NAME OF THE MEDICINAL PRODUCT

Imovax d.T. , Adsorbed Diphtheria and Tetanus Vaccine, Suspension for Injection In 0.5 mL Pre-Filled Syringe

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One dose (0.5 mL suspension for injection) contains:

Purified diphtheria toxoid	at least 2 I.U.*
Purified tetanus toxoid	at least 20 I.U.*
Adsorbed on aluminium hydroxide (expressed as Al^{3+})	0.6 mg
Excipients with known effect	
Sodium	less than 23 mg
Potassium	less than 39 mg

* I.U. = International Units, as lower confidence limit (p = 0.95) of activity measured according to the assay described in the European Pharmacopoeia.

Imovax d.T. may contain traces of formaldehyde used during the manufacturing process (see section **Contraindications**).

For the full list of excipients, see section **List of excipients.**

PHARMACEUTICAL FORM

White-cloudy suspension for injection in a pre-filled syringe.

CLINICAL PARTICULARS

Therapeutic indications

Imovax d.T. is indicated for booster vaccination against tetanus and diphtheria in individuals from 6 years of age.

The use of this vaccine should be in accordance with the official recommendations.

Posology and method of administration

Posology
For adults, adolescents and children from 6 years of age, the dose is 0.5 mL.

Booster vaccination of previously immunized individuals

Booster vaccination against tetanus and diphtheria should be based on official recommendations regarding the type of tetanus-diphtheria containing vaccine to be used and interval since previous vaccination.

Booster vaccination with Imovax d.T. consists of one dose (0.5 mL) of Imovax d.T. (see section **Pharmacodynamic properties**).

In adults previously vaccinated and with important delay since last tetanus-diphtheria vaccination (range 11 to 60 years) a second booster dose (0.5 mL) may be required at least one month after the first booster dose for some individuals (see section **Pharmacodynamic properties**). The decision to administer a second booster dose should be based on the assessment of antibodies level (serological test) achieved after the first booster dose.

Post-exposure prophylaxis of tetanus
In subjects previously immunized against tetanus, Imovax d.T. could be used for post-exposure prophylaxis of tetanus if in accordance with official recommendations.

Other pediatric population

The safety and efficacy of Imovax d.T. in children less than 6 years of age have not been established.

Method of administration

Imovax d.T. should be given by intramuscular injection. The preferred injection site is the deltoid muscle.
Imovax d.T. must not be administered by intradermal or intravascular routes.

For instructions on handling, see section **Special precautions for disposal and other handling**.

Contraindications

Hypersensitivity to the active substances or any of the excipients listed in section **List of excipients** or any of the possible production residues of formaldehyde

Allergic reactions or neurological dysfunction after previous administration of a vaccine with the same antigen components.

As a rule, there are no contraindications for vaccination in the event of injury, except in the case of a severe allergy.

Special warnings and precautions for use

As with all vaccinations, in the event of an allergic reaction following vaccination, appropriate medical treatment must be available for immediate treatment and adequate monitoring must be carried out.

To reduce the severity of adverse reactions, avoid administering the vaccine to persons who have received a complete primary vaccination or a booster vaccination in the previous 5 years. As with other intramuscular injections, the vaccine should be given with caution in subjects receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these vaccines.

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection, except in case of a tetanus-prone wound. The presence of a minor infection and/or low-grade fever should not delay vaccination.

If Guillain-Barré syndrome or plexus brachialis neuritis has occurred after a previous administration of a tetanus vaccine, the decision to give any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.

Antibody formation may be impaired during immunosuppressive treatment or in patients who suffer from weakened immune function. In these cases, vaccination should be deferred until therapy is completed or the antibody titer is checked. Nevertheless, in individuals with chronic immunodeficiency

disease, such as HIV infection, vaccination is recommended if the course of the disease allows a reduced triggering of the antibody response.

Syncope can occur following, or even before, administration of injectable vaccines, including Imovax d.T. Procedures should be in place to prevent falling injury and manage syncopal reactions.

As with any vaccine, vaccination with Imovax d.T. may not protect all vaccine recipients.

Imovax d.T. contains less than 1 mmol (39 mg) of potassium and less than 1 mmol (23 mg) of sodium per dose, that is to say essentially "potassium-free" and "sodium-free".

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Interaction with other medicinal products and other forms of interaction

Co-administration of Imovax d.T. with inactivated polio vaccine, or tetanus immunoglobulin did not show clinically relevant interference.

Separate injection sites and preferably separate limbs must be used in case of concomitant administration.
Interference of Imovax d.T. with laboratory and/or diagnostic tests have not been investigated.

