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## Smallpox Vaccines

Vacunas de la viruela.

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

**Ph. Eur. 6.2** (Smallpox Vaccine (Live)). A liquid or freeze-dried preparation of live vaccinia virus grown in the membranes of the chick embryo, in cell cultures, or in the skin of living animals. The cell culture medium may contain suitable antibacterials at the lowest effective concentration. Store at 2° to 8° and protect from light. The liquid vaccine should not be allowed to freeze.

**USP 31** (Smallpox Vaccine). A suspension or solid containing a suitable strain of the living virus of vaccinia grown in the skin of bovine calves; it may contain a suitable preservative. The liquid vaccine should be stored below 0° and the dried vaccine at 2° to 8°.

### Adverse Effects and Precautions

As for vaccines in general, p.2201.

Both first and second generation live smallpox vaccines have been associated with a high incidence of adverse effects. The most common adverse effects are injection site reactions, fatigue, fever, headache, malaise, myalgia, erythema, and generalised rash. Rarely there may be generalised vaccinial infection, or severe skin or CNS infection resulting in encephalitis, encephalomyelitis, encephalopathy, necrotising skin infection (progressive vaccinia, vaccinia necrosum), eczema vaccinatum, and erythema multiforme (including Stevens-Johnson syndrome). Fatalities have occurred, particularly from post-vaccination encephalitis and progressive vaccinia. Inadvertent contamination of other body sites (such as the face, mouth, nose, lips, and genitalia) from the site of vaccination also occurs frequently; autoinoculation of the eye (ocular vaccinia) may result in blindness. Benign and malignant lesions have also been reported at the vaccination site.

There have been reports of myocarditis or pericarditis or both, including some fatalities, associated with smallpox vaccination. Smallpox vaccination is not recommended for infants under 12 months of age, for persons with a history of eczema or other skin conditions, those who are immunocompromised, for pregnant women, or for women who breast feed. Household contacts of these groups should also not be vaccinated. Vaccination is best avoided in persons with known cardiac disease.

◊ References.

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6. Casey CG, *et al.* Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. *MMWR* 2006; **55** (RR-1): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5501.pdf (accessed 05/11/07)

### Uses and Administration

After the global eradication of smallpox in 1980, vaccination against smallpox (using first generation vaccinia virus vaccine) has been indicated for those considered to be at high risk such as laboratory workers handling certain orthopoxviruses, and key emergency, healthcare, and military personnel who may have to respond to a bioterrorist release of smallpox. A second generation smallpox vaccine has been licensed in the USA for inclusion to the National Stockpile for vaccination of those considered to be at high risk for smallpox infection. Persons at high risk and who have received primary vaccination against smallpox, should be re-vaccinated every 10 years. Vaccination is not recommended for persons working with highly attenuated strains of orthopoxviruses.

WHO considers that mass vaccination against smallpox is currently not appropriate, although individuals who may be at risk of exposure to smallpox or those with confirmed infection may be vaccinated.

Recombinant vaccinia viruses are being investigated as vectors of foreign antigens, for example in a candidate AIDS vaccine (p.2203).

**Vaccine development.** Smallpox[1] is an acute contagious and sometimes fatal disease caused by variola virus, a member of the Poxviridae family and of the orthopoxvirus genus. There is substantial cross-protection between poxviruses of the same genus; the very effective first generation smallpox vaccine used in the global vaccination programme was created from an orthopoxvirus, vaccinia. In 1980 WHO declared smallpox to have been globally eradicated.

