See under Atropine Sulfate, p.1221, for details of dosages. As soon as the effects of atropine become apparent, 1 to 2 g of *pralidoxime* chloride, iodide, or mesilate, should be given intramuscularly or intravenously and repeated after 1 hour and then every 8 to 12 hours if necessary. Alternatively, the *BNF* recommends pralidoxime chloride in an initial dose of 30 mg/kg given by intravenous infusion over 20 minutes, or by intravenous injection over at least 5 minutes if pulmonary oedema is present or infusion cannot be given; the initial dose is then followed by intravenous infusion at a rate of 8 mg/kg per hour. In some countries, auto-injectors are available for emergency use containing pralidoxime, either alone or combined with atropine and/or avizafone, a prodrug of diazepam. Typical doses are 600 mg of pralidoxime chloride or 500 mg of pralidoxime mesilate given intramuscularly up to 3 times, depending on symptoms. Another alternative, in severe poisoning, is the use of a continuous infusion of 200 to 500 mg/hour, titrated against response. A maximum dose of 12 g in 24 hours has been suggested. The dose of pralidoxime may need to be reduced in patients with renal impairment.

Treatment should preferably be monitored by the determination of blood-cholinesterase concentrations and clinical symptoms. Patients should be closely observed for at least 24 hours after resolution of symptoms.

Other oximes with cholinesterase-reactivating properties that have been used similarly include asoxime chloride (p.1438), obidoxime chloride (p.1456), and trimedoxime bromide (p.1467).

**Organophosphorus poisoning.** Oximes such as pralidoxime are widely used in poisoning with organophosphate *pesticides*. Although benefit has been shown in *animal* studies, reviews[1,2] have pointed out that there is little good evidence from human studies to support their use and that randomised controlled studies are needed to confirm their efficacy and safety, as well as the optimum regimens to use. A randomised study[3] in patients with moderately severe poisoning with organophosphorus pesticides found that a continuous infusion of pralidoxime iodide 1 g/hour for 48 hours was more effective than a dose of 1 g every 4 hours.

Cholinesterase reactivators such as the oximes have also been used for poisoning with organophosphate *nerve agents*. Studies in *animals* have suggested that the efficacy of the different oximes depends on the organophosphate involved; asoxime (p.1438) and HLö-7 may be more effective than pralidoxime or obidoxime for poisoning with nerve agents, particularly for soman poisoning.[4]


1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003; **22:** 165–90.
2. Buckley NA, *et al*. Oximes for acute organophosphate pesticide poisoning. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 04/10/05).
3. Pawar KS, *et al*. Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet* 2006; **368:** 2136–41.
4. Kassa J. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J Toxicol Clin Toxicol* 2002; **40:** 803–16.


### Preparations

***USP 31:*** Pralidoxime Chloride for Injection.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Contrathion; ***Braz.:*** Contrathion; ***Canad.:*** Protopam; ***Fr.:*** Contrathion; ***Gr.:*** Contrathion; ***India:*** Neopam; ***Ital.:*** Contrathion; ***Malaysia:*** Pampara; ***NZ:*** Pam†; ***Turk.:*** Contrathion; ***USA:*** Protopam.

**Multi-ingredient:** ***UK:*** Nerve Agent Antidote L4A1; ***USA:*** DuoDote.

## Protamine *(rINNM)*

Protamina; Protaminum.

Протамин
*CAS — 9012-00-4.*
*ATC — V03AB14.*
*ATC Vet — QV03AB14.*

### Protamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Protamina; Hidrocloruro de protamina; Protaminihydrokloridi; Protamine, chlorhydrate de; Protamin-hidroklorid; Protamin-hydrochlorid; Protaminhydroklorid; Protamini hydrochloridum; Protamino hidrochloridas.

Протамина Гидрохлорид
*ATC — V03AB14.*
*ATC Vet — QV03AB14.*

**Pharmacopoeias.** In *Eur.* (see p.vii).
**Ph. Eur. 6.2** (Protamine Hydrochloride). A mixture of the hydrochlorides of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Soluble in water; practically insoluble in alcohol. Store in airtight containers.

### Protamine Sulfate *(rINN)*

Protamiinisulfaatti; Protamine, sulfate de; Protamine Sulphate *(BAN)*; Protamini sulfas; Protamino sulfatas; Protaminsulfat; Protamin-sulfát; Protamin-szulfát; Protaminy siarczan; Sulfato de protamina.

Протамина Сульфат
*CAS — 9009-65-8.*
*ATC — V03AB14.*
*ATC Vet — QV03AB14.*

**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
**Ph. Eur. 6.2** (Protamine Sulphate). A mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. Store in airtight containers.
**USP 31** (Protamine Sulfate). A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish. Store at 2° to 8° in airtight containers.

### Adverse Effects and Precautions

Intravenous injections of protamine, particularly if given rapidly, may cause hypotension, bradycardia, and dyspnoea. A sensation of warmth, transitory flushing, nausea and vomiting, and lassitude may also occur.