Fertility, pregnancy and lactation

Pregnancy
The effects of Imovax d.T. on embryo-foetal development have not been studied. No teratogenic effects have been observed after administration of diphtheria or tetanus toxoids to pregnant women.
Imovax d.T. should be used during pregnancy only if the expected benefits for the mother outweigh the potential risks, including those for the foetus.

Breast-feeding
The effects of vaccination of mothers on their breastfed children have not been studied. Imovax d.T. should only be used during breast-feeding when the potential benefits outweigh the potential risks.

Fertility
There are no data on the effect on fertility.

Effects on ability to drive and use machines

Imovax d.T. has no or a negligible effect on the ability to drive and operate machinery

Undesirable effects

In adults, the safety of Imovax d.T. was evaluated in a controlled, randomized, double-blind clinical trial with 252 participants aged 18 to 49 years. Participants received one dose of Imovax d.T. and simultaneously one dose of inactivated polio vaccine (IPV).
At the Td vaccine injection site, pain was the most common adverse reaction; most injection site reactions occurred within 3 days of vaccination. The most common systemic adverse reactions were headache, diarrhea, temperature ≥ 38°C and nausea/vomiting.

Other pediatric population
In adolescents, the safety of Imovax d.T. was evaluated in two studies where 1000 adolescents from 13 to 17 years of age received one dose of Imovax d.T. with or without concomitant Meningococcal C vaccine. The safety profile of Imovax d.T. in adolescents from 13 to 17 years of age was generally

similar to that in adults. Headache, feeling of sickness, and redness and oedema at the injection site were very common in adolescents from 13 to 17 years of age.

In children, the safety of Imovax d.T. was evaluated in a controlled, randomized, open clinical trial where 151 children 6 to 9 years old received one dose of Imovax d.T. The safety profile of Imovax d.T. in children from 6 years through 9 years of age was generally similar to that in adults. Redness and induration at the injection site were very common in children from 6 to 9 years of age.

Tabulated list of adverse reactions
The adverse reactions are listed by MedDRA system organ class under headings of frequency using the following convention:

Very common:	(≥1/10)
Common:	(≥1/100, < 1/10)
Uncommon:	(≥1/1,000, < 1/100)
Rare:	(≥1/10,000, < 1/1,000)
Very rare:	(<1/10,000)
Not known:	cannot be estimated from available data.

The following table lists the adverse reactions from the above-mentioned clinical studies and the adverse reactions that have been reported spontaneously by post-marketing surveillance of Imovax d.T.

Table 1: Tabulated summary of adverse reactions following administration of Imovax d.T. from clinical trials and post marketing surveillance in individuals from 6 years of age.

System organ class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Lymphadenopathy	Not known*
Immune system disorders	Type I allergic reactions / anaphylactic reactions, such as facial edema, angioedema, and Quincke's edema	Not known*
Nervous system disorders	Headache[1]	Very common
	Feeling of sickness[2,3]	Very common
Ear and labyrinth disorders	Vertigo	Common
Gastrointestinal disorders	Nausea/vomiting, diarrhea	Common
Vascular disorders	Hypotension (associated with type I allergic reactions)	Not known*
Skin and subcutaneous tissue disorders	Allergy-like symptoms such as general pruritus, urticaria or edema	Not known*
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Uncommon
General disorders and administration site conditions[4]	Injection site pain, Injection site redness[1,5], injection site nodule, injection site induration[5]	Very common
	Fever (over 38.0 °C), Injection site rash, injection site oedema[1]	Common
	Fatigue	Uncommon
	Injection site aseptic abscess	Not known*

* As adverse events from post-marketing surveillance were spontaneously reported from a total group of unknown size, it is not possible to reliably determine their frequency. Therefore, all adverse events from the post-marketing surveillance were assigned the frequency category "Not known".

[1] common in children from 6 to 9 years of age and adults 18 years of age and older

[2] uncommon in children from 6 to 9 years of age and adults 18 years of age and older

[3] within 15 minutes after vaccination

[4] Discomfort at the site of administration may occur within 48 hours and last for 1 – 2 days. The duration and severity of these local phenomena could be influenced by the site of administration, and the number of doses previously received.

[5] common in individuals from 13 years of age.

All these reactions have been observed more frequently in hyperimmunized individuals, especially in the case of too frequent booster vaccinations.
In adults previously vaccinated and with important delay since the last tetanus-diphtheria vaccination no increase of reactogenicity has been observed after a second dose of Td-IPV vaccine (containing the same content of diphtheria and tetanus antigens as Imovax d.T.) given one month after the first dose (see section **Pharmacodynamic properties**).

