SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE:

BOOSTRIX TETRA

Suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

1 dose (0,5 mL) contains:

Diphtheria toxoid	≥ 2 International Units (2,5 Lf)
Tetanus toxoid	≥ 20 International Units (5 Lf)
Bordetella pertussis antigens	
Pertussis toxoid	8 µg
Filamentous haemagglutinin	8 µg
Pertactin	2,5 µg
Inactivated poliovirus	
type 1 (Mahoney strain)	40 D-antigen unit
type 2 (MEF-1 strain)	8 D-antigen unit
type 3 (Saukett strain)	32 D-antigen unit
Adsorbed on aluminium hydroxide, hydrated	Total: 0,3 mg Al^{3+}
and aluminium phosphate	Total: 0,2 mg Al^{3+}

Sugar-free

3. PHARMACEUTICAL FORM:

Turbid liquid, white deposit. Colourless supernatant.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

BOOSTRIX TETRA is indicated for booster vaccination against diphtheria, tetanus, pertussis and poliomyelitis of individuals from the age of three years onwards (see section 4.2)

BOOSTRIX TETRA is also indicated for passive protection against pertussis in early infancy following maternal immunisation during pregnancy (see sections 4.2; 4.6; 5.1*)*

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

4.2 Posology and method of administration:

A single 0,5 mL dose of the vaccine is recommended. BOOSTRIX TETRA is only given as a single-dose regimen.

BOOSTRIX TETRA may be administered from the age of three years onwards.

BOOSTRIX TETRA contains reduced content of diphtheria, tetanus and pertussis antigens in combination with poliomyelitis antigens. Therefore, BOOSTRIX TETRA should be in accordance with official recommendations and/or local practice.

BOOSTRIX TETRA can be administered to pregnant women during the second or the third trimester in accordance with official recommendations (see section 4.; 4.6; 5.1*)*

BOOSTRIX TETRA 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, pertussis and polio (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 diptheria and tetanus (see section 5.1).

BOOSTRIX TETRA 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, pertussis and polio is indicated.

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

There are no data on the duration of protection against pertussis following vaccination with BOOSTRIX TETRA.

Repeat vaccination against diphtheria, tetanus and poliomyelitis should be performed at intervals as per official recommendations.

Method of administration:

BOOSTRIX TETRA is for deep intramuscular injection preferably in the deltoid region (see section 4.4).

4.3 Contraindications:

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

BOOSTRIX TETRA contains traces of neomycin sulphate, polymyxin B sulphate and polysorbate 80**.**

The vaccine should not be used in subjects with known hypersensitivity to these substance

BOOSTRIX TETRA is contraindicated 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, tetanus and poliomyelitis vaccines.

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

4.4 Special warnings and precautions for use:

Administration of BOOSTRIX TETRA should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contraindication.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine in infancy, 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.

Collapse or shock-like state (hypotonic-hyporesponsive episode) and convulsions have been reported very rarely following immunisation of children with products containing one or more of the antigenic constituents of BOOSTRIX TETRA.

BOOSTRIX TETRA 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.

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.

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

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.

BOOSTRIX TETRA should in no circumstances be administered intravascularly.

A protective immune response may not be elicited in all vaccinees.

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

Appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

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

4.5 Interaction with other medicines and other forms of interaction:

BOOSTRIX TETRA can be given concomitantly with any of the following monovalent or combination vaccines: measles, mumps, rubella, varicella and human papilloma virus vaccine (see section 4.8)

Concomitant use with other inactivated vaccines and with immunoglobulin is unlikely to result in interference with the immune responses.

If BOOSTRIX TETRA is to be given at the same time as another injectable vaccine or immunoglobulin, the products should always be administered at different sites.

Patients receiving immunosuppressive therapy or patients with immunodeficiency may not achieve an adequate response.

4.6 Fertility, pregnancy and lactation:

Fertility: No human data are available.