Hypersensitivity reactions can occur; patients at risk include diabetics who have received protamine-insulin preparations, those who have previously received protamine (including those who have undergone procedures such as coronary angioplasty or cardiopulmonary bypass surgery where protamine is frequently used), and those allergic to fish. Protamine is a constituent of sperm and men who are infertile or who have had a vasectomy may also be at increased risk since they may have antibodies to protamine. Anaphylactoid reactions have been reported.

Protamine has an anticoagulant effect when given in the absence of heparin.

When repeated doses of protamine are used to neutralise large doses of heparin, rebound bleeding which responds to further doses of protamine, may occur. Clotting parameters should be closely monitored in patients receiving such prolonged therapy.

◊ In a report on 4 patients given protamine sulfate after cardiac surgery to neutralise the effect of heparin, severe adverse reactions including marked hypotension, vascular collapse, and pulmonary oedema were described.[1] Previous reports of similar reactions to protamine were reviewed. A total of 17 patients had immediate anaphylactic reactions; in 1 patient a complement-dependent IgG antibody-mediated reaction had been demonstrated and 3 patients tested for allergy to protamine had positive skin tests. In 15 of these 17 patients there was evidence of previous exposure to protamine; those with a high risk of sensitisation included leucapheresis donors who had received the drug, diabetics using insulin containing protamine, and patients with fish allergy. Suspected reactions to protamine occurred in a further 10 patients after cardiac surgery. However, these reactions were characterised by severe vascular damage, manifested as noncardiogenic pulmonary oedema or persistent hypotension, and onset was delayed for 30 minutes to several hours. Evidence suggested that these reactions were not antibody mediated; only 2 of 7 evaluable patients had previous exposure. All patients required aggressive therapy.

In a review of the toxicity of protamine,[2] adverse cardiovascular responses were considered to be of 3 types: transient hypotension related to rapid drug administration, occasional anaphylactoid responses, and rarely, catastrophic pulmonary vasoconstriction.


1. Holland CL, *et al*. Adverse reactions to protamine sulfate following cardiac surgery. *Clin Cardiol* 1984; **7:** 157–62.
2. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985; **64:** 348–61.


### Uses and Administration

Protamine is a basic protein that combines with heparin to form a stable inactive complex. Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin or low-molecular-weight heparin overdosage. It is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulfate, although the hydrochloride may also be used.

Protamine sulfate is given by slow intravenous injection over a period of about 10 minutes. The dose is dependent on the amount of heparin to be neutralised and ideally should be titrated against the coagulability of the patient's blood. Protamine has weak anticoagulating properties and if given in gross excess its anticoagulant action could be significant. As heparin is being continuously excreted the dose should be reduced if more than 15 minutes have elapsed since intravenous heparin injection; for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Alternative regimens may be necessary if heparin has been given subcutaneously or by continuous intravenous infusion. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required.

For *unfractionated heparin* the Ph. Eur. 6.2 specifies that 1 mg of either protamine hydrochloride or protamine sulfate precipitates not less than 100 units of heparin, assayed against a specific reference batch of heparin sodium. One UK manufacturer has stated that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous). In the USA stated values are that each mg of protamine sulfate neutralises about 90 USP units of heparin (lung) or about 115 USP units of heparin (mucous).

For *low-molecular-weight heparins*, protamine neutralises the anti-thrombin activity but only partially neutralises the anti-factor-Xa effect; 1 mg of protamine is stated to inhibit the effects of:

- 71 units of bemiparin sodium
- 80 to 120 units of certoparin sodium
- 100 units of dalteparin sodium
- 1 mg (100 units) of enoxaparin sodium
- 82 units of reviparin sodium
- 100 units of tinzaparin sodium

**Haemorrhagic disorders.** Endogenous production of heparin-like substances may, rarely, be responsible for some bleeding disorders. It has been suggested that protamine could be useful as a diagnostic aid *in vitro* and could be given intravenously for transient control of bleeding in such patients.[1,2]


1. Tefferi A, *et al*. Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med* 1990; **88:** 184–8.
2. Bayly PJM, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; **73:** 840–2.


### Preparations

***BP 2008:*** Protamine Sulphate Injection;
***USP 31:*** Protamine Sulfate for Injection; Protamine Sulfate Injection.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Denpru; ***Hong Kong:*** Prosulf; ***India:*** Prota; ***Israel:*** Prosulf; ***UK:*** Prosulf.

## Prussian Blue

Azul de Prusia; Berlin Blue; CI Pigment Blue 27; Colour Index No. 77510; Ferric Ferrocyanide; Ferric Hexacyanoferrate (II); Insoluble Prussian Blue; Prussian Blue Insoluble *(USAN)*.

$Fe_4[Fe(CN)_6]_3$ = 859.2.
*CAS — 14038-43-8 (insoluble Prussian blue); 12240-15-2 (soluble Prussian blue); 25869-00-5 (soluble Prussian blue).*
*ATC — V03AB31.*
*ATC Vet — QV03AB31.*