Possible side effects
(i.e. adverse reactions reported with other vaccines containing one or more of the antigenic components of Imovax d.T. and not directly with Imovax d.T.):

Brachial neuritis and Guillain-Barré syndrome have been reported after administration of tetanus toxoid-containing vaccines.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of medicinal products is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Overdose

Not applicable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Tetanus vaccines; tetanus toxoid, combinations with diphtheria toxoid, ATC code: J07AM51

Anti-diphtheria and anti-tetanus antibody levels ≥ 0.01 IU/mL are considered as the minimum level providing some degree of protection, while antibody levels ≥ 0.1 IU/mL are considered protective.
The immune responses to Imovax d.T. were evaluated in clinical trials carried out in participants of different ages having different vaccination histories. The immune responses observed one-month after vaccination with Imovax d.T. are presented in the table below.

Table 2: Immune responses in children, adolescents and adults one month after administration of a booster dose of Imovax d.T.

Antibody	Criteria	Children (6 -11 years) N=142[a]	Adolescents (12 – 17 years) N=964[b]	Adults (≥ 18 years) N= 686[c]
Diphtheria (IU/mL)	≥ 0.1	100%	99 - 100%	91.5 - 99.2%
	≥ 0.01	100%	NA	92 – 99.6%
Tetanus (IU/mL)	≥ 0.1	100%	99 - 100%	99 - 100%
	≥ 0.01	100%	NA	99 – 100%

IU: international units; N: number of participants who received Imovax d.T. for whom immunogenicity was assessed; NA: not available
[a] Imovax d.T. administered alone, delay since last tetanus-diphtheria vaccination (at least 5 years)
[b]Imovax d.T. administered alone or concomitantly with a meningococcal C conjugate vaccine, delay since last tetanus-diphtheria vaccination (at least 2 years)

[c]Imovax d.T. administered alone or concomitantly with a IPV vaccine; delay since last tetanus-diphtheria vaccination (5 to 20 years)

Immunity is reinforced in the days (5 to 7 days) following the booster injection and is generally considered to last for 5 to 10 years.

Persistence of immune response in adults

Persistence of immune response following administration of Imovax d.T. in adults has not been investigated.

Following administration of Td-IPV (containing the same content of diphtheria and tetanus antigens as Imovax d.T.) s a booster in adults (18.5 to 57 years of age with 5 to 20 years since last tetanus-diphtheria-poliomyelitis booster, N=131), immune responses against tetanus and diphtheria have been shown to persist for 2 years post-vaccination with anti-tetanus antibody levels ≥ 0.1 IU/mL and ≥1 IU/mL (long-term protection) observed in 100% and 80.7% of participants respectively, and, anti-diphtheria antibody levels ≥ 0.1 IU/mL and ≥ 1 IU/mL observed in 94.7% and 49.1% of participants respectively.

Persistence of immune response in children

Persistence of immune response following administration of Imovax d.T. in children has not been investigated.

Following administration of Td-IPV (containing the same content of diphtheria and tetanus antigens as Imovax d.T.) as a booster in children from 6 years of age (N=128), immune responses against tetanus and diphtheria have been shown to persist for 5-7 years post-vaccination with anti-tetanus antibody levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL observed in 100% and 96.1% of participants respectively, and, anti-diphtheria antibody levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL observed in 98.4% and 63.3% of participants respectively.

Immune response after a 2nd dose in older adults

In adults (40 to 78 years) previously vaccinated and with important delay since last tetanus-diphtheria vaccination (28 to 33±11 years [range 11 to 60 years]) receiving 2 doses of Td-IPV vaccine (containing the same tetanus and diphtheria antigen content as Imovax d.T.), antibody levels ≥ 0.1 IU/mL were observed in 97.3% of participants one month after the first dose and 100% of participants one month after the second dose for tetanus, and in 80.5% of participants one month after the first dose and 93.7% of participants one month after the second dose for diphtheria.

Pharmacokinetic properties

No pharmacokinetic studies have been performed.

Preclinical safety data

Not documented.

PHARMACEUTICAL PARTICULARS

List of excipients

Sodium chloride
Disodium phosphate dihydrate
monopotassium phosphate
Acetic acid and/or sodium hydroxide and/or hydrochloric acid (for pH adjustment)

Water for injections

For adjuvant and traces from the manufacturing process, see section **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Incompatibilities

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

Special precautions for storage

Store in the refrigerator (2°C -8°C). Do not freeze. Frozen vaccine should be discarded.
Store in the original package in order to protect from light.

Nature and contents of container

0.5 mL pre-filled syringe (glass type I) with attached capped needle and a plunger-stopper (chlorobutyl elastomer)

Pack size: 1 pre-filled syringe

Special precautions for disposal and other handling

Parenteral biological products should be inspected visually for particulate matter and/or discoloration prior to administration. In the event of either being observed, discard the vaccine.
The normal appearance is a whitish turbid suspension for injection in a pre-filled syringe. Shake before use to obtain a homogeneous suspension.

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

MARKETING AUTHORISATION HOLDER
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