## Aprotinin *(BAN, USAN, rINN)*

Aprotiniini; Aprotinina; Aprotininas; Aprotinine; Aprotininum; Aprotynina; Bayer A-128; Riker 52G; RP-9921.

Апротинин

*CAS — 9087-70-1.*
*ATC — B02AB01.*
*ATC Vet — QB02AB01.*

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), and *US.*

**Ph. Eur. 6.2** (Aprotinin). A polypeptide consisting of 58 amino acids that inhibits the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It contains not less than 3 Ph. Eur. units/mg calculated with reference to the dried substance. An almost white, hygroscopic powder. Soluble in water and in isotonic solutions; practically insoluble in organic solvents. Store in airtight containers. Protect from light.

**Ph. Eur. 6.2** (Aprotinin Concentrated Solution). A solution of aprotinin containing not less than 15 Ph. Eur. units/mL. A clear colourless solution. Store in airtight containers. Protect from light.

**USP 31** (Aprotinin). A polypeptide consisting of a chain of 58 amino acid residues, which inhibits stoichiometrically the activity of several proteolytic enzymes such as chymotrypsin, kallikrein (kallidinogenase), plasmin (fibrinolysin), and trypsin. It is obtained from bovine tissues and purified by a suitable process, and is stored as a bulk solution or lyophilised powder. Its potency is not less than 3 USP units/mg calculated with reference to the dried substance.

The lyophilised powder should be stored in airtight containers at a temperature between 8° and 15°. Protect from light. The bulk solution should be stored in airtight containers at a temperature not exceeding 25°. Do not allow to freeze.

**Incompatibility.** Aprotinin is reported to be incompatible with corticosteroids, heparin, tetracyclines, and nutrient solutions containing amino acids or fat emulsions.

### Units

The potency of aprotinin is expressed in terms of kallikrein (kallidinogenase) inactivator units (KIU) or of trypsin inactivation (Ph. Eur. units). One KIU is contained in 140 nanograms of aprotinin. One Ph. Eur. and one USP unit is equivalent to about 1800 KIU.

Potency has also been expressed in terms of plasmin inactivation (antiplasmin units).

### Adverse Effects and Precautions

Aprotinin is usually well tolerated. Local thrombophlebitis can occur. Adverse effects including bronchospasm, hypotension, cardiac arrhythmias, gastrointestinal disturbances, and skin rashes are considered to be hypersensitivity reactions; anaphylaxis, including fatalities, has occurred. Licensed UK product information warns that the risk of anaphylactic reaction increases when re-exposure occurs within 6 months, but product information in the US extends this warning to contra-indicate the use of aprotinin for 12 months after a previous exposure. A test dose is recommended for all patients and the use of prophylactic histamine antagonists may be considered; a hypersensitivity reaction to the therapeutic dose of aprotinin can still occur even after an uneventful test dose. There have been reports of renal dysfunction and reversible renal failure in patients given aprotinin during open-heart surgery with extracorporeal circulation; the risk may be increased in patients with pre-existing renal impairment or risk factors for altered renal function. For further details of an increased risk of cardiovascular and cerebrovascular events, renal failure, and death in patients undergoing surgery, see Haemorrhagic Disorders under Uses and Administration, below.

**Disseminated intravascular coagulation.** Fatal disseminated intravascular coagulation has been reported in a patient after the use of intraoperative autotransfusion and aprotinin during surgery.[1] Activation of the clotting system occurs during autotransfusion although this usually causes no systemic adverse effects. While there were other possible causes, it was suggested that aprotinin could have contributed to deposition of fibrin microthrombi in the microvasculature and prevented subsequent fibrinolysis.

1. Milne AA, *et al.* Disseminated intravascular coagulation after aortic aneurysm repair, intraoperative salvage autotransfusion, and aprotinin. *Lancet* 1994; **344:** 470–1.

**Effects on coagulation tests.** In patients receiving heparin, aprotinin may prolong the activated clotting time when measured by some methods, but this may not represent increased anticoagulation. It has been recommended that an alternative to the activated clotting time should be used to monitor heparin therapy when aprotinin is used concurrently.

