BOOSTRIX™

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

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.

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

Indications

Boostrix™ is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards.

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 adult-type combined diphtheria-tetanus vaccine, when a booster against pertussis is desired.

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 also *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 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 *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

Concomitant use with other inactivated vaccines and with immunoglobulin is unlikely to result in an 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.

Pregnancy and Lactation

Fertility

No human data available. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility (see section *Pre-clinical Safety Data*).

Pregnancy

Safety data from a prospective observational study where ***Boostrix***™ was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from post-marketing surveillance where pregnant women were exposed to ***Boostrix***™ or to ***Boostrix***™ ***Polio*** (dTpa-IPV vaccine) have shown no vaccine related adverse effect on pregnancy or on the health of the foetus/newborn child.

The use of ***Boostrix***™ may be considered during the third trimester of pregnancy.

Human data from prospective clinical studies on the use of ***Boostrix***™ during the first and second trimester of pregnancy are not available.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with ***Boostrix***™ during pregnancy. The clinical relevance of this observation is unknown.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section *Pre-clinical Safety Data*).

Boostrix™ should only be used during pregnancy when the possible advantages outweigh the possible risks for the foetus.

Lactation

The safety of ***Boostrix***™ when administered to breast-feeding women has not been evaluated.

It is unknown whether ***Boostrix***™ is excreted in human breast milk.

Boostrix™ should only be used during breast-feeding 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

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

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.

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

Pharmaco-therapeutic group: Bacterial vaccines combined, ATC code J07AJ52

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 1690 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.

Protective efficacy of 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%.

Five to 6 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).

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.

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. Two additional doses of a diphtheria and tetanus containing vaccine maximized the vaccine response against diphtheria and tetanus when administered one and six months after the first dose.

Clinical Studies

See *Pharmacodynamics.*

Pre-clinical 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Aluminium hydroxide, aluminium phosphate, sodium chloride, water for injections. Formaldehyde, polysorbate 80, glycine are present as residues from the manufacturing process.

Incompatibilities

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

Shelf Life

The expiry date is indicated on the label and packaging.

Special Precautions for Storage

Boostrix™ should be stored 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.

Nature and Contents of Container

Boostrix™ is presented as a turbid white suspension in a single dose glass vial or pre-filled syringe.

The vials and pre-filled syringes are made of neutral glass type I, which conform to European Pharmacopoeia Requirements.

Not all presentations are available in every country.

Instructions for Use/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, discard the vaccine.

The vaccine should be administered immediately after opening the container (not later than 8 hours after opening).

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

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