Preparations

Ph. Eur.: Diphtheria Vaccine (Adsorbed); Diphtheria Vaccine (Adsorbed, Reduced Antigen Content).

Proprietary Preparations (details are given in Part 3)
Cz.: Aldiana†; ***NZ:*** Di Anatoxal.

Diphtheria and Tetanus Vaccines

Vacunas de la difteria y el tétanos.

ATC — J07AM51.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed); Vaccinum Diphtheriae et Tetani Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid adsorbed on a mineral carrier. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid and not less than 40 international units of tetanus toxoid per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DT/Vac/Ads(Child) may be used on the label.

The BP 2008 gives Adsorbed Diphtheria-Tetanus Prophylactic as an approved synonym.

Ph. Eur. 6.2 (Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content); Vaccinum Diphtheriae et Tetani, Antigeni-o(-is) Minutum). It is diphtheria and tetanus vaccine (adsorbed) containing not less than 2 units of diphtheria toxoid and not less than 20 units of tetanus toxoid per dose.

The BP 2008 states that for a vaccine for use in the UK, the amount of diphtheria toxoid used is adjusted so that the final vaccine contains not more than 2.0 flocculation equivalents of diphtheria toxoid per dose.

The BP 2008 states that dT may be used on the label.

USP 31 (Diphtheria and Tetanus Toxoids Adsorbed). A sterile suspension prepared by mixing suitable quantities of plain or adsorbed diphtheria toxoid and plain or adsorbed tetanus toxoid and, if plain toxoids are used, an aluminium adsorbing agent. The antigenicity or potency and the proportions of the toxoids are such as to provide an immunising dose of each toxoid in the labelled dose. It should be stored at 2° to 8° and not be allowed to freeze.

USP 31 (Tetanus and Diphtheria Toxoids Adsorbed for Adult Use). A sterile suspension prepared by mixing suitable quantities of adsorbed diphtheria toxoid and adsorbed tetanus toxoid using the same precipitating or adsorbing agent for both toxoids. The antigenicity or potency and the proportions of the toxoids are such as to provide, in the labelled dose, an immunising dose of adsorbed tetanus toxoid and one-tenth of the immunising dose of adsorbed diphtheria toxoid specified for children and not more than 2 Lf of diphtheria toxoid. It should be stored at 2° to 8° and not be allowed to freeze.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, above, and Tetanus Vaccines, p.2240. Diphtheria and tetanus vaccines are reported to produce fewer adverse effects than diphtheria, tetanus, and pertussis vaccines (see under Incidence of Adverse Effects, p.2210).

Dose-related effects. A high incidence of adverse effects was reported in teenagers inadvertently given a high-dose diphtheria and tetanus vaccine intended for use in infants.[1] Most reactions were classified as mild or moderately severe, but severe local or systemic reactions occurred in a third of those reporting reactions.

1. Sidebotham PD, Lenton SW. Incidence of adverse reactions after administration of high dose diphtheria with tetanus vaccine to school leavers: retrospective questionnaire study. *BMJ* 1996; **313:** 533–4.

Effects on the nervous system. Encephalopathy more commonly follows vaccination with diphtheria, tetanus, and pertussis vaccine than with diphtheria and tetanus vaccine (p.2210). Several cases of encephalopathy occurred in a small region in Italy in children after immunisation against diphtheria and tetanus,[1] although it was not possible to infer a causal relationship. A case of polyradiculoneuritis has been reported in a patient after the use of a diphtheria-tetanus vaccine and was considered most likely to have been due to the tetanus component.[2]

1. Greco D. Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy. *Bull WHO* 1985; **63:** 919–25.
2. Holliday PL, Bauer RB. Polyradiculoneuritis secondary to immunization with tetanus and diphtheria toxoids. *Arch Neurol* 1983; **40:** 56–7.

GUILLAIN-BARRÉ SYNDROME. Evidence mainly from case reports and uncontrolled studies favoured a causal relationship between vaccination with diphtheria and tetanus vaccines or single-antigen tetanus vaccines and Guillain-Barré syndrome. The data came primarily from immunocompromised patients.[1] However, a later analysis of active surveillance epidemiological studies of Guillain-Barré syndrome and tetanus vaccination history concluded that if an association exists, it must be extremely rare and not of public health significance.[2]

1. Stratton KR, *et al.* Adverse events associated with childhood vaccines other than pertussis and rubella: summary of a report from the Institute of Medicine. *JAMA* 1994; **271:** 1602–5.
2. Tuttle J, *et al.* The risk of Guillain-Barré syndrome after tetanus-toxoid-containing vaccines in adults and children in the United States. *Am J Public Health* 1997; **87:** 2045–8.