There has since been concern that smallpox may be used as a terrorist weapon (although WHO considers this risk to be extremely low in most countries). Therefore, research into safer vaccines against smallpox has continued. First generation vaccine was produced from vaccinia strains grown on the skin of live animals or calf lymph. Despite purification processes, the vaccine contained some bacteria, animal proteins, and adventitious animal viruses, and produced a high incidence of adverse effects, some of which were extremely serious (see Adverse Effects and Precautions, above). Second generation vaccines are single clones of vaccinia isolated from the set of genetically related viruses that made up the first generation ones; they are grown in tissue culture (rather than on animal skin or calf lymph) and are free of bacteria and adventitious animal viruses. A second generation vaccine has been found to be effective and is licensed in the USA for inclusion to the National Stockpile. However, this vaccine still has a high incidence of adverse effects. Third generation vaccines are in the early stages of development. They are being developed from vaccinia strains attenuated by serial passage on non-human tissue or by genetic manipulation, and are expected to be safer than either first or second generation vaccines. Interest has also been shown in monoclonal variola antibodies for passive immunisation.[1,2]

Stocks of smallpox (variola) virus are being kept in a few secure laboratories in the USA and Russia. Since the eradication of smallpox, WHO maintains a stockpile of smallpox vaccine, and recommends vaccination for people with occupational exposure to fully potent orthopoxviruses, such as certain laboratory and healthcare workers. Because of concern that smallpox may be used for bioterrorism, WHO and several countries have increased the number of doses kept in stock.[1] Policies for the use of smallpox vaccine, including bioterrorism preparedness, have been developed in many countries such as the USA[3,4] and UK[5,6] with some countries recommending vaccination for key emergency and military personnel.

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3. CDC. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *MMWR* 2001; **50** (RR-10): 1–25. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf (accessed 25/05/06)
4. CDC. Recommendations for using smallpox vaccine in a pre-event vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR* 2003; **52** (RR-7): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5207.pdf (accessed 25/05/06)
5. Health Protection Agency. Interim guidelines for action in the event of a deliberate release: smallpox (issued January 2008). Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947373093 (accessed 15/07/08)
6. Department of Health. Guidelines for smallpox response and management in the post-eradication era (smallpox plan) (issued December 2003). Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4070830 (accessed 15/07/08)

### Preparations

***Ph. Eur.:*** Smallpox Vaccine (Live);
***USP 31:*** Smallpox Vaccine.

**Proprietary Preparations** (details are given in Part 3)
***USA:*** ACAM2000; Dryvax.

# Snake Venom Antisera

Antisuero contra el veneno de serpiente; Snake Antivenins; Snake Antivenoms.

*ATC — J06AA03.*

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

**Ph. Eur. 6.2** (Viper Venom Antiserum, European; Immunoserum Contra Venena Viperarum Europaearum). A preparation containing the specific antitoxic globulins that have the power of neutralising the venom of one or more species of viper (*Vipera ammodytes*, *V. aspis*, *V. berus*, or *V. ursinii*). The globulins are obtained by fractionation of the serum of animals that have been immunised against the venom or venoms. Each mL neutralises the venoms in not less than 100 mouse $LD_{50}$ of *V. ammodytes*, 100 of *V. aspis*, 50 of *V. berus*, or 50 of *V. ursinii*. It should be stored at 2° to 8°, and not be allowed to freeze.

The BP 2008 states that the only poisonous snake native to the British Isles is the adder or common viper, *Vipera berus*. In a geographical region where other species of snake (including elapids) are found, antisera able to neutralise the venoms of the species of snake indigenous to the region should be used. When the preparation is intended to neutralise the venom or venoms of one or more snakes other than vipers, the title Snake Venom Antiserum is used.

**USP 31** (Antivenin (Crotalidae) Polyvalent). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against 4 species of pit vipers, *Crotalus atrox* (western diamondback), *Crotalus adamanteus*, *Crotalus durissus terrificus* (South American rattlesnake), and *Bothrops atrox* (South American fer de lance). One dose neutralises the venoms in not less than 180 mouse $LD_{50}$ of *C. atrox*, 1320 of *C. durissus terrificus*, and 780 of *B. atrox*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

**USP 31** (Antivenin (Micrurus Fulvius)). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against venom of *Micrurus fulvius* (eastern coral snake). One dose neutralises the venom in not less than 250 mouse $LD_{50}$ of *M. fulvius*. It may contain a suitable preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

### Adverse Effects and Precautions

As for antisera in general, p.2201.

