minocycline hydrochloride, and prochlorperazine edisilate during simulated Y-site administration.

1. Trissel LA, Martinez JF. Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 2208–12.

Adverse Effects, Treatment, and Precautions

Amifostine may cause a transient reduction, usually in systolic, or, less frequently, in diastolic blood pressure. However, more pronounced reductions in blood pressure may occur and transient loss of consciousness has been reported very rarely. To minimise hypotension, patients should be adequately hydrated before treatment begins and should be in a supine position. Amifostine is contra-indicated in patients who are hypotensive or dehydrated. Patients taking antihypertensive drugs should discontinue treatment 24 hours before starting amifostine. Arterial blood pressure must be monitored during the amifostine infusion and if systolic blood pressure decreases significantly, the infusion must stop. It may be continued if blood pressure returns to normal within 5 minutes.

Nausea and vomiting are frequently reported and concurrent antiemetic therapy is recommended.

Amifostine reduces serum-calcium concentrations, although clinical hypocalcaemia has occurred only very rarely in patients who received multiple doses of amifostine within 24 hours. Serum-calcium concentrations should be monitored in patients at risk of hypocalcaemia.

Other adverse effects include flushing, chills, somnolence, hiccups, and sneezing. Hypersensitivity reactions and anaphylactoid reactions have been reported. Skin rashes may occur and there have been reports of more severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, in some cases resulting in fatality.

Administration of amifostine over a longer period than the recommended 15 minutes is associated with a higher incidence of adverse effects.

Effects on the skin. Amifostine has been associated with severe skin reactions, including Stevens-Johnson syndrome[1,2] and toxic epidermal necrolysis,[1,2] and fatalities have occurred.[2] The reactions appear to be more common in patients receiving radiotherapy.[2]

1. Lale Atahan I, *et al*. Two cases of Stevens-Johnson syndrome: toxic epidermal necrolysis possibly induced by amifostine during radiotherapy. *Br J Dermatol* 2000; **143:** 1072–3.
2. Boccia R, *et al*. Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004; **60:** 302–9.

Pharmacokinetics

Amifostine is rapidly cleared from the plasma after intravenous administration and is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065, a free thiol compound. The elimination half-life of amifostine after a 15-minute infusion is less than 10 minutes. About 6% or less of a dose is excreted in the urine.

Uses and Administration

Amifostine, an aminothiol compound, is a cytoprotective agent. It is converted in the body to its active metabolite WR-1065, which protects noncancerous cells against the toxic effects of antineoplastics and ionising radiation. It is used in patients with advanced ovarian cancer to reduce neutropenia-related infection associated with cyclophosphamide and cisplatin therapy and, in patients with advanced solid tumours of non-germ cell origin, to reduce the cumulative renal toxicity associated with repeated cisplatin use. It is also used to reduce the incidence of xerostomia (dry mouth) in patients undergoing radiation therapy for head and neck cancer. Amifostine is under investigation in ameliorating the adverse effects of other antineoplastics and in the treatment of myelodysplasia.

In chemotherapy, amifostine is given by intravenous infusion over 15 minutes starting no more than 30 minutes before the antineoplastic therapy. The dose in adults is 910 mg/m^2 once daily. Subsequent doses should be reduced to 740 mg/m^2 in patients unable to tolerate the full dose. A dose of 740 mg/m^2 is also recommended for the reduction of renal toxicity of cisplatin if doses of cisplatin of less than 100 mg/m^2 are used.

In the prevention of xerostomia, amifostine is given in a dose of 200 mg/m^2 daily as a 3-minute intravenous infusion started 15 to 30 minutes before radiotherapy.

Cytoprotection. WR-1065, the active metabolite of amifostine, readily enters non-malignant cells where it deactivates cytotoxics such as alkylating and platinum-containing antineoplastics and protects against the effects of ionising radiation.[1-3] The cytoprotective effects of amifostine are reported to be selective for normal cells and not to interfere with the cytotoxic effects of antineoplastics and radiation on malignant cells. Several factors contribute to this selectivity, including the lower alkaline phosphatase content of malignant cells compared with normal cells, and the lower pH of malignant tissues, both of which decrease the formation and uptake of WR-1065 by malignant cells.[2,3]

Benefit has been reported with amifostine in various malignancies and the American Society of Clinical Oncology currently recommends[4] that its use may be considered in patients receiving cisplatin- or alkylating agent-based chemotherapy, and in patients receiving radiation therapy in the head and neck region. Although it is usually given intravenously, there is some evidence[5,6] that the subcutaneous route may be effective and may be associated with fewer adverse effects.