Pregnancy: No teratogenic effect of vaccines containing diphtheria or tetanus toxoids, or inactivated poliovirus has been observed following use in pregnant women.

BOOSTRIX TETRA 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 randomised controlled clinical trail (341 pregnancy outcomes) and from a prospective observational study (793 pregnancy outcomes) where Boostrix (dTpa component of BOOSTRIX TETRA) 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 TETRA or Boostrix during the first and second trimester of pregnancy are not available.

Data from post-marketing surveillance where pregnant women were exposed to BOOSTRIX TETRA or to Boostrix 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 TETRA harms the foetus at any trimester of pregnancy.

Lactation: The safety of BOOSTRIX TETRA when administered to breastfeeding women has not been established. It is unknown whether BOOSTRIX TETRA is excreted in breast milk.

It is preferable to avoid the use of BOOSTRIX TETRA during breastfeeding.

4.7 Effects on ability to drive and use machines:

BOOSTRIX TETRA is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable effects:

Clinical Trial Data:

The safety profile presented in Table 1 is based on data from clinical trials where BOOSTRIX TETRA was administered to 908 children (from 4 to 9 years of age) and 955 adults, adolescents and children (above 10 years of age). The most common events occurring after vaccine administration in both groups were local injection site reactions (pain, redness and swelling) reported by 31,3-82,3 % of subjects overall. These had their onset within the first 48 hours after vaccination. All resolved without sequelae.

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.

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

System Organ Class	***Frequency***	***Adverse reactions***	
		Children from 4 to 9 years of age	***Adults, adolescents and children from the age of 10 years onwards***

Infections and infestations	Uncommon		oral herpes
Blood and lymphatic system disorders	Uncommon	lymphadenopathy	lymphadenopathy
Metabolism and nutrition disorders	Common	anorexia	
	Uncommon		decreased appetite
Psychiatric disorders	Common	irritability	
	Uncommon	sleep disorder, apathy	
Nervous system disorders	Very common	somnolence	headache
	Common	headache	
	Uncommon		paraesthesia, somnolence, dizziness
Respiratory, thoracic and mediastinal disorders	Uncommon	dry throat	asthma
Gastrointestinal disorders	Common		gastrointestinal disorders
	Uncommon	diarrhoea, vomiting, abdominal pain, nausea	
Skin and subcutaneous tissue disorders	Uncommon		pruritus
Musculoskeletal and connective tissue disorders	Uncommon		myalgia, arthralgia
General disorders and administration site conditions	Very common	injection site reactions (including pain, redness and swelling)	injection site reactions (including pain, redness and swelling), fatigue
	Common	fever ≥ 37,5 °C (including fever > 39°C), injection site reactions (such as haemorrhage)	fever ≥ 37,5 °C, injection site reactions (such as haematoma)
	Uncommon	fatigue	fever > 39 °C, chills, pain

Coadministration with MMR/V vaccines in children aged 3-6 years*:*

BOOSTRIX TETRA was coadministered with MMR/V vaccines in 2 clinical studies with 406 children aged 3-6 years.

In these studies, upper respiratory tract infection and rash were commonly reported.

Fever, irritability, fatigue, loss of appetite and gastrointenstinal disorders (including diarrhoea and vomiting) were reported with a higher frequency (very common) when compared to Table 1 while all other adverse reactions occurred at the same or lower frequency.

Adverse reactions additionally reported during clinical studies with Boostrix (dTpa component of BOOSTRIX TETRA) was administered to 839 children (from 4 to 9 years of age) and 1931 adults, adolescents and children (above 10 years of age), are listed in Table 2:

