

BOOSTRIX 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 children from 4 to 9 years of age as well as for adults, adolescents and children from the age of 10 years onwards, were injection site reactions (including pain, redness and swelling).

Tabulated list of adverse reactions

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10

common: ≥ 1/100 and < 1/10

uncommon: ≥ 1/1 000 and < 1/100

rare: ≥ 1/10 000 and < 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	Uncommon		cough

disorders			
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

Description of selected adverse reactions

Children from 4 to 9 years of age:

General disorders and administration site conditions:

Very common: injection site reactions (including pain, redness and swelling), fatigue

Common: fever ≥ 37,5 °C (including fever > 39 °C)

Uncommon: other injection site reactions (such as induration), pain.

Adults, adolescents and children from the age of 10 years onwards:

General disorders and administration site conditions:

Very common: injection site reactions (including pain, redness and swelling), fatigue, malaise

Common: fever ≥ 37,5 °C, injection site reactions (such as injection site mass and injection site abscess sterile)

Uncommon: fever > 39 °C, influenza like illness, pain.

Paediatric population

The safety of Boostrix in children below 4 years of age have not been established.

Reactogenicity after repeat dose of BOOSTRIX:

Data on 146 subjects suggests 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).

Subjects fully primed with 4 doses of DTP followed by a BOOSTRIX dose around 10 years of age show an increase of local reactogenicity after an additional BOOSTRIX dose administered 10 years later.

Post-Marketing Data:

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*
Blood and lymphatic system disorders:	*Unknown*	*angioedema*
Immune system disorders:	*Unknown*	*allergic reactions, including anaphylactic and anaphylactoid reactions*
Nervous system disorders:	*Unknown*	*convulsions (with or without fever)*
Skin and subcutaneous tissue disorders:	*Unknown*	*urticaria*
General disorders and administration site conditions	*Unknown*	*extensive swelling of the vaccinated limb, asthenia.*

Reporting of suspected adverse events:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”,

found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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:

A 30.2 Antigens

Immune response: Immune response results to the diphtheria, tetanus and acellular pertussis components in clinical studies are presented in the table below. Approximately one month following booster vaccination with BOOSTRIX, the following seroprotection/seropositivity rates were observed:

Antigen	Seroprotection/ Seropositivity	Adults and adolescents from the age of 10 years onwards, at least 1 690 subjects (% vaccinees)	Children from 4 to 9 years of age, at least 415 subjects (% 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	≥ 5 EL.U/ml	99,9 %	100,0 %
- Pertactin	≥ 5 EL.U/ml	99,4 %	99,8 %

*cut-off accepted as indicative of protection

Results of the comparative studies with commercial dT vaccines indicates that the degree and duration of protection would not be different from those obtained with these vaccines.

***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 (N=291) versus placebo (N=292) during the third trimester of pregnancy. The concentrations of antibodies against the pertussis antigens PT, FHA and PRN were respectively 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

In follow-up trials in more than 500 infants and toddlers born to vaccinated mothers, clinical data did not show clinically relevant interference between maternal vaccination with BOOSTRIX and the infant and toddler response to diphtheria, tetanus, hepatitis B, inactivated polio virus, *Haemophilus influenzae* type b or pneumococcal antigens. Although lower concentrations of antibodies against some

pertussis antigens were observed post primary and post booster vaccination, 92.1-98.1% of subjects born to vaccinated mothers showed a booster response against all pertussis antigens. Current epidemiological data on pertussis disease 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 GlaxoSmithKline Biologicals' dTpa-IPV 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 the table below.

VE against pertussis disease for infants below 3 months of age born to mothers vaccinated during the third trimester of pregnancy with BOOSTRIX/GlaxoSmithKline Biologicals' dTpa-IPV:

Study Location	Vaccine	Study design	Vaccination Effectiveness
UK	GSK's dTpa-IPV	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.

Persistance of the immune response: 3 to 3,5 years, 5 to 6 years and 10 years following vaccination with BOOSTRIX, the following seroprotection/seropositivity rates were observed:

Antigen	Seroprotection/ seropositivity	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	Adole-scent	Adult	Adole-scent	Adult	Adole-scent		
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*	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 haemag-glutinin		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 %

* 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).

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: In adolescents aged from 11 to 18 years, without previous pertussis vaccination and no vaccination against diphtheria and tetanus in the previous 5

years, one dose of BOOSTRIX induced an antibody response against pertussis and all subjects were protected against tetanus and diphtheria.

In subjects ≥ 40 years of age that had not received any diphtheria or tetanus containing vaccine in the past 20 years (including those who have never been vaccinated or whose vaccination status was unknown), one dose of BOOSTRIX induced an antibody response against pertussis and protected against tetanus and diphtheria in the majority of cases.

5.2 Pharmacokinetic Properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Sodium chloride, water for injections.

For adjuvants, see section 2.

Sugar-free.

6.2 Incompatibilities:

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

6.3 Shelf life:

48 months.

6.4 Special Precaution and Storage:

BOOSTRIX should be stored in a refrigerator at +2 °C to +8 °C. During transport, recommended conditions of storage must be respected.

Do not freeze. Discard if the vaccine has been frozen.

Stability data indicate that the vaccine is stable at temperatures up to 37°C for 7 days. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Protect from light.

Keep out of reach of children.

6.5 Nature of contents and container:

Carton containing a clear, colourless glass (type1) pre-filled syringe with a grey, butyl rubber, plunger stopper, with or without needles.

Carton containing a clear, colourless glass (type 1), 3 ml vial with a grey butyl rubber stopper and capped with natural, aluminium flip-off caps.

Pack sizes of 1, 10, 20, 25 and 50. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling:

Use and Handling:

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

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Epping Industria 1, 7460

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