Serum sickness is not uncommon and anaphylactic reactions may occur.

**Anaphylaxis.** Conjunctival or cutaneous hypersensitivity testing failed to predict early (anaphylactic) reactions to the antivenom given in a study of patients in Nigeria with systemic envenoming by the saw-scaled or carpet viper (*Echis carinatus*) and in Thailand with local or systemic envenoming by green pit vipers (*Trimeresurus albolabris* and *T. macrops*), the monocellate Thai cobra (*Naja kaouthia*), or the Malayan pit viper (*Calloselasma rhodostoma*). It was considered that conventional hypersensitivity testing has no predictive value for the occurrence of allergic reactions to antivenom and that it is not justifiable to delay treatment for 20 or 30 minutes to read the results of these tests. Although the rate at which antiserum can be given is more easily controlled by intravenous infusion, this method has serious practical disadvantages in the rural tropics where most cases of snake bite occur and an advantage of the intravenous push injection is that the person giving the antiserum must remain with the patient during the period when most severe anaphylactic reactions develop.

Pretreatment with low-dose subcutaneous adrenaline may reduce the incidence of anaphylaxis and other acute adverse reactions to the antiserum.[1] However, premedication with adrenaline, antihistamines, and corticosteroids, although widely practiced, is controversial. In one study,[2] prophylaxis with promethazine was ineffective in preventing anaphylaxis from antiserum against *Bothrops* envenomation.

1. Premawardhena AP, *et al.* Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: randomised, placebo controlled trial. *BMJ* 1999; **318:** 1041–3.
2. Fan HW, *et al.* Sequential randomised and double blind trial of promethazine prophylaxis against early anaphylactic reactions to antivenom for bothrops snake bites. *BMJ* 1999; **318:** 1451–2.

### Uses and Administration

Venomous snakes comprise the Viperidae (vipers), Elapidae (cobras, kraits, and mambas), and the Hydrophiidae (sea snakes).

The venom of snakes is a complex mixture chiefly of proteins, many of which have enzymatic activity, and may provoke local inflammatory reactions. The venom may have profound effects on tissue, blood vessels and other organs, blood cells, coagulation, and myotoxic or neurotoxic effects with sensory, motor, cardiac, renal, and respiratory involvement.

Snake venom antisera are the only specific treatment available for venomous snake bites, but can produce severe adverse reactions. They are generally only used if there are clear indications of systemic involvement, severe local involvement, or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement. Adrenaline should be available in case of anaphylactic reactions to the antiserum; premedication with adrenaline, corticosteroids, and/or antihistamines is widely practiced but is regarded as controversial.

In Great Britain, the only indigenous poisonous snake is the adder, *Vipera berus*; its bite is rarely fatal but European Viper Venom Antiserum (or Zagreb antivenom) may sometimes be indicated as part of the overall treatment. The usual dose for adults and children is 10 mL by intravenous injection over 10 to 15 minutes or by intravenous infusion over 30 minutes after diluting in 5 mL/kg body-weight of sodium chloride 0.9%; the dose may be repeated after about 1 to 2 hours if symptoms of systemic envenoming persist.

In the USA, a polyvalent crotalidae antiserum against *Bothrops atrox*, *Crotalus adamanteus*, *C. atrox*, and *C. durissus terrificus*, and an antiserum against the North American coral snake, *Micrurus fulvius*, are available. In Australia, polyvalent antisera against the brown snake, death adder, taipan, and tiger snake, together with either the king brown snake or black snake, are available. A variety of polyvalent and monovalent antisera are also available as appropriate to the indigenous species of snakes in many other countries.