Table 2: *Adverse reactions reported in clinical trails with Boostrix*

System Organ Class	***Frequency***	***Adverse reactions***	
		Children from 4 to 9 years of age	***Adults, adolescents and children from the age of 10 years onwards***
Infections and infestations	Uncommon	upper respiratory tract infection	upper respiratory tract infection, pharyngitis
Nervous system disorders	Uncommon	disturbances in attention	syncope
Eye disorders	Uncommon	conjunctivitis	
Respiratory, thoracic and mediastinal disorders	Uncommon		cough
Gastrointestinal disorders	Common	gastrointestinal disorders	nausea
	Uncommon		diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	rash	hyperhidrosis, rash
Musculoskeletal and connective tissue disorders	Uncommon		joint stiffness, musculoskeletal stiffness

General disorders and administration site conditions	Very common		malaise
	Common		injection site reactions (such as injection site mass and injection site abscess sterile)
	Uncommon	injection site reactions (such as induration), pain	influenza like illness

Reactogenecity after repeat dose of BOOSTRIX TETRA or Boostrix:

Subjects fully primed with 4 doses of DTPa followed by BOOSTRIX TETRA at around 4-8 years of age show no increased reactogenicity after the second BOOSTRIX TETRA dose administered 5 years later. Subjects aged 15 years onwards without recent vaccination for diphtheria, tetanus, pertussis and TETRA, who received a dose of BOOSTRIX TETRA or another reduced-antigen content vaccine, followed by an additional dose of BOOSTRIX TETRA 10 years after, showed no increased reactogenicity.

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:

Table 3: Adverse reactions reported with BOOSTRIX TETRA during post-marketing surveillance

System Organ Class	***Frequency***	***Adverse reactions***
Blood and lymphatic system disorders	Rare	angioedema
Immune system disorders	Very rare	allergic reactions, including anaphylactic and anaphylactoid reactions

Nervous system disorders	Rare	convulsions (with or without fever)
Skin and subcutaneous tissue disorders	Rare	urticaria
General disorders and administration site conditions	Rare	extensive swelling of the vaccinated limb, 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).

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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:

A 30.2 Antigens

5.1 Pharmacodynamic properties:

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA.

Immune response:

The following immune responses were observed across studies one month post vaccination with BOOSTRIX TETRA in children, adolescents and adults (Table 4).

Table 4: Immune response in children, adolescents and adults

Antigen	**Response**	**Children aged 3 to 9 years** N=1195 (% vaccinees)	**Adults, adolescents and children aged from 10 years onwards** N=923 (% vaccinees)
Diphtheria	≥ 0.1 IU/mL	100%	82,2 – 100%
Tetanus	≥ 0.1 IU/mL	99,9 – 100%	99,6 – 100%
Pertussis			
Pertussis toxoid	Booster response*	84,6 – 9,6%	79,8 – 94,0%
Filamentous haemagglutinin		90,1 – 98,8%	90,7 – 97,2%
Pertactin		94,2 – 96,6%	90,0 – 96,7%
Inactivated poliovirus	≥8 ED50		

type 1		98,8 – 100%	99,6 – 100%
type 2		99,2 – 100%	99,6 – 100%
type 3		99,4 – 100%	99,1 – 100%

N=number of subjects

*Booster response defined as:

- for initially seronegative subjects, antibody concentrations at least four times the cut-off (post-vaccination concentration ≥ 20 El.U/mL);
- for initially seropositive subjects with Pre booster vaccination concentration ≥ 5 El.U/mL and < 20 El.U/mL: an increase in antibody concentrations of at least four times the Pre booster vaccination concentration.
- for initially seropositive subjects with Pre booster vaccination concentration ≥ 20 El.U/mL: an increase in antibody concentrations of at least two times the Pre booster vaccination concentration

Efficacy in protecting against pertussis:

The pertussis antigens contained in BOOSTRIX TETRA 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 TETRA are at least as high, or higher than those observed during the household contact efficacy trial. Based on these comparisons, BOOSTRIX TETRA 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 (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.

Immunogenecity 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 BOOSTRIX TETRA 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 TETRA

Study location	Vaccine	Study design	Vaccination Effectiveness
UK	BOOSTRIX TETRA	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 immune response:

The following seroprotection/seropositivity rates were observed five years after vaccination with BOOSTRIX TETRA in children and 10 years after vaccination with BOOSTRIX TETRA in adolescents and adults (Table 6).