It should also be noted that aprotinin injection and heparin injection are pharmaceutically incompatible.

**Effects on the respiratory system.** Acute respiratory distress syndrome developed in a 24-year-old male 2 hours after the start of an intravenous infusion of aprotinin for bleeding after tonsillectomy.[1] Mechanical ventilation was required for 4 days.

1. Vucicevic Z, Suskovic T. Acute respiratory distress syndrome after aprotinin infusion. *Ann Pharmacother* 1997; **31:** 429–32.

**Hypersensitivity.** Hypersensitivity reactions, including anaphylaxis, can occur with the use of aprotinin both on primary and secondary exposure. In a study[1] of 248 re-exposures to aprotinin in 240 patients undergoing cardiac surgery, there were 7 cases of anaphylactic reactions ranging from mild to severe with a higher incidence of reactions occurring in those patients re-exposed within 6 months of the previous dose. A review[2] of 124 reported reactions in 122 patients also found that reactions ranged from mild to severe, and that about half were life-threatening and 11 were fatal. The risk of reaction was greatest with re-exposure to aprotinin as this had been the situation in 80% of the cases, although there were 19 cases associated with the first use of aprotinin. The average risk of anaphylaxis was estimated to be 2.8% in re-exposed patients. Most reactions occurred within 6 months of previous exposure, and the risk was greatest in the first 3 months. Various diagnostic tests have been tried in an attempt to predict hypersensitivity risk. Aprotinin-specific serum-IgG was reported to be detectable in about 50% of patients who had received only one aprotinin treatment, but other tests such as preoperative skin testing were not found to be reliable.

A number of measures have been suggested in order to reduce the risk of hypersensitivity reactions to aprotinin, including the use of an intravenous test dose in all patients, but it must be noted that these also have the potential to trigger a reaction.[1] For patients who have previously received aprotinin it has been recommended that re-exposure should be avoided for at least 6 months,[1,2] that aprotinin-specific antibody screening should be done,[2] and that prophylactic histamine $H_1$- and $H_2$-antagonists should be given to ameliorate severe anaphylactic reactions[1] although there are reports of reactions occurring despite antihistamine and corticosteroid prophylaxis.[2] It has also been suggested that in cardiac surgery, aprotinin should only be given when cardiopulmonary bypass is available to assist resuscitation.[1,2]

There have also been rare reports of hypersensitivity reactions on re-exposure to aprotinin used locally as a component of fibrin sealant.[3,4] In one fatal case[4] the previous exposure to fibrin sealant had been 5 years before.

1. Dietrich W, *et al.* Prevalence of anaphylactic reactions to aprotinin: analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *J Thorac Cardiovasc Surg* 1997: **113:** 194–201.
2. Beierlein W, *et al.* Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; **79:** 741–8.
3. Beierlein W, *et al.* An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. *Transfusion* 2000; **40:** 302–5.
4. Oswald A-M, *et al.* Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99:** 762–3.

### Interactions

**Heparin.** For comment on the use of aprotinin with heparin, see Effects on Coagulation Tests, above.

**Neuromuscular blockers.** For reports of apnoea when aprotinin was used with neuromuscular blockers, see p.1904.

**Retinoids.** Aprotinin should be used with caution in patients receiving oral *tretinoin* (see Antifibrinolytics, p.1619).

### Pharmacokinetics

Aprotinin, being a polypeptide, is inactivated in the gastrointestinal tract. After intravenous use, it is excreted in the urine as inactive degradation products. The terminal elimination half-life is about 5 to 10 hours.

**Renal impairment.** The terminal elimination half-life of aprotinin was reported as 13.3 and 14.9 hours, respectively, in two patients with chronic renal impairment given aprotinin by intravenous infusion over 30 minutes.[1] A study[2] of cardiac surgical patients undergoing cardiopulmonary bypass also found that aprotinin clearance was reduced in those with renal impairment. The elimination half-life was about 20 hours in patients with end stage renal disease compared with about 8 hours in those with creatinine clearance greater than 50 mL/min.

