Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum. 2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.

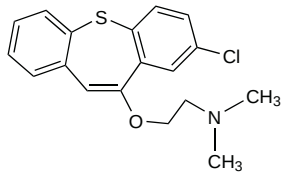
Зотепин

$C_{18}H_{18}ClNOS$ = 331.9.

CAS — 26615-21-4.

ATC — N05AX11.

ATC Vet — QN05AX11.



Adverse Effects, Treatment, and Precautions

Although zotepine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. Common adverse effects include asthenia, headache, hypotension and, less commonly, orthostatic hypotension, tachycardia, gastrointestinal disturbances, elevated liver enzyme values, leucopenia, agitation, anxiety, dizziness, insomnia, somnolence, rhinitis, sweating, and blurred vision. Other less common adverse effects include thrombocytopenia, hyperglycaemia, hyperlipidaemia, convulsions, sexual dysfunction, and urinary incontinence. Extrapyramidal symptoms have been reported and tardive dyskinesia may occur with prolonged therapy. Neuroleptic malignant syndrome has been reported rarely. Prolactin levels may be increased and weight gain has been noted.

Zotepine can prolong the QT interval and patients with pre-existing prolongation of the QT interval should not be given the drug. It should be used with caution in patients at risk of developing arrhythmias; in such patients an ECG should be performed before starting treatment. Electrolytes should also be measured and any imbalance corrected. Monitoring of ECG and electrolytes should be continued during treatment especially at each dose increase. Zotepine may also increase the heart rate and, consequently, it should be used with care in patients with angina pectoris due to coronary artery disease. Caution is also recommended in patients with other cardiovascular disorders such as severe hypertension.

Zotepine has uricosuric properties and should not be given to patients with acute gout or a history of nephrolithiasis; it should be used with caution in patients with a history of gout or hyperuricaemia. Zotepine lowers the seizure threshold and should not be used in patients with a personal or family history of epilepsy unless the potential benefit outweighs the risk of convulsions. It has antimuscarinic actions and should be used with caution in patients with disorders such as benign prostatic hyperplasia, urinary retention, angle-closure glaucoma, and paralytic ileus. It should also be used with caution in patients with hepatic impairment; in such patients, weekly monitoring of liver function is recommended for at least the first 3 months of therapy. Zotepine may exacerbate the symptoms of Parkinson's disease. It should be used with caution in patients with tumours of the adrenal medulla such as phaeochromocytoma or neuroblastoma.

Zotepine may affect the performance of skilled tasks including driving.

Gradual withdrawal of zotepine is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Dementia. The FDA has issued advice against the use of atypical antipsychotics in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class. See under Risperidone, p.1024.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also under Adverse Effects of Clozapine, p.981.

Pregnancy. For comments on the use of some atypical antipsychotics during pregnancy, see under Precautions of Clozapine, p.983.

Interactions

Zotepine may enhance the effects of other CNS depressants and antimuscarinics. The risk of seizures is particularly increased when zotepine is given with high doses of other antipsychotics and the combination is not recommended. Additive hypotensive effects may theoretically occur with antihypertensives and some anaesthetic drugs; however its α-blocking actions might reduce the effects of methyldopa or clonidine.

The risk of arrhythmias with zotepine may be increased by use with other drugs that prolong the QT interval or cause hypokalaemia. Use of zotepine with fluoxetine or diazepam may lead to increased plasma concentrations of zotepine.

Pharmacokinetics

Zotepine is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations being achieved 2 to 3 hours later. It undergoes extensive first-pass metabolism to the equipotent metabolite norzotepine and inactive metabolites. CYP1A2 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of zotepine. Plasma protein binding of zotepine and norzotepine is 97%. Zotepine is excreted mainly in the urine and faeces as inactive metabolites and has an elimination half-life of about 14 hours. It is thought to be distributed into breast milk on the basis of studies in *rats*.