Table 6: Persistence of immune response in children, adolescents and adults

Antigen	Seroprotection/ seropositivity	5 years after vaccination of children (aged 4-8 years) (N=344)	10 years after vaccination of adolescents and adults (aged 15 years onwards) (N=201)
		(% vaccinees)	(% vaccinees)
Diphtheria	≥ 0.1 IU/mL	89,4 %*	81,0 %**
Tetanus	≥ 0.1 IU/mL	98,5 %	98,4 %
Pertussis			
Pertussis toxoid	≥ 5 EL.U/mL	40,9 %	78,7 %
Filamentous haemagglutinin		99,7 %	100 %
Pertactin		97,1 %	88,7 %
Inactivated poliovirus			
type 1	≥ 8 ED50	98,8 %	100 %
type 2		99,7 %	100 %
type 3		97,1 %	98,3 %

*98,2% of subjects with antibody concentrations associated with protection against disease ≥ 0,016 IU/mL by an *in-vitro* Vero-cell neutralisation assay.

**92,1 % of subjects with antibody concentrations associated with protection against disease ≥ 0,01 IU/mL by an *in-vitro* Vero-cell neutralisation assay.

Immune response after a repeat dose of BOOSTRIX TETRA:

The immunogenicity of BOOSTRIX TETRA, administered 5 years after a previous booster dose of BOOSTRIX TETRA at 4 to 8 years of age, has been evaluated. One month post vaccination, > 99 % of subjects were seropositive against pertussis and seroprotected against diphtheria, tetanus and all three polio types.

In adults one dose of BOOSTRIX TETRA administered 10 years after the previous dose, elicited a protective immune response in > 96,8 % of the subjects (for the diphtheria antigen) and in 100% of the subjects (for the tetanus and polio antigens).
The booster response against the pertussis antigens was between 74,2 % and 98,4%.

Immune response in subjects without prior or without unknown vaccination history:

In adolescents 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 (dTpa component of BOOSTRIX TETRA) induced an antibody response against pertussis and all subjects were protected against tetanusand 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 TETRA induced an antibody response against pertussis and protected against tetanus and diphtheria in the majority of cases.

Immune response and safety profile in subjects on active treatment for obstructive airway diseases:

The safety and immunogenicity of Boostrix have been evaluated in a descriptive meta-analysis study combining data from 222 subjects ≥ 18 years of age vaccinated with Boostrix while on active treatment for obstructive airway disease such as asthma or Chronic Obstructive Pulmonary Disease (COPD). One month after Boostrix vaccination, the immune responses against diphtheria and tetanus antigens in terms of seroprotective rates (≥ 0,1 IU/mL) were respectively 89,0 % and 97,2 %, and against pertussis in terms of booster responses these were 78,3 %, 96,1 % and 92,2 % against pertussis toxoid [PT], filamentous haemagglutinin [FHA] and pertactin [PRN], respectively. These results are consistent with the responses obtained in the general adult population and with a similar safety profile.

5.2 Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not required for vaccines.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

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

Residues: formaldehyde, neomycin and polymyxin

Sugar-free

6.2 Incompabilities:

Not Applicable.

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

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

Store in a refrigerator (2 °C – 8 °C).

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

Protect from light.

Upon removal from refrigerator, the vaccine is stable for 8 hours at 21 °C.

6.5 Nature and contents of container:

0,5 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

Pack sizes of 1 and 10, with or without needles.

The tip cap and rubber plunger stopper of the pre-filled syringe are not made with natural rubber latex.

Not all pack sizes may be marketed.

6.6 Special precaution for disposal and other handling:

Prior to use, the vaccine should be at room temperature and well shaken in order to obtain a homogenous 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 product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

43/30.2/0526

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Registration date: 30 September 2011

10. DATE OF REVISION OF TEXT:

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