BOOSTRIX

Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content)
Suspension for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 2 International Units (IU) (2.5 Lf)
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+}

Boostrix is a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal finding.

CLINICAL INFORMATION

Indications

Boostrix is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards (see *Posology*).

The use of ***Boostrix*** should be in accordance with official recommendations.

Dosage and 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 *Pregnancy and Pharmacodynamics*).

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 *Pharmacodynamics*). 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.

Method of administration

Boostrix is for deep intramuscular injection, preferably in the deltoid region (see *Warnings and Precautions*).

Contraindications

Boostrix should not be administered to subjects with known hypersensitivity to any component of the vaccine (see *Quantitative and Qualitative Composition* and *List of Excipients*), or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines.

Boostrix 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 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 *Warnings and Precautions*).

Warnings and Precautions

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 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.

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) immunization 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.

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 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.

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 contraindication 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.

Boostrix **should under no circumstances be administered intravenously.**

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.

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 clinically relevant interference with the immune responses.

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.

Pregnancy and Lactation

Fertility

No human data available. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility (see *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 *Pharmacodynamics*.

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 post-marketing surveillance where pregnant women were exposed to ***Boostrix*** or to ***Boostrix Polio*** (dTpa-IPV vaccine) in the second or 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.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical Trial Data

The safety profile below is based on data from clinical trials where ***Boostrix*** was administered to 839 children (from 4 to 9 years of age) and 1931 adults, adolescents and children (above 10 years of age).

Adverse reactions reported are listed according to the following frequency:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10,000 and <1/1000
Very rare	<1/10,000

Children from 4 to 9 years of age

Infections and infestations
Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders
Common: anorexia

Psychiatric disorders
Very common: irritability

Nervous system disorders
Very common: somnolence
Common: headache
Uncommon: disturbances in attention

Eye disorders
Uncommon: conjunctivitis

Gastrointestinal disorders
Common: diarrhoea, vomiting, gastrointestinal disorders

Skin and subcutaneous tissue disorders
Uncommon: rash

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

Infections and infestations
Uncommon: upper respiratory tract infection, pharyngitis

Blood and lymphatic system disorders
Uncommon: lymphadenopathy

Nervous system disorders
Very common: headache
Common: dizziness
Uncommon: syncope

Respiratory, thoracic and mediastinal disorders
Uncommon: cough

Gastrointestinal disorders
Common: nausea, gastrointestinal disorders
Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders
Uncommon: 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 (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

Reactogenicity after repeat dose of ***Boostrix***

Data on 146 subjects suggest 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 DTPw 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

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

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Bacterial vaccines combined, ATC code J07AJ52

Immune response

Approximately one month following booster vaccination with ***Boostrix***,

- seropositivity/seroprotection rate against the different vaccine components was at least 99% in children from 4 to 9 years of age.
- seropositivity/seroprotection rate against the different vaccine components was at least 97% in adults and adolescents from 10 years of age.

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.

Efficacy in protecting against pertussis

There is currently no correlate of protection defined for pertussis; however, the protective efficacy of GlaxoSmithKline Biologicals' DTPa (***Infanrix***) vaccine against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough with laboratory confirmation) was demonstrated in the following 3-dose primary studies:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%. Protection against laboratory confirmed mild disease, defined as 14 days or more of cough of any type was 73% and 67% when defined as 7 days or more of cough of any type.
- an NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%. When the definition of pertussis was expanded to include clinically milder cases with respect to type and duration of cough, the efficacy of ***Infanrix*** was calculated to be 71% against >7 days of any cough and 73% against >14 days of any cough.

Vaccinees receiving ***Boostrix*** achieved anti-pertussis antibody titres greater than those in the German household contact study where the protective efficacy was 88.7%.

Immunogenicity against pertussis antigens 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 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 concentrations of antibodies against the pertussis antigens PT, FHA and PRN that are 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

The immunogenicity of ***Infanrix hexa*** in infants and toddlers born to health mothers vaccinated with dTpa at 27-36 weeks of pregnancy was evaluated in two clinical studies.

Infanrix hexa was co-administered with 13-valent pneumococcal conjugate vaccine to infants at 2, 4 and 6 months or 2, 3 and 4 months in three-dose primary vaccination schedules (N=241), or at 3 and 5 months or 2 and 4 months in two-dose primary vaccination schedules (N=27) 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 dTpa on the infant's and toddler's responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b or pneumococcal antigens.

For diphtheria, at the pre-booster timepoint 81.2% of infants in the dTpa Group and 90.2% in the Control Group were seroprotected. Post-booster vaccination, all subjects in both study groups were seroprotected.

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 dTpa 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 dTpa 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 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/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.

Persistence of the immune response

Five to six years following vaccination with ***Boostrix***, at least 94% of children from the age of 4 years onwards were seroprotected or seropositive against all vaccine components, except for the pertussis toxoid component (52% of subjects were seropositive against pertussis toxoid).

Ten years following vaccination with ***Boostrix***, at least 86% of adults were seroprotected or seropositive against all vaccine components.

In adolescents, the percentage of subjects who were seroprotected or seropositive was at least 82% against all vaccine components, except for the pertussis toxoid component (61% of subjects were seropositive against pertussis toxoid).

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.

Clinical Studies

See *Pharmacodynamics.*

Non-Clinical Information

Animal toxicology and/or pharmacology

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

PHARMACEUTICAL INFORMATION

List of Excipients

Aluminium hydroxide, aluminium phosphate, sodium chloride, water for injections.

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

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

The storage conditions are detailed on the packaging.

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.

0.5 ml of suspension in a vial (type I glass) with a stopper (butyl rubber).

Pack sizes of 1 and 10.

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

Not all presentations are available in every country.

Incompatibilities

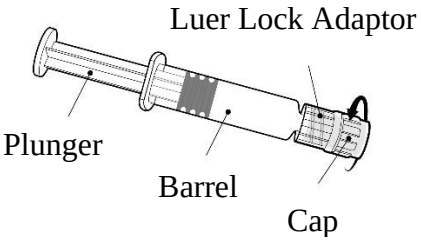
Boostrix should not be mixed with other vaccines in the same syringe.

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

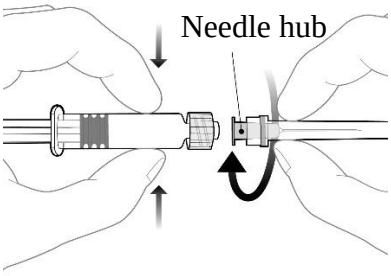
variation of physical aspect prior to administration. In the event of either being observed, do not administer the vaccine.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal:

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

Version number: GDS16/IPI17SI
Date of issue: 15 August 2022

Product Registrant
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[GSK Logo]