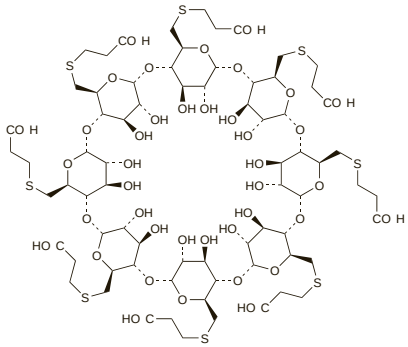
Sugammadex Sodium *(USAN, rINNM)*

Natrii Sugammadexum; Org-25969; Sugammadex sódico; Sugammadex Sodique.

Натрий Сугаммадекс

$C_{72}H_{104}Na_8O_{48}S_8$ = 2178.0.

CAS — 343306-79-6.



(sugammadex)

Profile

Sugammadex sodium is a modified gamma cyclodextrin under investigation as a selective relaxant binding agent for the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

◊ Reviews.

1. Nicholson WT, *et al.* Sugammadex: a novel agent for the reversal of neuromuscular blockade. *Pharmacotherapy* 2007; **27:** 1181–8.

Tiopronin *(rINN)*

Thiopronine; Thioproninum; Tioproniini; Tiopronina; Tiopronine; Tioproninum. *N*-(2-Mercaptopropionyl)glycine.

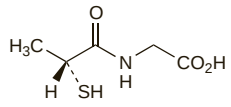
Тиопронин

$C_5H_9NO_3S$ = 163.2.

CAS — 1953-02-2.

ATC — R05CB12.

ATC Vet — QG04BC90; QR05CB12.



and enantiomer

Adverse Effects and Precautions

Tiopronin has similar adverse effects and precautions to those of penicillamine (p.1456).

Incidence of adverse effects. In a study of 140 patients[1] with rheumatoid arthritis receiving long-term treatment with tiopronin, adverse effects necessitated withdrawal of treatment in 56 patients (40%). The majority of adverse effects occurred within the first 6 months of treatment. The most common were those affecting the skin and mucous membranes (46 patients) including stomatitis, pruritus, erythema, and 1 case of pemphigus. Proteinuria developed in 5 patients and nephrotic syndrome in 3. Haematological disorders developed in 13 patients. Gastrointestinal disorders and ageusia were also reported.

In another study of 74 patients[2] with rheumatoid arthritis adverse effects were reported in 32 patients (43%) and necessitated withdrawal in 24%. The most common adverse effects were ageusia (21%), mucocutaneous lesions (16%), and gastrointestinal disturbances (14%). Haematological disorders occurred in 5 patients and proteinuria in 3 patients.

In a comparative study in 200 patients,[3] treatment was withdrawn due to toxicity in 27% of patients taking tiopronin and 21% of patients treated with gold.

1. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.
2. Ehrhart A, *et al.* Effets secondaires dus au traitement par la tiopronine de 74 polyarthrites rhumatoïdes. *Rev Rhum* 1991; **58:** 193–7.
3. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.

Effects on the blood. Haematological disorders including leucopenia or thrombocytopenia have been reported during long-term studies of tiopronin. Isolated cases of agranulocytosis[1] and bone marrow aplasia[2] have also occurred.

See also Incidence of Adverse Effects, above.

1. Corda C, *et al.* Thiopronin-induced agranulocytosis. *Therapie* 1990; **45:** 161.
2. Taillan B, *et al.* Aplasie médullaire au cours d'une polyarthrite rhumatoïde traitée par tiopronine. *Rev Rhum* 1990; **57:** 443–4.

Effects on the kidneys. Proteinuria developed in 3 patients 4 to 14 months after starting treatment with tiopronin for cystinuria.[1] None of the patients had clinical symptoms of nephrotic syndrome. Renal biopsies in 2 patients demonstrated membranous glomerulonephritis. Proteinuria disappeared in all 3 patients 4 to 5 months after tiopronin was discontinued. However, there was histological evidence of irreversible changes and signs of progressive glomerular lesions in 1 patient.

1. Lindell A, *et al.* Membranous glomerulonephritis induced by 2-mercaptopropionylglycine (2-MPG). *Clin Nephrol* 1990; **34:** 108–15.

