# WHO PRODUCT INFORMATION

## NAME OF THE MEDICINAL PRODUCT

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

## QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5 ml) of Boostrix contains:

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|---|---|
| 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 $Al^{3+}$ |

Excipients: sodium chloride, water for injections.

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

The vaccine may contain traces of formaldehyde which is used during the manufacturing process (see *Contraindications*).

## CLINICAL PARTICULARS

### Therapeutic indications

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

Boostrix is also indicated for passive protection against pertussis in early infancy following maternal immunisation during pregnancy (see sections *Posology*, *Pregnancy and lactation* and *Pharmacodynamic properties*).

The administration of Boostrix should be based on official recommendations.

### 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 *Therapeutic indications*, *Pregnancy and lactation* and *Pharmacodynamic properties*).

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 *Pharmacodynamic properties*). 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 also *Special warnings and precautions for use*).

**Contraindications**

Boostrix should not be administered to subjects with known hypersensitivity to any component of the vaccine or formaldehyde (see *Qualitative and Quantitative composition*), 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 *Special warnings and precautions for use*).

**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.

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. If in accordance with official recommendations, the vaccine may 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 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.

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.

*Excipients*
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free.

**Interaction with other medicinal products and other forms of interaction**

Boostrix may be administered concomitantly with human papilloma virus vaccine with no clinically relevant interference with antibody response to any of the components of either vaccine.

Boostrix can be given concomitantly with meningococcal serogroups A, C, W-135 and Y (MenACWY) conjugate vaccines. Clinical studies in subjects aged 9 to 25 years demonstrated that the immune responses to the tetanus, diphtheria and meningococcal antigens were unaffected. Lower geometric mean concentrations (GMCs) were observed for the pertussis antigens; however, these data do not suggest clinically relevant interference.

Boostrix can be given concomitantly with unadjuvanted inactivated seasonal influenza vaccines. When Boostrix was co-administered with a trivalent inactivated influenza vaccine in subjects aged between 19 and 64 years, clinical data demonstrated that the immune responses to the tetanus, diphtheria, pertussis toxoid (PT) and influenza antigens were unaffected. Lower 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.

Boostrix can be given concomitantly with non-live herpes zoster vaccine. Clinical data 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.

Concomitant use with other inactivated vaccines and with immunoglobulin is unlikely to result in clinically relevant 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 from prospective clinical studies are 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 *Pharmacodynamic properties*.

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 (dTpa-IPV vaccine) during the first and second trimester of pregnancy are not available.

Data from passive surveillance where pregnant women were exposed to Boostrix or to Boostrix Polio in the 3$^{rd}$ or 2$^{nd}$ 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 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.

**Undesirable effects**

Frequencies per dose are defined as follows:
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

**Clinical trial data**

**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 surveillance**

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

### Pharmacodynamic properties

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

*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:<br>- Pertussis toxoid<br>- Filamentous haemagglutinin<br>- Pertactin | <br>≥ 5 EL.U/ml<br>≥ 5 EL.U/ml<br>≥ 5 EL.U/ml | <br>97.8%<br>99.9%<br>99.4% | <br>99.0%<br>100.0%<br>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.

*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%.

*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 (dTpa group; N=291) versus placebo (control group; N=292) at 27-36 weeks 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 antibody titres that are 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 (diphtheria, tetanus, pertussis, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b conjugate vaccine) in infants and toddlers born to healthy mothers vaccinated with Boostrix at 27-36 weeks of pregnancy was evaluated in two clinical studies.

Infanrix hexa was co-administered with a 13-valent pneumococcal conjugate vaccine to infants for primary vaccination (n=268); 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 Boostrix on the infant’s and toddler’s responses to diphtheria, tetanus, hepatitis B, inactivated poliovirus, *Haemophilus influenzae* type b or pneumococcal antigens.

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 Boostrix 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 Boostrix 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 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 65 % of adults were seroprotected or seropositive against all vaccine components.

In adolescents, the percentage of subjects who were seroprotected or seropositive 10 years following vaccination 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.

## PHARMACEUTICAL PARTICULARS

### 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

Store in a refrigerator (2°C – 8°C). During transport, recommended conditions of storage must be respected.

Stability data indicate that Boostrix is stable at temperatures up to 37°C for 7 days. At the end of this period Boostrix should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Do not freeze; discard if vaccine has been frozen.
Protect from light.

### Nature and contents of container

Boostrix: 0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (butyl rubber) - pack size of 10.

Not all pack sizes may be marketed.

**Special precautions for disposal and other 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.

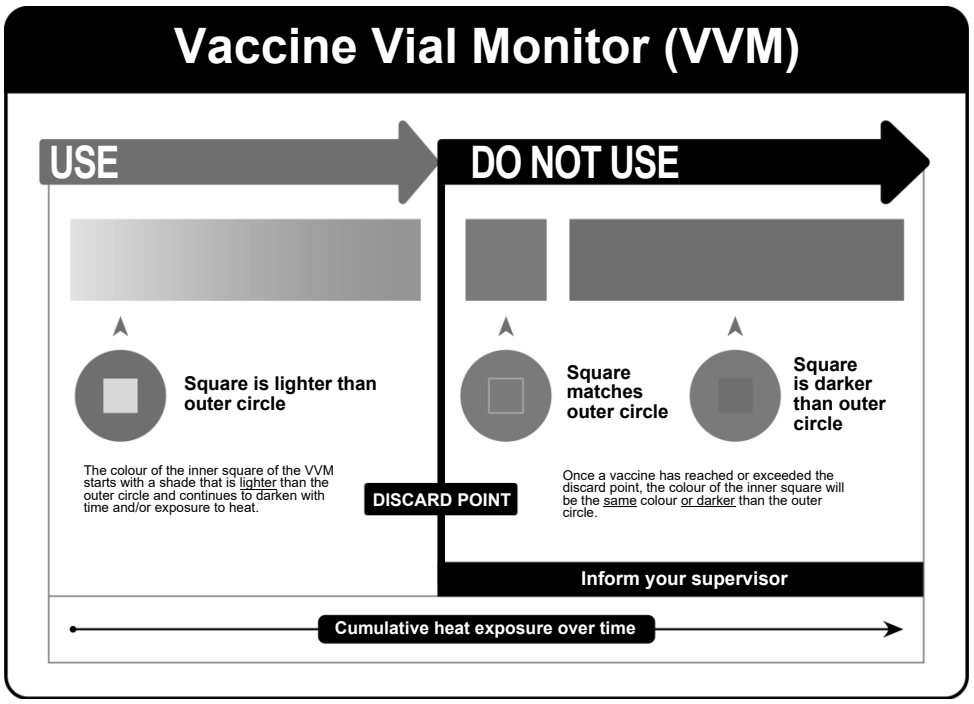
Any unused product or waste material should be disposed of in accordance with local requirements.

**Vaccine Vial Monitor (see VVM infographic at the end of the leaflet)**

The Vaccine Vial Monitor (VVM) is part of the label used for all Boostrix batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the inner square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the inner square is the same colour as the outer circle or of a darker colour than the outer circle, then the vial should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event Boostrix has not been stored in compliance with the storage instructions.




For further information, please contact the manufacturer.

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