Interactions

As for vaccines in general, p.2202.

Uses and Administration

Combined adsorbed diphtheria and tetanus vaccines may be used for active immunisation, although vaccines used for primary immunisation usually combine diphtheria, tetanus, and pertussis, and sometimes also Haemophilus influenzae and poliomyelitis. Diphtheria and tetanus vaccines are used in some countries for reinforcing doses after primary immunisation; in the USA they are given to adults every 10 years. For discussion of immunisation schedules, see under Vaccines, p.2202.

The non-adsorbed combined diphtheria and tetanus vaccines have weaker immunogenic properties than adsorbed vaccines and are no longer recommended.

Booster doses. In many countries, booster doses of combined diphtheria and tetanus vaccines are recommended every 10 years, and studies have been conducted to assess whether this is necessary. Since the incidence of clinical diphtheria in many countries in western Europe and North America approaches zero, it had been considered that there was no need for booster doses in adults, despite low antibody titres, so long as the policy of immunisation during infancy was maintained.[1,2] However, after a report[3] of an outbreak of clinical diphtheria in Sweden after a period of many years during which no indigenous cases of diphtheria had occurred and the disease was regarded as being eliminated from the country, the question of immunity in adults and the need for revaccination again arose. In the USA, it was considered[4] that re-immunisation every 10 years with a diphtheria and tetanus combined vaccine was mandatory and that this combined vaccine should be used whenever a tetanus vaccine was indicated as in treating emergency wounds. This policy is also adopted in the UK. Outbreaks of diphtheria in Russia and neighbouring countries[5] have prompted recommendations for booster doses in travellers to these countries.

1. Mathias RG, Schechter MT. Booster immunisation for diphtheria and tetanus: no evidence of need in adults. *Lancet* 1985; **i:** 1089–91.
2. Anonymous. Diphtheria and tetanus boosters. *Lancet* 1985; **i:** 1081–2.
3. Rappuoli R, *et al.* Molecular epidemiology of the 1984–1986 outbreak of diphtheria in Sweden. *N Engl J Med* 1988; **318:** 12–14.
4. Karzon DT, Edwards KM. Diphtheria outbreaks in immunized populations. *N Engl J Med* 1988; **318:** 41–3.
5. Anonymous. Diphtheria immunisation—advice from the Chief Medical Officer. *Commun Dis Rep* 1993; **3:** 27.

Preparations

Ph. Eur.: Diphtheria and Tetanus Vaccine (Adsorbed); Diphtheria and Tetanus Vaccine (Adsorbed, Reduced Antigen(s) Content);
USP 31: Diphtheria and Tetanus Toxoids Adsorbed; Tetanus and Diphtheria Toxoids Adsorbed for Adult Use.

Proprietary Preparations (details are given in Part 3)
Arg.: Diftavax†; DT Vax†; Imovax DT; Vacuna Doble; ***Austral.:*** ADT; CDT; ***Austria:*** DT-reduct; Td-pur; ***Belg.:*** Ditemer†; Tedivax; ***Braz.:*** Dif-Tet-All; DT Vax†; Refortrix†; ***Canad.:*** Td Adsorbed; ***Cz.:*** Alditeana†; ***Denm.:*** DiTe Booster; ***Fin.:*** DiTe Booster; ***Ger.:*** DT-Impfstoff†; Td-Impfstoff; Td-pur; Td-Rix; ***Gr.:*** Anatoxal Di Te Berna†; DT Vax; ***Hong Kong:*** DiTe Anatoxal†; ***India:*** DT-Vac; Dual Antigen; ***Irl.:*** Diftavax; ***Ital.:*** Anatoxal Adulti; Dif-Tet-All; Diftavax; Ditanrix; ***Malaysia:*** Di Te Anatoxal†; ***Norw.:*** DiTe Booster; ***NZ:*** ADT; CDT; DiTe Anatoxal; ***Philipp.:*** Di Te Anatoxal; ***Pol.:*** DT; ***S.Afr.:*** DT Vax; ***Singapore:*** Di Te Anatoxal†; ***Spain:*** Anatoxal Di Te†; Anatoxal Te Di; Diftavax; Ditanrix; TD; ***Swed.:*** DiTe Booster; ***Switz.:*** Anatoxal Di Te; Ditanrix; ***Thai.:*** Adsorbed DT Vaccine; Di Te Anatoxal†; Dif-Tet-All†; DT Vax†; ***Turk.:*** Di Te Anatoxal; ***UK:*** Diftavax†; ***USA:*** Decavac.