Uses and Administration

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin (5-HT_2), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It is given in the treatment of schizophrenia in an initial oral dose of 25 mg three times daily; this is increased according to response, at intervals of 4 days, to a maximum of 100 mg three times daily. There is an appreciable increase in the incidence of seizures at total daily doses above the recommended maximum of 300 mg. For elderly patients, the recommended starting dose is 25 mg given twice daily, increased gradually up to a maximum of 75 mg twice daily. Doses should also be reduced in patients with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, the recommended initial oral dose of zotepine is 25 mg given twice daily increased gradually up to a maximum of 75 mg twice daily.

Schizophrenia. A systematic review[1] of short-term studies of zotepine for schizophrenia (p.955) concluded tentatively that it was as effective as classical antipsychotics and might be of benefit in patients with negative symptoms; in addition, it seemed less likely to provoke extrapyramidal disorders. Comparisons with atypical antipsychotics were too scanty for a meaningful comparison to be drawn.

1. DeSilva P, *et al.* Zotepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews ; Issue 4. Chichester: John Wiley; 2006 (accessed 10/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nipolept; ***Cz.:*** Zoleptil; ***Ger.:*** Nipolept; ***Indon.:*** Lodopin; ***Jpn:*** Lodopin; ***Port.:*** Zoleptil; ***UK:*** Zoleptil.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *Z*-Clopenthixol; *cis*-Clopenthixol; α-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol. (*Z*)-2-{4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl}ethanol.

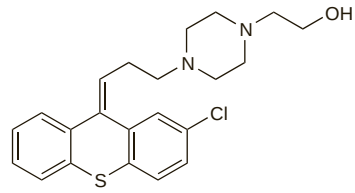
Зуклопентиксол

$C_{22}H_{25}ClN_2OS$ = 401.0.

CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).

ATC — N05AF05.

ATC Vet — QN05AF05.



NOTE. Clopenthixol (*BAN*, *INN*, *USAN*) is the racemic mixture.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuklopentiksol Asetat.

Зуклопентиксола Ацетат

$C_{24}H_{27}ClN_2O_2S$ = 443.0.

CAS — 85721-05-7.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Acetate). A yellowish, viscous oil. Very slightly soluble in water; very soluble in alcohol, in dichloromethane, and in ether. Store at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, décanoate de; Zuclopenthixoli decanoas; Zuklopenthixol-dekanoát; Zuklopentiksol Dekanoat; Zuklopentiksolio dekanoatas; Zuklopentixoldekanoat; Zuklopentyksolu dekanonian.

Зуклопентиксола Деканоат

$C_{32}H_{43}ClN_2O_2S$ = 555.2.

CAS — 64053-00-5.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zuclopenthixol Decanoate). A yellow viscous oily liquid. Very slightly soluble in water; very soluble in alcohol and in dichloromethane. Store under an inert gas in airtight containers at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuklopentiksol Dihidroklorür.

Зуклопентиксола Гидрохлорид

$C_{22}H_{25}ClN_2OS,2HCl$ = 473.9.

CAS — 58045-23-1.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Hydrochloride). An off-white granular powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. Zuclopenthixol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Zuclopenthixol is absorbed after oral doses with peak plasma concentrations occurring 3 to 6 hours later. The biological half-life after oral doses is reported to be about 1 day. Paths of metabolism of zuclopenthixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. It is mainly excreted in the faeces as unchanged drug and its *N*-dealkylated metabolite. Zuclopenthixol is about 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Small amounts of drug or metabolites cross the placenta and are distributed into breast milk.

On intramuscular injection the acetate and decanoate esters of zuclopenthixol are hydrolysed to release zuclopenthixol. Zuclopenthixol acetate has a relatively quick onset of action after injection and a duration of action of 2 to 3 days. It is therefore useful for the control of acute psychotic symptoms while avoiding repeated injections. The decanoate has a much longer duration of action and is a suitable depot preparation for maintenance treatment.

Metabolism. Determination of metaboliser phenotype with regard to cytochrome P450 isoenzyme CYP2D6 appeared to be of limited value in patients receiving zuclopenthixol as interindividual variation appeared to be the main factor affecting dose to serum concentration ratios.[1]

1. Linnet K, Wiborg O. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. *Ther Drug Monit* 1996; **18:** 629–34.

Uses and Administration

Zuclopenthixol is a thioxanthene of high potency with general properties similar to the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain.