1. Müller FO, *et al.* Pharmacokinetics of aprotinin in two patients with chronic renal impairment. *Br J Clin Pharmacol* 1996; **41:** 619–20.
2. O'Connor CJ, *et al.* The impact of renal dysfunction on aprotinin pharmacokinetics during cardiopulmonary bypass. *Anesth Analg* 1999; **89:** 1101–7.

### Uses and Administration

Aprotinin is a haemostatic. It is an inhibitor of proteolytic enzymes including chymotrypsin, kallikrein (kallidinogenase), plasmin, and trypsin.

Aprotinin has been used to reduce blood loss and transfusion requirements in patients at increased risk of major blood loss during coronary artery bypass graft surgery with cardiopulmonary bypass. However, the marketing of aprotinin injection has been suspended worldwide because of a possible increased risk of death associated with its use in cardiac surgery (see Haemorrhagic Disorders, below). Nevertheless, it may be available in some countries, such as the USA, using a special access protocol. It has also been used in the treatment of hyperfibrinolytic haemorrhage associated with raised plasma concentrations of plasmin. Aprotinin is applied topically as a component of fibrin glues (p.1069).

It is recommended that because of the risk of hypersensitivity reactions an intravenous test dose of 10 000 KIU should be given to all patients at least 10 minutes before the therapeutic dose. All intravenous doses of aprotinin should be given through a central venous line.

In **coronary artery bypass graft surgery**, the test dose is followed by a loading dose given with the patient in a supine position, after induction of anaesthesia but before incision; 2 000 000 KIU is given intravenously over 20 to 30 minutes. The loading dose is followed by a continuous infusion of 500 000 KIU/hour until the end of the operation. An additional dose of 2 000 000 KIU is added to the prime volume of the extracorporeal circuit. In patients with septic endocarditis, a dose of 3 000 000 KIU is added to the prime volume of the circuit and the continuous infusion may be continued into the early postoperative period. The total amount of aprotinin used is usually no more than 7 000 000 KIU. A regimen using half the dose for loading, maintenance, and to prime the circuit, may be used in low-risk patients.

**Haemorrhagic disorders.** Aprotinin has been used in the treatment of life-threatening haemorrhage caused by raised plasma concentrations of plasmin. It has also been used in the treatment of severe bleeding arising from overdosage with thrombolytics (see Treatment of Adverse Effects under Streptokinase, p.1404).

Aprotinin has been used to reduce blood loss in patients undergoing surgery, particularly cardiac surgery involving cardiopulmonary bypass. This bypass procedure is complicated by a postperfusion syndrome that includes impairment of haemostasis and pulmonary dysfunction. Contributing factors include ischaemia reperfusion, surgical trauma, endotoxaemia, and blood contact with the artificial surfaces of the bypass apparatus. This syndrome has been interpreted as a 'whole body inflammatory response', and the beneficial effect of aprotinin has been attributed to an attenuation of this response. As well as its inhibitory effect on fibrinolysis, aprotinin is thought to have effects on the complement system, cytokines, neutrophil activation, and platelet function.[1,2] Aprotinin has reduced blood loss and transfusion requirements in patients undergoing both primary and repeat cardiac surgery.[1,3-6] The usual dosage regimen (as given in Uses and Administration, above) and low-dosage regimens (50% of the usual dose) appear to be equally effective, but regimens that use aprotinin only as a pump prime dose appear to be less effective.[1,5]