**Snake bites.** Most snake species are non-venomous and belong to the colubrid family although a few colubrids are technically venomous. The 3 families of venomous front-fanged snakes are the elapids, vipers, and sea snakes. Elapids include cobras, mambas, kraits, coral snakes, and the Australasian venomous land snakes. Vipers are subdivided into crotalids (pit vipers) and viperids. Viper bites are much more common than elapid bites, except in Australasia, where vipers do not occur naturally. Sea snake bites occur among fishermen of the Asian and western Pacific coastal areas. Although there are some notable exceptions, viper bites tend to cause vasculotoxicity, elapids cause neurotoxicity, and sea snakes cause myotoxicity.

Only a few snakes are known to be of medical importance. Of the vipers these include *Bothrops atrox* (Central and South America), *Bitis arietans* (Africa), *Echis carinatus* (Africa and Asia), *Vipera russelli* (Asia), and *Agkistrodon rhodostoma* (south-east Asia). In a few restricted areas of Africa and Asia, cobra bites are common; bites by mambas (Africa) and kraits (Asia) are rare. The carpet viper, *Echis pyramidum*, and saw-scaled viper, *Echis carinatus*, can justifiably be labelled the most dangerous snakes in the world and they cause more deaths and serious poisoning than any other snake.

Management of snake bite involves general supportive care and monitoring of vital functions but in a systemic snake-bite poisoning, specific snake venom antiserum is the most effective therapeutic agent available. If used correctly, it can reverse systemic poisoning when given hours or even days after the bite. It is highly desirable to wait for clear clinical evidence of systemic poisoning before giving an antiserum and therefore it should not be given routinely in all cases of snake bite. Monospecific antisera are more effective, and less likely to cause reactions, than polyvalent antisera. The dosage of antiserum to be used is dependent on the species of snake and the consequent potency of the requisite antiserum. The antiserum should be given intravenously diluted in isotonic saline, either by infusion or bolus injection (see under Adverse Effects and Precautions, above). First aid measures including incisions and suction to remove the venom and application of tourniquets are generally to be discouraged. In most cases, the bitten limb should be immobilised and the victim transferred to a medical facility, together with the snake if possible. For bites by elapids, when respiratory failure may occur before the patient reaches hospital, a tourniquet may be justified to delay the onset of neurotoxicity. Supportive treatment is necessary even in patients who have received an adequate dose of antiserum. Local pain may be treated with a suitable analgesic. Artificial respiration may be required in patients with symptoms of neurotoxicity. Anticholinesterases may be of benefit against the neurotoxic effects of some snake venoms and it has been recommended that an intravenous test dose of edrophonium preceded by atropine should be tried in patients with severe symptoms of neurotoxicity. For those patients who respond, treatment with neostigmine should be started but anticholinesterases are unlikely to affect outcome in patients who already require assisted respiration. Hypovolaemia should be corrected cautiously with parenteral fluids. Hypotension may be treated with subcutaneous adrenaline or, in patients bitten by Russell's viper, a response to dopamine has been noted. Patients with renal impairment may require dialysis if they do not respond to rehydration, diuretics, and dopamine. Broad spectrum antibacterials and a tetanus vaccine should be given as prophylactic measures. Surgical decompression and debridement of necrotic tissue may be necessary once normal haemostasis has been restored.

References.
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15. Gutiérrez JM, *et al.* Trends in snakebite envenomation therapy: scientific, technological and public health considerations. *Curr Pharm Des* 2007; **13:** 2935–50.
16. Prenzel F, *et al.* Kreuzotterbisse—Klinik, Diagnostik und Behandlung. *Dtsch Med Wochenschr* 2008; **133:** 1075–80.

## Preparations

***Ph. Eur.:*** European Viper Venom Antiserum;
***USP 31:*** Antivenin (Crotalidae) Polyvalent; Antivenin (Micrurus Fulvius).

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Suero Antiofidico Polivalente; ***Austral.:*** Polyvalent Snake Antivenom; ***Fr.:*** Viperfav; ***Hong Kong:*** Tiger Snake; ***Mex.:*** Antivipmyn; Coralmyn; ***USA:*** CroFab.