Zuclopenthixol is used for the treatment of schizophrenia (see below), mania (see Bipolar Disorder, p.372), and other psychoses. It may be particularly suitable for agitated or aggressive patients who may become overexcited with flupentixol. Zuclopenthixol hydrochloride is usually given orally with doses expressed in terms of the base; zuclopenthixol hydrochloride 11.8 mg is equivalent to about 10 mg of zuclopenthixol. Zuclopenthixol hydrochloride has also been given intramuscularly. Zuclopenthixol acetate and zuclopenthixol decanoate are given by deep intramuscular injection; doses are expressed in terms of the ester. The acetate ester has a rapid onset of action and a duration of action of 2 to 3 days; it is used as a 5% oily solution for the initial treatment of acute psychoses and for exacerbations of chronic psychoses. The longer-acting decanoate ester is used as a 20% oily solution for the maintenance treatment of chronic psychoses; a 50% solution is available for those requiring high doses.

- The usual initial *oral* dose of the hydrochloride for the treatment of **psychoses** is the equivalent of 20 to 30 mg of the base daily in divided doses; in severe or resistant cases up to 150 mg daily has been given. The usual maintenance dose is 20 to 50 mg daily.
- The usual dose of zuclopenthixol acetate is 50 to 150 mg by deep *intramuscular* injection repeated, if necessary, after 2 or 3 days. Some patients may need an additional injection between 1 and 2 days after the first dose.

  Zuclopenthixol acetate is not intended for maintenance treatment; no more than 4 injections should be given in a maximum course of 2 weeks and the total dose should not exceed 400 mg. When maintenance treatment is required, *oral* zuclopenthixol hydrochloride may be introduced 2 to 3 days after the last injection of zuclopenthixol acetate, or *intramuscular* injections of the decanoate (see below) begun with the last injection of the acetate.
- The long-acting decanoate should be given by deep *intramuscular* injection; treatment is usually started with a test dose of 100 mg. This may be followed after at least 1 week by a dose of 200 to 500 mg or more, every 1 to 4 weeks, adjusted according to response. Injection volumes greater than 2 mL should be divided between 2 separate injection sites. The maximum recommended dose of zuclopenthixol decanoate is 600 mg weekly.

Elderly or debilitated patients should be given reduced doses of zuclopenthixol. Licensed product information states that the dose of the hydrochloride or the decanoate may need to be reduced to one-quarter or one-half of the usual initial dose; in addition, the maximum single dose of the acetate should be limited to 100 mg.

Administration in hepatic or renal impairment. Licensed product information recommends that for zuclopenthixol acetate, half the normal recommended intramuscular dose should be used for patients with hepatic impairment; a dosage reduction is considered to be unnecessary in patients with renal impairment but where there is renal failure half the normal intramuscular dosage is recommended.

Schizophrenia. A systematic review[1] comparing zuclopenthixol decanoate with other depot antipsychotics considered that although it may induce more adverse effects, limited data suggested it might offer advantages such as lower relapse rates and increased acceptability in the treatment of schizophrenia (p.955) and similar serious mental illnesses. Similar reviews of the use of the acetate[2] or hydrochloride[3] found, however, that evidence of additional benefit over other antipsychotics was lacking.

1. Coutinho E, *et al*. Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 14/04/05).
2. Gibson RC, *et al*. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).
3. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).

Preparations

BP 2008: Zuclopenthixol Acetate Injection; Zuclopenthixol Decanoate Injection; Zuclopenthixol Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Clopixol; ***Austral.:*** Clopixol; ***Austria:*** Cisordinol; ***Belg.:*** Clopixol; ***Braz.:*** Clopixol; ***Canad.:*** Clopixol; ***Chile:*** Cisordinol; ***Cz.:*** Cisordinol; ***Denm.:*** Cisordinol; ***Fin.:*** Cisordinol; ***Fr.:*** Clopixol; ***Ger.:*** Ciatyl-Z; ***Gr.:*** Clopixol; ***Hong Kong:*** Clopixol; ***Hung.:*** Cisordinol; ***India:*** Clopixol; ***Irl.:*** Clopixol; ***Israel:*** Clopixol; ***Ital.:*** Clopixol; ***Malaysia:*** Clopixol; ***Mex.:*** Clopixol; ***Neth.:*** Cisordinol; Clopixol; ***Norw.:*** Cisordinol; ***NZ:*** Clopixol; ***Philipp.:*** Clopixol; ***Pol.:*** Clopixol; ***Port.:*** Cisordinol; ***Rus.:*** Clopixol (Клопиксол); ***S.Afr.:*** Clopixol; Colpixol; ***Singapore:*** Clopixol; ***Spain:*** Cisordinol; Clopixol; ***Swed.:*** Cisordinol; ***Switz.:*** Clopixol; ***Thai.:*** Clopixol; ***Turk.:*** Clopixol; ***UK:*** Clopixol.