The safety of aprotinin in cardiac surgery has been questioned, however, because of the results of two observational studies. One analysis[7] of patient outcome after the use of aminocaproic acid, aprotinin, tranexamic acid, or no treatment, found that although the three drugs had reduced blood loss to a similar extent, aprotinin was associated with an increased risk of cardiovascular and cerebrovascular events (myocardial infarction, heart failure, stroke, or encephalopathy) and renal failure. Observational follow-up also found that aprotinin, but not aminocaproic acid or tranexamic acid, was associated with an increased risk of death in the 5 years after surgery.[8] In another study[9] that compared data from patients who had received either aprotinin or tranexamic acid, there was an increased risk of renal dysfunction associated with aprotinin, particularly in patients with abnormal pre-operative renal function. In response to these studies, the FDA recommended[10] that patients receiving aprotinin should be carefully monitored, and that physicians should consider limiting its use to situations where the clinical benefit of reduced blood loss is essential and outweighs the potential risks. The concerns raised by these studies and the FDA's recommendation prompted further analysis of data relating to the effects of aprotinin. A meta-analysis[5] that included studies in different types of surgery, although the majority were in cardiac surgery, found no increased risk of death, cardiovascular events, or renal failure. However, because the reporting of renal function was lacking for many studies, and therefore a potential for bias, the authors were not confident that a modest increase in risk could be ruled out. Another meta-analysis[11] that was limited to studies in cardiac surgery also found no increased risk of death or cardiovascular events with aprotinin. There was also no increase in the risk of dialysis-dependent renal failure, but high-dose aprotinin did increase the risk of renal dysfunction, compared with placebo. Two large retrospective studies, which attempted to account for confounding variables, were also undertaken in cohorts of patients who had undergone coronary artery bypass graft surgery. One study found that, compared with aminocaproic acid, aprotinin increased the risk of in-hospital death.[12] The other found increased in-patient renal dysfunction, and death at 30 days and 1 year, in patients given aprotinin compared with aminocaproic acid or no antifibrinolytic therapy. Survival estimates also found an association between aprotinin use and reduced survival for up to 10 years after surgery.[13] Preliminary data analysis from a randomised study (BART) also found an increased risk of death with aprotinin, compared with aminocaproic acid or tranexamic acid, and in November 2007, authorities such as the FDA[14] and EMEA[15] recommended that marketing of aprotinin injection be suspended.

Aprotinin has been used to reduce transfusion requirements during liver transplantation, by its effect on intra-operative hyperfibrinolysis.[16,17] However, concerns about an increased risk of thromboembolism in these patients has been raised.[18] A systematic review[19] of 23 studies using antifibrinolytic drugs, 18 of which used aprotinin, found no evidence of an increased risk of thromboembolic complications in liver transplant patients, but noted that the studies were underpowered and that identification

of subgroups of patients at risk may have been missed. Aprotinin has also been used to reduce transfusion requirements during orthopaedic surgery.[20]


1. Peters DC, Noble S. Aprotinin: an update of its pharmacology and therapeutic use in open heart surgery and coronary artery bypass surgery. *Drugs* 1999; **57** 233–60.
2. Mojcik CF, Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *Ann Thorac Surg* 2001; **71:** 745–54.
3. Bidstrup BP, *et al.* Aprotinin cardiac centers in the United Kingdom. *Ann Thorac Surg* 1993; **55:** 971–6.
4. Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. *Anesth Analg* 1997; **85:** 1258–67.
5. Henry DA, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/06/08).
6. Sedrakyan A, *et al.* Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg* 2004; **128:** 442–8.
7. Mangano DT, *et al.* The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; **354:** 353–65.
8. Mangano DT, *et al.* Mortality associated with aprotinin during 5 years following coronary artery bypass graft surgery. *JAMA* 2007; **297:** 471–9.
9. Karkouti K, *et al.* A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; **46:** 327–38.
10. FDA. Aprotinin injection (marketed as Trasylol) (issued 8th February, 2006). Available at: http://www.fda.gov/cder/drug/advisory/aprotinin.htm (accessed 26/11/07)
11. Brown JR, *et al.* Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation* 2007; **115:** 2801–13.
12. Schneeweiss S, *et al.* Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med* 2008; **358:** 771–83.
13. Shaw AD, *et al.* The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med* 2008; **358:** 784–93.
14. FDA. FDA requests marketing suspension of Trasylol (issued 5th November, 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01738.html (accessed 26/11/07)
15. EMEA. European Medicines Agency recommends suspension of marketing authorisation of aprotinin-containing medicines for systemic use (issued 21st November, 2007). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/53467807en.pdf (accessed 26/11/07)
16. Porte RJ, *et al.* Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. *Lancet* 2000; **355:** 1303–9.
17. Rentoul TM, *et al.* The effect of aprotinin on transfusion requirements in pediatric orthotopic liver transplantation. *Pediatr Transplant* 2003; **7:** 142–8.
18. Lentschener C, *et al.* A review of aprotinin in orthotopic liver transplantation: can its harmful effects offset its beneficial effects? *Anesth Analg* 2005; **100:** 1248–55.
19. Molenaar IQ, *et al.* Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant* 2007; **7:** 185–94.
20. Kokoszka A, *et al.* Evidence-based review of the role of aprotinin in blood conservation during orthopaedic surgery. *J Bone Joint Surg Am* 2005; **87-A:** 1129–36.