1. Foster-Nora JA, Siden R. Amifostine for protection from antineoplastic drug toxicity. *Am J Health-Syst Pharm* 1997; **54:** 787–800.
2. Mabro M, *et al*. A risk-benefit assessment of amifostine in cytoprotection. *Drug Safety* 1999; **21:** 367–87.
3. Culy CR, Spencer CM. Amifostine: an update on its clinical status as a cytoprotectant in patients with cancer receiving chemotherapy or radiotherapy and its potential therapeutic application in myelodysplastic syndrome. *Drugs* 2001; **61:** 641–84.
4. Schuchter LM, *et al*. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2002; **20:** 2895–903. Also available at: http://www.jco.org/cgi/reprint/20/12/2895.pdf (accessed 4/10/05)
5. Koukourakis MI, *et al*. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. *J Clin Oncol* 2000; **18:** 2226–33.
6. Bonner HS, Shaw LM. New dosing regimens for amifostine: a pilot study to compare the relative bioavailability of oral and subcutaneous administration with intravenous infusion. *J Clin Pharmacol* 2002; **42:** 166–74.

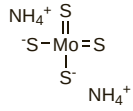
Preparations

USP 31: Amifostine for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Erifostine; Ethyol†; ***Austral.:*** Ethyol; ***Belg.:*** Ethyol; ***Braz.:*** Ethyol; ***Chile:*** Ethyol; ***Cz.:*** Ethyol; ***Denm.:*** Ethyol; ***Fin.:*** Ethyol; ***Fr.:*** Ethyol; ***Ger.:*** Ethyol; ***Gr.:*** Ethyol; ***Hong Kong:*** Ethyol†; ***Hung.:*** Ethyol†; ***India:*** Amiphos; ***Israel:*** Ethyol; ***Ital.:*** Ethyol; ***Malaysia:*** Ethyol†; ***Mex.:*** Ethyol; ***Neth.:*** Ethyol; ***NZ:*** Ethyol; ***Philipp.:*** Ethyol; ***Pol.:*** Ethyol; ***Port.:*** Ethyol; ***S.Afr.:*** Ethyol; ***Singapore:*** Ethyol†; ***Spain:*** Ethyol; ***Swed.:*** Ethyol; ***Switz.:*** Ethyol; ***Thai.:*** Cytofos; Ethyol; ***Turk.:*** Ethyol; ***UK:*** Ethyol†; ***USA:*** Ethyol; ***Venez.:*** Ethyol.

Ammonium Tetrathiomolybdate

Tetratiomolibdato de amonio.
$(NH_4)_2MoS_4$ = 260.3.
CAS — 15060-55-6.



Profile

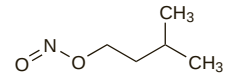
Ammonium tetrathiomolybdate is a chelator that aids the elimination of copper from the body. It is under investigation in the treatment of Wilson's disease.

Wilson's disease. Ammonium tetrathiomolybdate forms a complex with protein and copper. When it is taken with food it blocks the intestinal absorption of copper, and when given between meals it combines with albumin- and caeruloplasmin-bound copper. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels in patients with Wilson's disease (p.1459); it may be particularly suitable for patients with neurological symptoms.[1] Bone marrow depression[1,2] and raised liver enzymes[1] have been reported; both have responded to temporary withdrawal or dose reduction.

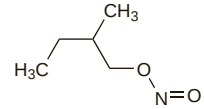
1. Brewer GJ, *et al*. Treatment of Wilson disease with ammonium tetrathiomolybdate III: initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003; **60:** 379–85.
2. Harper PL, Walshe JM. Reversible pancytopenia secondary to treatment with tetrathiomolybdate. *Br J Haematol* 1986; **64:** 851–3.

Amyl Nitrite

Amyli Nitris; Amylis Nitris; Amylium Nitrosum; Amylnitrit; Amyylinitriitti; Azotito de Amilo; Isoamyl Nitrite; Isopentyl Nitrite; Nitrito de amilo; Pentanolis Nitris.
$C_5H_{11}NO_2$ = 117.1.
ATC — V03AB22.
ATC Vet — QV03AB22.



and



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of amyl nitrite:
60 second trip; Aimes; Aimies; Ames; Amys; Boppers; Hard on; Pearls; Poppers; Sixty second trip; Snappers; Whiffenpoppers.

Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Amyl Nitrite). A mixture of the nitrite esters of 3-methyl-1-butanol and 2-methyl-1-butanol. A clear, yellowish liquid having a peculiar, ethereal, fruity odour. It is very flammable. It is volatile even at low temperatures. B.p. about 96°. Practically insoluble in water; miscible with alcohol and with ether. Store in a cool place in airtight containers. Protect from light.

Stability. Amyl nitrite is liable to decompose with evolution of nitrogen, particularly if it has become acid in reaction.

Adverse Effects, Treatment, and Precautions

Amyl nitrite inhalation commonly causes flushing, headache, and dizziness; nausea and vomiting, hypotension, restlessness, and tachycardia may also occur. Overdosage may result in cyanosis, syncope, dyspnoea, and muscular weakness, due to vasodilatation and methaemoglobinaemia. Methylthioninium chloride may be required for severe methaemoglobinaemia but should not be used if cyanide poisoning is suspected since cyanide may be displaced.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

Abuse. Volatile nitrites (commonly known as 'poppers'), including amyl, butyl, or isobutyl nitrite, have been abused in the belief that they expand creativity, stimulate music appreciation, promote a sense of abandon in dancing, and intensify sexual experience.[1,2]

Inhalation causes headache, tachycardia, syncope, acute psychosis, increased intra-ocular pressure, transient hemiparesis, methaemoglobinaemia, coma, and, rarely, sudden death. Haemolytic anaemia has also been reported;[3-5] in some subjects, Heinz body formation has been detected.[3] Methaemoglobinaemia may be severe,[6] and has also been reported after ingestion of volatile nitrites.[7-10] Symptoms are similar to those of hypoxia[9] and may be reversed by methylthioninium chloride.[6-10]

Amyl nitrite inhalation has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body.[11]

1. Sigell LT, *et al*. Popping and snorting volatile nitrites: a current fad for getting high. *Am J Psychiatry* 1978; **135:** 1216–18.
2. Lockwood B. Poppers: volatile nitrite inhalants. *Pharm J* 1996; **257:** 154–5.
3. Romeril KR, Concannon AJ. Heinz body haemolytic anaemia after sniffing volatile nitrites. *Med J Aust* 1981; **1:** 302–3.
4. Brandes JC, *et al*. Amyl nitrite-induced hemolytic anemia. *Am J Med* 1989; **86:** 252–4.
5. Graves TD, Mitchell S. Acute haemolytic anaemia after inhalation of amyl nitrite. *J R Soc Med* 2003; **96:** 594–5.
6. Modarai B, *et al*. Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 2002; **19:** 270–1.
7. Laaban JP, *et al*. Amyl nitrite poppers and methemoglobulinemia. *Ann Intern Med* 1985; **103:** 804–5.
8. Osterloh J, Olson K. Toxicities of alkyl nitrites. *Ann Intern Med* 1986; **104:** 727.
9. Pierce JMT, Nielsen MS. Acute acquired methaemoglobinaemia after amyl nitrite poisoning. *BMJ* 1989; **298:** 1566.
10. Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. *Arch Dis Child* 1991; **66:** 152.
11. Bos JD, *et al*. Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis* 1985; **12:** 109.

Handling and storage. Amyl nitrite is very flammable and must not be used where it may be ignited.

Uses and Administration

Amyl nitrite is rapidly absorbed on inhalation and has been used in the immediate treatment of patients with definite cyanide poisoning (p.2045) to induce the formation of methaemoglobin, which combines with the cyanide to form non-toxic cyanmethaemoglobin. The value of such treatment has been questioned since only low levels of methaemoglobin are formed, but other mechanisms may also be important. A suggested procedure has

been to give amyl nitrite by inhalation for up to 30 seconds every minute until other measures can be instituted. It has also been suggested for use in the management of hydrogen sulfide poisoning (p.1690).

Amyl nitrite has an action similar to that of glyceryl trinitrate (p.1297) and used to be given by inhalation for the relief of acute attacks of angina pectoris but is seldom used now.

Homoeopathy. Amyl nitrite has been used in homoeopathic medicines under the following names: Amyl nitrosum; Am. nit.

Preparations

USP 31: Amyl Nitrite Inhalant.

Proprietary Preparations (details are given in Part 3)

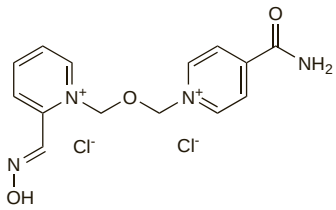
Multi-ingredient: ***Austria:*** Percucor†; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package; Emergent-Ez.

Asoxime Chloride

Asoxima, cloruro de; HI-6. 1-({[4-(Aminocarbonyl)pyridinio]methoxy}methyl)-2-[(hydroxyimino)methyl]pyridinium dichloride.