Diphtheria, Tetanus, and Haemophilus Influenzae Vaccines

Vacunas de la difteria, el tétanos y Haemophilus influenzae.

Profile

Combined adsorbed diphtheria, tetanus, and *Haemophilus influenzae* type b vaccines have been used in some countries for active immunisation of infants. For discussion of immunisation schedules see under Vaccines, p.2202. For concern over the antigenicity of *Haemophilus influenzae* type b vaccine in combined vaccines, see under Haemophilus Influenzae Vaccines, Interactions, p.2213.

Diphtheria, Tetanus, and Hepatitis B Vaccines

ATC — J07CA07.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus, and Hepatitis B (rDNA) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Hepatitidis B (ADNr) Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, hepatitis B surface antigen, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

Profile

Combined diphtheria, tetanus, and hepatitis B vaccines have been used in some countries for active immunisation.

Preparations

Ph. Eur.: Diphtheria, Tetanus and Hepatitis B (rDNA) Vaccine (Adsorbed).

Proprietary Preparations (details are given in Part 3)
Gr.: Primavax†.

Diphtheria, Tetanus, and Pertussis Vaccines

Vacunas de la difteria, el tétanos y la tos ferina.

Pharmacopoeias. Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Adsorbatum). A preparation of diphtheria formol toxoid and tetanus formol toxoid on a mineral carrier to which a suspension of killed *Bordetella pertussis* has been added. The mineral carrier may be hydrated aluminium phosphate or aluminium hydroxide and the resulting mixture is approximately isotonic with blood. The antigenic properties are adversely affected by certain antimicrobial preservatives particularly those of the phenolic type. It contains not less than 30 international units of diphtheria toxoid, not less than 40 international units if the test is performed in *guinea-pigs*, or 60 international units if the test is performed in *mice*, of tetanus toxoid, and not less than 4 international units of the pertussis component per dose. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP 2008 states that DTwP may be used on the label.

Ph. Eur. 6.2 (Diphtheria, Tetanus and Pertussis (Acellular, Component) Vaccine (Adsorbed); Vaccinum Diphtheriae, Tetani et Pertussis Sine Cellulis ex Elementis Praeparatum Adsorbatum). A combined vaccine composed of diphtheria formol toxoid, tetanus formol toxoid, individually purified antigenic components of *Bordetella pertussis*, and a mineral carrier such as aluminium hydroxide or hydrated aluminium phosphate. It should be stored at 2° to 8°, not be allowed to freeze, and be protected from light.

The BP2008 states that DTaP may be used on the label.

Adverse Effects and Precautions

As for vaccines in general, p.2201. See also under Diphtheria Vaccines, p.2209, Pertussis Vaccines, p.2230, and Tetanus Vaccines, p.2240.

The incidence of local reactions and fever is reported to be lower with the current accelerated immunisation schedules than the formerly used schedules spreading primary immunisation over 6 months. Local reactions and pyrexia occur less commonly after acellular pertussis vaccines than whole-cell pertussis vaccines, especially in children older than 6 months.

In infants with a personal or close family history of seizures, precautions should be taken to avoid pyrexia. See under Pertussis Vaccines for further details of precautions and contra-indications in individuals with a history of neurological problems.

Incidence of adverse effects. The incidence of local reactions is lower with diphtheria and tetanus vaccines combined with an acellular pertussis component (acellular DTP) than with a whole-cell pertussis component, and is similar to that after diphtheria and tetanus (DT) vaccines. Such reactions are generally mild and self-limiting. Rarely, high fever, persistent or inconsolable crying (possibly as a reaction to pain), hypotonic-hyporesponsive collapse, or short-lived convulsions (frequently febrile convulsions) may occur, and have been reported after both DT and acellular DTP vaccines with equal frequency. These reactions do not appear to have any long-term consequences. Rare but serious acute neurological complications including encephalopathy and prolonged seizures have been reported after DTP vaccines and have been attributed to the whole-cell pertussis component (see Effects on the Nervous System, p.2230) but the association could be coincidental. Epidemiological studies have shown that such events are exceedingly rare and only occasionally followed by long-term neurological damage. Analysis of these studies has been difficult but authorities in the UK and USA concluded that the evidence was insufficient for a link.

A causal relationship between DTP vaccination and sudden infant death syndrome (SIDS) has not been established and any temporal relationship is likely to be due to chance.[1,2] There is evidence that the risk of SIDS is lower in infants who have been vaccinated.[3]

Immediate anaphylactic reactions have been reported and are regarded as a contra-indication to further use of DTP vaccine. However, the appearance of a rash is not generally regarded as a contra-indication to further doses.