**Pancreatitis.** Aprotinin has been tried in the management of pancreatitis (p.2361) because of the postulated role of proteolytic enzymes in this condition. However, results have been largely disappointing.

### Preparations

***BP 2008:*** Aprotinin Injection;
***USP 31:*** Aprotinin Injection.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Quagu-Test; Rivilina; ***Austral.:*** Trasylol†; ***Austria:*** Pantinol†; Trasylol†; ***Belg.:*** Trasylol†; ***Braz.:*** Trasylol†; ***Canad.:*** Trasylol†; ***Chile:*** Trasylol†; ***Cz.:*** Antilysin†; Gordox†; Trasylol†; ***Denm.:*** Trasylol†; ***Fin.:*** Trasylol†; ***Fr.:*** Trasylol†; ***Ger.:*** Trasylol†; ***Gr.:*** Trasylol†; ***Hong Kong:*** Trasylol†; ***Hung.:*** Gordox†; Trasylol†; ***Indon.:*** Trasylol; ***Israel:*** Protosol; ***Malaysia:*** Trasylol†; ***Mex.:*** Protinin†; Trasylol†; ***Neth.:*** Trasylol†; ***NZ:*** Trasylol†; ***Pol.:*** Traskolan†; Trasylol†; ***Rus.:*** Aprotex (Апротекс); Contrykal (Контрикал); Gordox (Гордокс); Trasylol (Трасилол)†; ***S.Afr.:*** Trasylol†; ***Singapore:*** Trasylol†; ***Spain:*** Trasylol†; ***Swed.:*** Trasylol†; ***Switz.:*** Trasylol†; ***Thai.:*** Trasylol†; ***Turk.:*** Trasylol†; ***UK:*** Trasylol†; ***USA:*** Trasylol†; ***Venez.:*** Trasylol†.

**Multi-ingredient:** ***Arg.:*** Beriplast P; Lacrimax; Maxus; Optilac; Tissucol; Tissucol Duo Quick†; ***Austral.:*** Tisseel Duo; ***Austria:*** Beriplast; TachoComb; Tissucol; Tissucol Duo Quick; ***Belg.:*** Tissucol Duo; ***Braz.:*** Beriplast P; Tissucol†; ***Canad.:*** Tisseel; ***Chile:*** Beriplast P; ***Cz.:*** TachoComb†; Tissucol; ***Denm.:*** Tisseel Duo Quick; ***Fin.:*** Tisseel Duo Quick; ***Fr.:*** Beriplast; Tissucol; ***Ger.:*** Beriplast; TachoComb†; Tissucol Duo S; Tissucol-Kit; ***Gr.:*** Beriplast P; ***Hong Kong:*** Beriplast P; TachoComb; Tisseel; ***Hung.:*** Beriplast P; TachoComb†; Tissucol-Kit; ***Indon.:*** Beriplast; ***Israel:*** Beriplast; Tisseel; ***Ital.:*** Beriplast; Tissucol; ***Mex.:*** Beriplast P; Tissucol†; ***Neth.:*** Beriplast P; Tissucol; Tissucol Duo; ***Pol.:*** Beriplast; ***Port.:*** Tissucol Duo; ***Rus.:*** TachoComb (ТахоКомб); ***Spain:*** Beriplast P Combi; Tissucol Duo; ***Swed.:*** Tisseel Duo Quick; ***Switz.:*** Beriplast P; Tissucol; Tissucol Duo S; ***Thai.:*** TachoComb†; ***Turk.:*** Beriplast P; Tisseel VH; ***UK:*** Tisseel.