$C_{14}H_{16}Cl_2N_4O_3$ = 359.2.

CAS — 34433-31-3.



Profile

Asoxime chloride is a cholinesterase reactivator that has been tried in the treatment of poisoning by organophosphorus pesticides and related compounds, including nerve agents.

◊ References.

1. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; **9:** 49–51.
2. Kušić R, *et al.* HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 1991; **10:** 113–18.

AST-120

CAS — 90597-58-3.

Profile

AST-120 is an adsorbent consisting of spherical microcrystalline carbonaceous particles with oxygen complex including surface oxides. It is given orally to delay the progression of chronic renal failure by removing uraemic toxins and their precursors from the gastrointestinal tract. It is also under investigation in gastrointestinal disorders.

◊ References.

1. Takahashi N, *et al.* Therapeutic effects of long-term administration of an oral adsorbent in patients with chronic renal failure: two-year study. *Int J Urol* 2005; **12:** 7–11.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Kremezin.

Atipamezole *(BAN, USAN, rINN)*

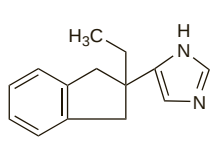
Atipamezol; Atipamézole; Atipamezolum; MPV-1248. 4-(2-Ethyl-2-indanyl)imidazole.

Атипамезол

$C_{14}H_{16}N_2$ = 212.3.

CAS — 104054-27-5.

ATC Vet — QV03AB90.



Atipamezole Hydrochloride *(BANM, rINNM)*

Atipametsolihydrokloridi; Atipamézole, Chlorhydrate d'; Atipamezolhydroklorid; Atipamezoli Hydrochloridum; Hidrocloruro de atipamezol.

Атипамезола Гидрохлорид

$C_{14}H_{16}N_2$,HCl = 248.8.

CAS — 104075-48-1.

Profile

Atipamezole is a selective alpha$_2$-adrenergic receptor antagonist that is used as the hydrochloride in veterinary medicine to reverse the sedative effects of medetomidine.

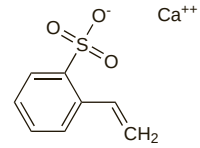
Calcium Polystyrene Sulfonate

Calcium Polystyrene Sulphonate; Poliestirenosulfonato cálcico; Polistiren Sülfonat Kalsiyum.

CAS — 37286-92-3.

ATC — V03AE01.

ATC Vet — QV03AE01.



Pharmacopoeias. In *Br.* and *Jpn*.

BP 2008 (Calcium Polystyrene Sulphonate). A cream to light brown, fine powder. The calcium content is not less than 6.5% and not more than 9.5%, calculated with reference to the dried substance. Each g exchanges not less than 1.3 mmol and not more than 2.0 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water and in alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Sodium Polystyrene Sulfonate, p.1465. Sodium overloading is not a problem with calcium polystyrene sulfonate, but calcium overloading and hypercalcaemia may occur. It should therefore be avoided in patients with conditions such as hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma who may present with renal failure together with hypercalcaemia. Patients should be monitored for electrolyte disturbances, especially hypokalaemia and hypercalcaemia.

Effects on the lungs. An elderly man who died from cardiac arrest was found at autopsy to have bronchopneumonia associated with inhalation of calcium polystyrene sulfonate;[1] the resin had been given by mouth to treat hyperkalaemia.

1. Chaplin AJ, Millard PR. Calcium polystyrene sulphonate: an unusual cause of inhalation pneumonia. *BMJ* 1975; **3:** 77–8.

Interactions

As for Sodium Polystyrene Sulfonate, p.1465. Calcium ions are released from the resin in the gastrointestinal tract and this may reduce the absorption of tetracycline given by mouth.

Uses and Administration

Calcium polystyrene sulfonate, the calcium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges calcium ions for potassium ions and other cations in the gastrointestinal tract. It is used similarly to sodium polystyrene sulfonate (p.1465) to enhance potassium excretion in the treatment of hyperkalaemia (p.1669) and may be preferred to the sodium resin in patients who cannot tolerate an increase in their sodium load. It is estimated that 1 g of calcium polystyrene sulfonate could bind 1.3 to 2 mmol of potassium but it is unlikely that such figures could be achieved in practice.

It is given orally, in a dose of 15 g three or four times daily, as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content. A dose for children is 1 g/kg daily in divided doses for acute hyperkalaemia, reduced to a maintenance dose of 500 mg/kg daily in divided doses; the oral route is not recommended for neonates.