## Spider Venom Antisera

Antisuero contra el veneno de arañas; Spider Antivenins; Spider Antivenoms.

**Pharmacopoeias.** Many pharmacopoeias, including *US*, have monographs.
**USP 31** (Antivenin (Latrodectus Mactans)). A sterile freeze-dried preparation of specific venom-neutralising globulins obtained from the serum of healthy horses immunised against venom of black widow spiders (*Latrodectus mactans*). One dose neutralises the venom in not less than 6000 mouse $LD_{50}$ of *L. mactans*. It contains thiomersal as preservative. It should be preserved in single-dose containers and stored at a temperature not exceeding 40°.

### Adverse Effects and Precautions
As for antisera in general, p.2201.

### Uses and Administration
The use of a spider venom antiserum suitable for the species of spider can prevent symptoms, provided that it is done with the least possible delay; other general supportive measures and symptomatic treatment may also be needed.

An antiserum against the black widow spider (*Latrodectus mactans*) is available in the USA and Canada. The contents of a vial containing at least 6000 antivenin units is the usual dose for adults and children. In severe cases and in children under 12 years of age it is given by intravenous infusion in sodium chloride 0.9% over 15 minutes; in less severe cases, it may be given by intramuscular injection.

Antivenoms are also available against other *Latrodectus* species, including the Australian red-back spider (*L. hasselti*) and the South African button spiders. An antiserum against the funnel-web spider (*Atrax robustus*) is available in Australia.

Antivenoms have also been developed against *Loxosceles* spiders and against *Phoneutria* spiders, but there is little evidence of their effectiveness.

**Spider bites.** Although many species of spider are venomous, relatively few pose a danger to man. Two main clinical syndromes are recognised; necrotic araneism, produced mainly by members of the genus *Loxosceles* which includes the brown recluse spider *L. reclusa*, and neurotoxic araneism produced by members of the genera *Latrodectus* (including the black widow and red-back spiders), *Phoneutria* (South American banana spiders), and *Atrax* (funnel-web spiders).

Necrotic araneism presents as local pain and erythema at the site of the bite, commonly developing into a necrotic lesion with a black eschar that sloughs after a few weeks, sometimes leaving an ulcer that heals gradually. The area affected can be extensive. Rarely, systemic symptoms including intravascular coagulation, haemolytic anaemia, respiratory distress, and renal failure, occur and may be life-threatening. A number of therapies have been suggested, but conservative management is usually adequate with surgical repair of any persistent defects if necessary. Dapsone is reported to produce beneficial effects on healing. Treatment for systemic manifestations is supportive. Antisera are available in some countries.

Neurotoxic araneism may involve severe pain, headache, vomiting, tachycardia, hypertension, muscle spasms, and occasionally pulmonary oedema, and coma, depending upon the species. Antisera are available and reported to be more effective than those for necrotic araneism, but should be reserved for serious envenomation. Intravenous injection of calcium gluconate 10% has been suggested to relieve muscle spasm as an alternative to conventional muscle relaxants.

References.
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2. Isbister GK, *et al.* Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003; **41:** 291–300.
3. Nimorakiotakis B, Winkel KD. The funnel web and common spider bites. *Aust Fam Physician* 2004; **33:** 244–51.
4. Saucier JR. Arachnid envenomation. *Emerg Med Clin North Am* 2004; **22:** 405–22, ix.
5. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352:** 700–707.

## Preparations

***USP 31:*** Antivenin (Latrodectus Mactans).

**Proprietary Preparations** (details are given in Part 3)
***Canad.:*** Antivenin (Latrodectus Mactans); ***Mex.:*** Aracmyn.

## Staphylococcal Immunoglobulins

### Profile
Staphylococcal immunoglobulins are under investigation for passive immunisation against infection with *Staphylococcus aureus*.