## Batroxobin *(rINN)*

Batroxobina; Batroxobine; Batroxobinum.

Батроксобин

*CAS — 9039-61-6 (batroxobin); 9001-13-2 (haemocoagulase).*
*ATC — B02BX03.*
*ATC Vet — QB02BX03.*

### Profile

Batroxobin is an enzyme obtained from the venom of the viper *Bothrops atrox*. It has also been obtained from *Bothrops moojeni* and a similar preparation is derived from *Bothrops jararaca*.

Batroxobin is reported to act on fibrinogen to produce a fibrin monomer that can be converted by thrombin to a fibrin clot. It is used both as a haemostatic and, in larger doses, to induce a hypofibrinogen state in the management of thromboembolic disorders. When used as a haemostatic it is usually given with a factor-X activator; such a combined preparation is known as haemocoagulase (hemocoagulase). Batroxobin has been given parenterally or by local application.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Austria:*** Defibrase; Reptilase; ***Fr.:*** Reptilase†; ***India:*** Reptilase; ***Ital.:*** Botropase†; ***Port.:*** Reptilase†.

## Blood ⊗

Sangre.

**Pharmacopoeias.** Many pharmacopoeias have monographs, including *US*.

**USP 31** (Whole Blood). It is blood that has been collected from suitable human donors under rigid aseptic precautions for transfusion or for further processing into one or more of its components for transfusion. It contains a citrate-based anticoagulant (Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or Anticoagulant Citrate Phosphate Dextrose Adenine Solution).

Whole blood must be tested for syphilis, hepatitis B virus, human T-cell lymphotropic virus (HTLV) type I and type II, hepatitis C, and HIV. It should also be tested for blood group and rhesus factors, and for unexpected antibodies to red cell antigens.

One unit (dose) of whole blood contains a minimum of 50 g of haemoglobin. One unit of whole blood filtered for removal of leucocytes (Whole Blood, Leukocytes Reduced), contains less than $5 \times 10^6$ residual leucocytes.

Whole blood is stored in the original container or transferred to an equivalent one using a technique that does not compromise sterility. It should be stored at 1° to 6°, unless platelets are to be prepared, in which case the blood is stored for no longer than 8 hours after collection at room temperature.

Whole blood collected in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at 1° to 6° after the blood has been drawn. Whole blood collected in Anticoagulant Citrate Phosphate Dextrose Adenine Solution may be stored for up to 35 days at 1° to 6°. If the hermetic seal of the container is broken during collection, preparation, or further processing, the expiry date is not later than 24 hours after the seal is broken (when blood is stored at 1° to 6°), but not to exceed the original expiry date of the unit.

It is a deep red, opaque liquid from which the corpuscles readily settle upon standing for 24 to 48 hours, leaving a clear, yellowish or pinkish supernatant layer of plasma.

The USP 31 gives the names ACD Whole Blood, CPD Whole Blood, CPDA-1 Whole Blood, and Heparin Whole Blood, which specify the anticoagulant used.

### Adverse Effects

The rapid transfusion of large volumes of whole blood may overload the circulation and cause pulmonary oedema. Transfusion of very large volumes of citrated blood can lead to hypocalcaemia, although this is not usually a problem unless there is hepatic impairment or hypothermia. Hyperkalaemia may occur but on its own is rarely clinically significant. Hypothermia may result from rapid transfusion of large volumes of cooled blood and may, combined with hypocalcaemia, hyperkalaemia, and resultant acidosis, lead to cardiac toxicity. Disseminated intravascular coagulation may also occur in patients receiving large-volume transfusions. Repeated transfusions of blood, as in thalassaemia, may lead to iron overload.