When oral administration is difficult, calcium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 100 mL of 2% methylcellulose '450' and 100 mL of water and retained, if possible, for at least 9 hours. Initial therapy may involve both oral and rectal routes. Following retention of the enema the colon should be irrigated to remove the resin. Children and neonates may be given rectal doses similar to the oral doses suggested for children.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Resincalcio; RIC Calcio†; ***Austral.:*** Calcium Resonium; ***Austria:*** CPS Pulver; Sorbisterit; ***Belg.:*** Kayexalate; ***Braz.:*** Sorcal; ***Canad.:*** Resonium Calcium; ***Chile:*** Sorbisterit; ***Cz.:*** Calcium Resonium; Resical; Sorbisterit†; ***Denm.:*** Resonium Calcium; ***Ger.:*** Anti-Kalium; Calcium Resonium; CPS Pulver; Elutit-Calcium; Sorbisterit; ***Gr.:*** Calcium Resonium†; ***Hong Kong:*** Calcium Resonium; ***Indon.:*** Kalitake; ***Irl.:*** Calcium Resonium; ***Jpn:*** Kalimate; ***Malaysia:*** Kalimate; ***Neth.:*** Sorbisterit; ***Norw.:*** Resonium Calcium; ***NZ:*** Calcium Resonium; ***Philipp.:*** Kalimate; ***Pol.:*** Calcium Resonium; ***Port.:*** Resical; ***Spain:*** Resincalcio; ***Swed.:*** Resonium Calcium; ***Switz.:*** Sorbisterit; ***Thai.:*** Kalimate; Resincalcio; ***Turk.:*** Anti-potasium; ***UK:*** Calcium Resonium.

Deferasirox *(USAN, rINN)*

CGP-72670; Déférasirox; Deferasiroxum; ICL-670; ICL-670A. 4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.

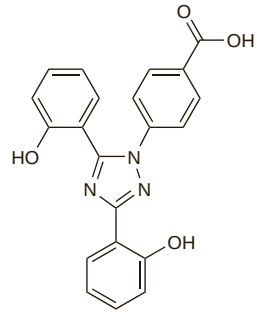
Деферазирокс

$C_{21}H_{15}N_3O_4$ = 373.4.

CAS — 201530-41-8.

ATC — V03AC03.

ATC Vet — QV03AC03.



Adverse Effects and Precautions

The commonest adverse effects with deferasirox are dose-related gastrointestinal disorders, such as nausea, vomiting, diarrhoea, and abdominal pain; diarrhoea may be more common in young children. Skin rashes are also common and may respond to a reduction in dose. Other adverse effects include headache, pyrexia, and cough.

Dose-dependent increases in serum creatinine are common and proteinuria may also occur; there have been reports of acute renal failure, including fatalities. Serum creatinine should be measured before starting deferasirox, and renal function should be assessed weekly for the first month (particularly in patients with risk factors for renal disease) and for a month after dosage increases, then monthly thereafter; tests for proteinuria should also be performed monthly. The dose should be reduced or treatment stopped if persistent increases in serum creatinine occur.

Liver enzyme values may increase in patients receiving deferasirox, and cases of hepatitis have occurred; gallstones and related biliary disorders have also been reported. Liver enzymes should be monitored monthly and treatment should be stopped if persistent increases occur.

As with other iron chelators, hearing loss and visual disorders, including cataracts, have occurred. Audiological and ophthalmological tests should be performed before starting deferasirox and then every 12 months. Serum ferritin should be measured monthly. In children, annual assessment of growth and development is also recommended.

There have been rare reports of blood disorders, some of which have been fatal, including agranulocytosis, neutropenia, and thrombocytopenia, in patients taking deferasirox. Blood counts should be monitored regularly.

Interactions

Deferasirox should not be given with aluminium-containing antacids since there is a possibility that it may chelate aluminium.

Pharmacokinetics

Deferasirox is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.5 to 4 hours after ingestion. The absolute bioavailability is about 70% but is increased in the presence of food. Deferasirox is about 99% bound to plasma proteins, mainly albumin. It is metabolised by glucuronidation and is excreted mainly in the faeces via bile, as metabolites and as unchanged drug; there is a possibility that enterohepatic recycling may occur. About 8% of a dose is excreted in the urine. The mean elimination half-life is about 8 to 16 hours.

Uses and Administration

Deferasirox is an orally active iron chelator that is used in the management of chronic iron overload (p.1442) due to blood transfusion. It is available as tablets that are made into a suspen-