ally present with fever of sudden onset, sore throat, mouth ulcers, headache, and malaise. This condition is also known as **agranulocytosis**. Other causes of acquired neutropenia include serious bacterial and viral infections, radiotherapy, neoplasms that invade bone marrow, and some auto-immune disorders.

The management of acquired neutropenia includes the treatment of any contributory condition. Drug-induced neutropenia is usually managed by withdrawal of the offending drug. After an idiosyncratic reaction the implicated drug should not be given again, since abrupt neutropenia will usually be precipitated. Colony-stimulating factors can be used to manage drug-induced neutropenia.

In all neutropenic patients onset of fever is indicative of serious infection and is treated immediately with empirical antibacterial therapy as described on p.174.

◊ General references.

1. Zeidler C, *et al.* Congenital neutropenias. *Rev Clin Exp Hematol* 2003; **7:** 72–83.
2. Bhatt V, Saleem A. Drug-induced neutropenia—pathophysiology, clinical features, and management. *Ann Clin Lab Sci* 2004; **34:** 131–7.
3. James RM, Kinsey SE. The investigation and management of chronic neutropenia in children. *Arch Dis Child* 2006; **91:** 852–8.

Albumin ⊗

Albümin; Albúmina; Albumine; Albuminum.

ATC — B05AA01.

ATC Vet — QB05AA01; QV08DA01 (microspheres of human albumin).

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

Ph. Eur. 6.2 (Human Albumin Solution; Albumini Humani Solutio). An aqueous solution of protein obtained from the plasma of healthy donors; the plasma is tested for the absence of hepatitis B surface antigen and antibodies against HIV-1 and HIV-2 and hepatitis C virus. It is prepared as a concentrated solution containing 15 to 25% of total protein or as an isotonic solution containing 3.5 to 5% of total protein; not less than 95% of the total protein is albumin. A suitable stabiliser, such as sodium octanoate or *N*-acetyltryptophan or a combination of the two, may be added but no antimicrobial preservative is added. It contains not more than 160 mmol of sodium per litre and not more than 200 micrograms of aluminium per litre. The solution is sterilised by filtration and distributed aseptically into containers which are sealed to prevent contamination and maintained at 59° to 61° for not less than 10 hours. Finally, the containers are incubated for not less than 14 days at 30° to 32° or for not less than 4 weeks at 20° to 25° and examined visually for signs of microbial contamination. It should be stored in a colourless glass container and protected from light.

A clear, almost colourless, yellow, amber, or green slightly viscous liquid. A solution in sodium chloride 0.9% containing 1% protein has a pH of 6.7 to 7.3.

The BP 2008 gives Albumin and Human Albumin as approved synonyms.

USP 31 (Albumin Human). A sterile, nonpyrogenic, preparation of serum albumin obtained by fractionating material (blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen. It is made by a process that yields a product that is safe for intravenous use. It contains 4, 5, 20, or 25% of serum albumin and not less than 96% of the total protein is albumin. It may contain sodium acetyltryptophanate with or without sodium caprylate as a stabilising agent; it contains no added antimicrobial agent. It contains 130 to 160 mmol of sodium per litre. It is a practically odourless, moderately viscous, clear, brownish fluid. It should be stored in airtight containers.