## Staphylococcal Vaccines

Vacunas estafilocócicas.

### Profile
Staphylococcal vaccines have been developed for the prophylaxis of staphylococcal infections.

◊ A vaccine containing *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides conjugated to non-toxic recombinant *Pseudomonas aeruginosa* exotoxin A showed promise[1] in early studies in patients with end-stage renal disease who were receiving haemodialysis; however, later work failed to confirm benefit and its development was stopped.

1. Shinefield H, *et al.* Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. *N Engl J Med* 2002; **346:** 491–6.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Braz.:*** Estafiloide; ***Cz.:*** Polystafana; Stafal; ***USA:*** SPL.

## Stone Fish Venom Antisera

Antisuero contra el veneno del pez piedra estuarino; Stone Fish Antivenins; Stone Fish Antivenoms.

### Adverse Effects and Precautions
As for antisera in general, p.2201.

### Uses and Administration
An antiserum for use in the management of stings by the stone fish (*Synanceja trachynis*) is available in Australia. The antiserum is prepared from the serum of horses that have been immunised with the venom of the stone fish. Other symptomatic and supportive treatments are given in addition.

Stone fish venom antiserum may be given by intramuscular injection or, in more severe cases, by intravenous infusion. When given by intravenous infusion, it should be diluted 1 in 10 with an intravenous solution. The initial dose of stone fish antivenom given to both adults and children is dependent on the number of visible puncture sites: 1 to 2 puncture sites, 2000 units; 3 to 4 puncture sites, 4000 units; and 5 or more puncture sites, 6000 units. The initial dose may be repeated if necessary should symptoms persist.

◊ References.

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2. Lehmann DF, Hardy JC. Stonefish envenomation. *N Engl J Med* 1993; **329:** 510–11.

## Streptococcus Group B Vaccines

Vacunas contra estreptococos del grupo B.

### Profile
Vaccines for active immunisation against group B streptococcal infections are being developed. Giving a vaccine to pregnant women to prevent neonatal infection has been proposed.

◊ References.

1. Baker CJ, Edwards MS. Group B streptococcal conjugate vaccines. *Arch Dis Child* 2003; **88:** 375–8.

## Tetanus Antitoxins

Antitoxinas tetánicas.
*ATC — J06AA02.*

**Pharmacopoeias.** Many pharmacopoeias, including *Eur.* (see p.vii), have monographs.
**Ph. Eur. 6.2** (Tetanus Antitoxin for Human Use; Immunoserum Tetanicum ad Usum Humanum). A sterile preparation containing the specific antitoxic globulins that have the power of neutralising the toxin formed by *Clostridium tetani*. It is obtained by fractionation from the serum of horses, or other mammals, that have been immunised against tetanus toxin. For prophylactic use, it has a potency of not less than 1000 international units/mL, and for therapeutic use not less than 3000 international units/mL. It should be stored at 2° to 8°, and not be allowed to freeze.
The BP 2008 states that Tet/Ser may be used on the label.

### Profile
Tetanus antitoxins neutralise the toxin produced by *Clostridium tetani* and have been used to provide temporary passive immunity against tetanus, but tetanus immunoglobulins (below) are preferred. A test dose of tetanus antitoxin should always be given to identify those who might suffer hypersensitivity reactions.

Whenever a non-immune patient is seen because of injury, a course of active immunisation should be instituted (see Tetanus Vaccines, p.2240).

### Preparations

***Ph. Eur.:*** Tetanus Antitoxin for Human Use.

# Tetanus Immunoglobulins

Inmunoglobulinas contra el tétanos.
*ATC — J06BB02.*

**Pharmacopoeias.** Many pharmacopoeias, including *Eur.* (see p.vii) and *US*, have monographs.
**Ph. Eur. 6.2** (Human Tetanus Immunoglobulin; Immunoglobulinum Humanum Tetanicum). A liquid or freeze-dried preparation