The transfusion of incompatible blood causes haemolysis, possibly with renal failure. Pyrexia, rigors, and urticaria may be due to antibodies towards a number of blood components. Severe allergic reactions and anaphylaxis can occur. Delayed reactions may occur more than 24 hours after transfusion in patients in whom previous transfusion or pregnancy has induced sensitisation; these reactions are usually mild and manifest as fever, chills, fall in haemoglobin concentration, and haemoglobinuria.

**Transmission of infections**. The use of blood, blood components, or blood products has been associated with the transmission of viruses, most notably hepatitis B virus and HIV; other reports of transmission include CMV, hepatitis C and possibly other hepatitis viruses, HTLV-I and -II, and the agent causing Creutzfeldt-Jakob disease. Transmission of bacterial and parasitic diseases is also possible including syphilis, Chagas' disease, and malaria.

The main methods of minimising the risk of transmission of infection are by rigorous selection of blood donors and by microbiological screening tests. Contamination during collection and processing is minimised by using closed systems and by strict aseptic technique. Treatment of blood products with heat or chemicals can inactivate some organisms including some viruses, in particular HIV-1, but blood and blood components cannot be treated in either of these ways. Patients receiving multiple transfusions of pooled plasma products are at increased risk of contracting infections and can be offered immunological protection, for example hepatitis B vaccine.

◊ Reviews.


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2. Barbara JAJ, Contreras M. Infectious complications of blood transfusion: bacteria and parasites. In: Contreras M. ed. *ABC of transfusion*. 3rd ed. London: BMJ Books, 1998: 58–61.
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8. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services*. 4th ed. London: The Stationery Office, 2007.
   Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 15/02/07)


**Creutzfeldt-Jakob disease.** While there is no proof that transmission of Creutzfeldt-Jakob disease by blood or blood products has occurred,[1] 3 cases have been reported of possible transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion.[2-4] It is recognised that there is a need for further assessment of the potential risk of transmission of vCJD by such products.

A number of precautionary measures have been implemented in the UK to minimise transmission of vCJD by blood or tissues:[5]

- plasma is imported from outside the UK for fractionation to manufacture plasma derivatives
- leucocytes are removed from donated blood (leucodepletion) as it was thought that this would remove infectivity. However, *animal* studies have shown that this is not the case and that prion concentration in the blood is likely to be reduced by only about 40%[6]
- plasma is imported for clinical use in patients born after January 1996 (this date was chosen because it was considered that foods infected with bovine spongiform encephalopathy had been largely eliminated from the diet by this time[6])
- donations of blood, platelets, and live bone are not accepted from donors who themselves have received blood components since 1 January 1980, or from any donors who have received intravenous immunoglobulin prepared from UK plasma or who have undergone plasma exchange anywhere in the world

Concern at the risk of transmitting Creutzfeldt-Jakob disease by albumin prepared from placental blood has led to restriction on this source of albumin (see Transmission of Infections under Albumin, p.1052).


1. Wilson K, *et al.* Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *BMJ* 2000; **321:** 17–19.
2. Llewelyn CA, *et al.* Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet* 2004; **363:** 417–21.
3. Peden AH, *et al.* Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; **364:** 527–9.
4. Wroe SJ, *et al.* Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006; **368:** 2061–7.
5. McClelland DBL, ed. *Handbook of transfusion medicine: United Kingdom Blood Services*. 4th ed. London: The Stationery Office, 2007.
   Also available at: http://www.transfusionguidelines.org.uk/docs/pdfs/htm_edition-4_all-pages.pdf (accessed 15/02/07)
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**Effects on leucocytes.** A study of 50 patients in an intensive care unit found that 45 of them developed leucocytosis after transfusion of packed red blood cells.[1] The leucocytosis, which was accounted for by neutrophils, occurred immediately after transfusion and persisted for 12 hours. A further study[2] of 96 critically ill patients found that leucocytosis commonly occurred in