Adverse Effects and Precautions

Adverse reactions to albumin infusion occur rarely and include nausea and vomiting, increased salivation, flushing, urticaria, hypotension, tachycardia, and febrile reactions. These effects usually respond to slowing or stopping the infusion. Allergic reactions, including severe anaphylactic shock, are possible. Rapid increases in circulatory volume can cause vascular overload, hypertension, haemodilution, and pulmonary oedema. Solutions containing albumin 20 or 25% are hyperosmotic and draw fluid from the extravascular compartment.

Infusion of albumin solutions is contra-indicated in patients with severe anaemia or heart failure. They should be given with caution to patients with hypertension or low cardiac reserve. Dehydrated patients may require additional fluids. Injured or postoperative patients should be observed carefully when given albumin as the rise in blood pressure may result in bleeding from previously undetected sites.

Human albumin preparations carry a risk of viral transmission. Manufacturing processes, including heating to about 60°, have reduced the risk of transmitting some viral infections.

Aluminium toxicity. Albumin solutions may contain appreciable amounts of aluminium. Marked increases in plasma-aluminium concentrations have been demonstrated in patients receiving large volumes by infusion and accumulation of aluminium may occur in patients with renal impairment.[1-3] In the UK albumin solutions with an aluminium content of less than 200 micrograms/litre are available for use in premature infants and patients undergoing dialysis.

1. Milliner DS, *et al.* Inadvertent aluminum administration during plasma exchange due to aluminum contamination of albumin-replacement solutions. *N Engl J Med* 1985; **312:** 165–7.
2. Maher ER, *et al.* Accumulation of aluminium in chronic renal failure due to administration of albumin replacement solutions. *BMJ* 1986; **292:** 306.
3. Maharaj D, *et al.* Aluminium bone disease in patients receiving plasma exchange with contaminated albumin. *BMJ* 1987; **295:** 693–6.

Critically ill patients. Volume expansion with albumin (a colloid) has been widely used in critically ill patients, although its use had never been formally tested in large controlled studies. A systematic review based on available studies up to March 1998 (relatively small, old trials that recorded only a small number of deaths) suggested that albumin was of no benefit in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia, and that it might be linked to increased mortality.[1] The authors of the review stressed that these results should be treated with caution but nevertheless called for an urgent reconsideration of the use of albumin in critically ill patients.

The review was severely criticised[2] and while it was recognised that albumin had probably been overused in the past it was considered that more studies were required to define the effect of albumin on mortality.[3-5] Another review[6] found that the use of albumin did not significantly affect mortality; this meta-analysis had broader criteria and included studies that were considered to be relevant but that had been excluded by the other review.

In response to this debate, albumin 4% was compared with sodium chloride 0.9% for resuscitation in a study of 6997 hypovolaemic patients in intensive care (the SAFE study).[7] This large, randomised, double-blind study found equivalent rates of death from any cause during the 28-day study period. Survival-time during the 28 days, length of stay in the intensive care unit and in hospital, time on mechanical inhalation or renal replacement therapy, and development of organ failure were also similar. Although these two fluids seem clinically equivalent in a heterogeneous population of patients in intensive care, further study of selected groups, such as those with trauma or severe sepsis, is required.

An update to the original 1998 review included the results of SAFE. The authors maintained that patients with burns (a group excluded from the large trial) or hypoproteinaemia might still be at risk of increased mortality, and although no longer suggesting a generally increased risk, concluded that there was no evidence that albumin reduced mortality in patients with hypovolaemia. Whether highly selected groups of critically ill patients might benefit is as yet unclear.[8]

Pharmacovigilance data reported to albumin suppliers over 3 years (1998 to 2000) has also been analysed.[9] During this period of heightened awareness about possible adverse effects of albumin, due to the publication of the 1998 review, a total of 1.62×10^7 doses of 40 g had been distributed. Serious adverse effects possibly or probably related to albumin were found to be rare, and no death was classified as probably related to albumin use.

On a broader level, debate continues about the relative merits and risks of such colloid solutions, compared with those of crystalloids such as glucose or sodium chloride solutions, in the management of hypovolaemia and shock (p.1183).

1. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317:** 235–40.
2. Various. Human albumin administration in critically ill patients. *BMJ* 1998; **317:** 882–6. [Letters.]
3. Tomlin M. Albumin usage in the critically ill. *Pharm J* 1998; **261:** 193.
4. McClelland B. Albumin: don't confuse us with the facts. *BMJ* 1998; **317:** 829–30.
5. Committee on Safety of Medicines/Medicines Control Agency. The safety of human albumin. *Current Problems* 1999; **25:** 11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023234&RevisionSelectionMethod=LatestReleased (accessed 08/06/06)
6. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; **135:** 149–64.
7. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; **350:** 2247–56.
8. The Albumin Reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 27/10/05).
9. Vincent J-L, *et al.* Safety of human albumin—serious adverse events reported worldwide in 1998–2000. *Br J Anaesth* 2003; **91:** 625–30.

Dilution. If concentrated albumin solutions are to be diluted before use, a suitable solution such as sodium chloride 0.9% or glucose 5% must be used. Albumin 25% that was erroneously diluted with water to produce a hypo-osmolar albumin 5% solution has produced severe haemolysis and renal failure in patients undergoing plasmapheresis,[1,2] including a fatality in one patient.[3]

1. Steinmuller DR. A dangerous error in the dilution of 25 percent albumin. *N Engl J Med* 1998; **338:** 1226.
2. Pierce LR, *et al.* Hemolysis and renal failure associated with use of sterile water for injection to dilute 25% human albumin solution. *Am J Health-Syst Pharm* 1998; **55:** 1057,1062, 1070.
3. Anonymous. Hemolysis associated with 25% human albumin diluted with sterile water—United States, 1994–1998. *MMWR* 1999; **48:** 157–9.

Transmission of infections. There has been concern that albumin preparations may carry a potential risk of transmission of viral and subviral particles, notably Creutzfeldt-Jakob disease. In 1993, *Pasteur-Mérieux* (one of the largest producers of blood products) withdrew all products containing albumin derived from placental blood[1] due to uncertainty regarding the adequacy of screening procedures for placentas as a source. It was considered that the agent responsible for Creutzfeldt-Jakob disease might be contained in placentas from women who have been treated with growth hormone derived from cadaver pituitaries. More recently, the production of blood products (including albumin) using plasma from UK donors has been phased out due to the possible risk of transmission of new variant Creutzfeldt-Jakob disease.

1. Anonymous. Placental-derived albumin preparations withdrawn. *WHO Drug Inf* 1994; **8:** 29–30.

Uses and Administration

Albumin is the major protein involved in maintaining colloid osmotic pressure in the blood. It also binds a number of endogenous and exogenous substances including bilirubin, steroid hormones, and many, mainly acidic, drugs.

Albumin solutions are used for plasma volume replacement and to restore colloid osmotic pressure. They have been used in conditions such as burns, severe acute albumin loss, and acute hypovolaemic shock (p.1183). They are also used as an exchange fluid in therapeutic plasmapheresis. Concentrated albumin solutions are used in neonatal hyperbilirubinaemia associated with haemolytic disease of the newborn (p.2204). They have also been suggested for short-term management of hypoproteinaemia in hepatic disease and in diuretic-resistant patients with nephrotic syndrome but are of little value in chronic hypoproteinaemias.

Albumin may be included in diagnostic preparations such as those labelled with technetium-99m (p.2055) for use as radiopharmaceuticals in scanning of the heart, lung, liver, spleen, bone marrow, veins, and lymphatic system. Albumin labelled with iodine-125 (p.2054) is used to measure blood and plasma volumes, blood circulation, and cardiac output. A suspension of albumin microspheres with perflutren (p.1488) is available for enhancing cardiac ultrasound imaging.

Recombinant forms of human albumin have been developed as excipients for vaccines and other drug products, and for the treatment of hypoalbuminaemia and hypovolaemic shock.

Albumin solutions are usually available as 4.5% or 5% solutions, which are iso-osmotic with plasma, and as 20% or 25% solutions which are hyperosmotic with respect to plasma, and cause a movement of fluid from the extravascular to the intravascular compartment. These concentrated solutions may be used undiluted or may be diluted with a suitable solution, commonly sodium chloride 0.9% or glucose 5%. Adequate hydration should be maintained and electrolytes monitored in patients receiving hyperosmotic solutions of albumin.