Boostrix™

1. Name of the medicinal product

Boostrix™ Combined diphtheria, tetanus, acellular pertussis vaccine.

2. Qualitative and quantitative composition

Boostrix™ contains diphtheria toxoid, tetanus toxoid, three purified pertussis antigens [pertussis toxoid (PT) filamentous hemagglutinin (FHA) and pertactin (PRN)], adsorbed onto aluminium salts. The tetanus and diphtheria toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins. The acellular pertussis vaccine components are obtained by extraction and purification from phase I *Bordetella pertussis* cultures, followed by irreversible detoxification of the pertussis toxin by glutaraldehyde and formaldehyde treatment of pertussis toxin, and formaldehyde treatment of FHA and PRN. The diphtheria toxoid, tetanus toxoid and acellular pertussis components are adsorbed onto aluminium salts. The final vaccine is formulated in saline.
Boostrix™ meets the World Health Organisation requirements for the manufacture of biological substances and for diphtheria and tetanus vaccines.
A 0.5 ml dose of vaccine contains not less than 2 IU ('International Units') or a 2.5 limit of flocculation ('Lf') of diphtheria toxoid, not less than 20 IU (5 Lf) of tetanus toxoid, 8 µg of PT, 8 µg of FHA and 2.5 µg of PRN.

3. Pharmaceutical form

Suspension for injection.

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.

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 adult-type combined diphtheria-tetanus vaccine, when a booster against pertussis is desired. Individuals with an incomplete, or no, history of a primary series of diphtheria and tetanus toxoids should not be vaccinated with ***Boostrix™***. ***Boostrix™*** is not precluded in subjects with an incomplete, or no, history of previous pertussis vaccination. However, a booster response will only be elicited in individuals who have been previously primed by vaccination or by natural infection.
In accordance with current recommendations for maintenance of protection against diphtheria and tetanus, the interval between doses should not exceed 10 years. It is not necessary to re-commence primary vaccination, should the inter-booster interval of ten years be exceeded. The duration of immunity afforded by the pertussis components of the vaccine has not yet been established.
Tetanus-prone injury: in case of tetanus-prone injury, ***Boostrix™*** can be used as an alternative to adult-type combined diphtheria-tetanus vaccine in individuals with no history of tetanus toxoid within the preceding five years, if a booster against diphtheria and pertussis is additionally desired.

Method of administration

Boostrix™ is for deep intramuscular injection.
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.

4.3 Contra-indications

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, adult-type combined diphtheria-tetanus vaccine should be used.
Boostrix™ should not be administered to subjects who have experienced transient thrombocytopenia or neurological complications following an earlier immunisation against diphtheria and/or tetanus.

4.4 Special warnings and special 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 not 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) 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.
A history or a family history of convulsions and a family history of an adverse event following DTP vaccination do not constitute contra-indications.
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.
***Boostrix™* should under no circumstances be administered intravenously.**

4.5 Interaction with other medicinal products and other forms of interaction

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 immunoglobulin, at a different injection site.
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 Use during pregnancy and lactation

As with all inactivated vaccines, one does not expect harm for the foetus. However, adequate human data on use of this pertussis containing vaccine during pregnancy are not available. Therefore, ***Boostrix™*** should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the foetus. When protection against tetanus is sought, consideration should be given to a licensed tetanus or combined diphtheria-tetanus vaccine.
Adequate human data on use during lactation and adequate animal reproduction studies are not available.

4.7 Effects on the 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

In controlled clinical studies, the most commonly reported reactions were those at the site of injection. They included pain (73%, 2% severe), redness (32%, 6% ≥ 50 mm) and swelling (28%, 6% ≥ 50 mm). All local symptoms resolved without any sequelae.
Systemic adverse events, considered to be probably or suspected to be related to vaccination, very commonly reported in adolescents and adults were malaise (11%, 0.7% severe), fatigue (19%, 0.8% severe) and headache (16%, 0.7% severe). Commonly reported symptoms in children included diarrhoea (4.0%, 0% severe), irritability (8.0%, 0% severe), loss of appetite (8.0%, 0.5% severe) and vomiting (3.0%, 0% severe). Fever > 39.0°C, considered as probably or suspected to be related to vaccination, was infrequently reported in adolescents and adults (0.1%).
All unsolicited symptoms were uncommonly reported. These included increased sweating (0.2%), hypertonia (0.3%), arthrosis (0.2%), myalgia (0.9%), pruritus (0.6%) and lymphadenopathy (0.7%).
Very rare allergic reactions, including anaphylactoid reactions, have been reported following vaccination with DTPa containing vaccines.

Extremely rare cases of collapse or shock-like state (hyoptonic-hyporesponsiveness episode) and convulsions within 2 to 3 days of vaccination have been reported in DTPa and DTPa combination vaccines. All of the subjects recovered totally and spontaneously without sequelae. At the present time, there have been no collapse or shock-like episodes reported following administration of ***Boostrix™***.

4.9. Overdose

Not applicable.

5. Pharmacological properties

5.1. Pharmacodynamic properties

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

Immune response results to the diphtheria, tetanus and acellular pertussis components in the comparative studies (dTpa versus dT) of booster vaccination in different age groups are presented in the table below.

Age at booster	Previous Vaccinations	Results following vaccination with dTpa				
		anti-PT*	anti-FHA*	anti-PRN*	anti-diphtheria†	anti-tetanus†
10-13 years	4 doses DTPw (primary plus booster)	92.1%	96.8%	98.9%	100%	100%
11-17 years	4 doses DTPw (primary plus booster)	100%	95.0%	100%	100%	100%
≥ 18 years	Heterogeneous	95%	99.2%	98.5%	92.7%	99.8%

† Percentage of vaccinees having anti-diphtheria and anti-tetanus antibody titres ≥ 0.1 IU/ml post-vaccination.
* Percentage of vaccinees having anti-PT, anti-FHA, anti-PRN antibody titres ≥ cut-off (ie, 5 EU/ml) post-vaccination for initially seronegative subjects; or the percentage of vaccinees having a 2-fold increase in anti-PT, anti-FHA, anti-PRN antibody titres post-vaccination for initially seropositive subjects.

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%.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

Appropriate safety tests have been performed.

6. Pharmaceutical particulars

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf-life

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

6.4 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.

6.5 Nature and content of container

Boostrix™ is presented as a turbid white suspension in a glass container. Upon storage, a white deposit and clear supernatant can be observed.
The containers are made of neutral glass type I, which conform to European Pharmacopoeia Requirements.

6.6 Instructions for use, handling and disposal (if appropriate)

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).

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