Effects on the skin. Mucocutaneous lesions are among the most common adverse effects of tiopronin (see Incidence of Adverse Effects, above). Reversible lichenoid eruptions have been reported[1] in a patient after treatment with tiopronin for 2 years, and may have been due to an immunological reaction to the sulfhydryl group. Lesions resembling pemphigus have also been reported in a few patients[2,3] and may require treatment with a corticosteroid or other immunosuppressant.

1. Kurumaji Y, Miyazaki K. Tiopronin-induced lichenoid eruption in a patient with liver disease and positive patch test reaction to drugs with sulfhydryl group. *J Dermatol* 1990; **17:** 176–81.
2. Trotta F, *et al.* Thiopronine-induced pemphigus vulgaris in rheumatoid arthritis. *Scand J Rheumatol* 1984; **13:** 93–5.
3. Verdier-Sevrain S, *et al.* Thiopronine-induced herpetiform pemphigus: report of a case studied by immunoelectron microscopy and immunoblot analysis. *Br J Dermatol* 1994; **130:** 238–40.

Pharmacokinetics

Tiopronin is absorbed from the gastrointestinal tract. Up to 48% of the dose is reported to be excreted in the urine during the first 4 hours and up to 78% by 72 hours.

◊ References.

1. Carlsson SM, *et al.* Pharmacokinetics of intravenous 2-mercaptopropionylglycine in man. *Eur J Clin Pharmacol* 1990; **38:** 499–503.
2. Carlsson MS, *et al.* Pharmacokinetics of oral tiopronin. *Eur J Clin Pharmacol* 1993; **45:** 79–84.

Uses and Administration

Tiopronin is a sulfhydryl compound and chelator with properties similar to those of penicillamine (p.1458). It is given orally in the management of cystinuria, in conjunction with adequate hydration and alkalinisation of the urine, in usual doses of 0.8 to 1 g daily in divided doses. The dose should be adjusted according to the urinary cystine concentration; up to 2 g daily has been given. Tiopronin should be given on an empty stomach. Tiopronin is used in similar doses in rheumatoid arthritis. It has been used in hepatic disorders and heavy-metal poisoning, and has been given by inhalation as a mucolytic in respiratory disorders. It may also be given by intravenous or intramuscular injection.

The sodium salt has also been used.

Cystinuria. Tiopronin may be used as an alternative to penicillamine in the management of cystinuria (p.1459). A multicentre study[1] in 66 patients with cystine nephrolithiasis found that addition of tiopronin in doses of up to 2 g daily (mean 1.193 g) to standard alkali and fluid therapy significantly reduced urinary-cystine concentrations and the rate of new stone formation. Adverse effects were similar to those reported with penicillamine. In the 49 patients who had previously received penicillamine, 41 had adverse effects with penicillamine, requiring cessation of therapy in 34, whereas 37 had adverse effects with tiopronin, requiring drug withdrawal in 15. In the remaining 17 patients, 11 had adverse effects with tiopronin and 1 discontinued treatment because of proteinuria. However, of the 34 patients who had been unable to tolerate penicillamine, 22 were able to continue treatment with tiopronin.

1. Pak CYC, *et al.* Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol (Baltimore)* 1986; **136:** 1003–8.

Mucolytic activity. Studies on the mucolytic activity of tiopronin.

1. Costantini D, *et al.* Evaluation of the therapeutic effectiveness of thiopronine in children with cystic fibrosis. *Curr Ther Res* 1982; **31:** 714–17.
2. Carratù L, *et al.* Clinico-functional and rheological research on mucolytic activity of thiopronine in chronic broncho-pneumopathies. *Curr Ther Res* 1982; **32:** 529–43.

Rheumatoid arthritis. Tiopronin has been reported to have activity comparable to that of gold salts[1] and penicillamine[2] in patients with rheumatoid disease, and has been used to treat rheumatoid arthritis (p.11), particularly in patients intolerant of penicillamine.

1. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; **7:** 577–81.
2. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; **57:** 105–11.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Thiola†; ***Fr.:*** Acadione; ***Ger.:*** Captimer; ***Hong Kong:*** Thiola†; ***Ital.:*** Mucolysin†; Mucosyt†; Thiola; Thiosol; ***Switz.:*** Mucolysin†; ***USA:*** Thiola.

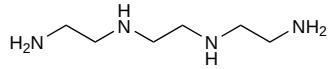
Trientine Dihydrochloride *(BAN, rINNM)*

Dihidrocloruro de trientina; MK-0681; Trien Hydrochloride; Trientin Dihidroklorür; Trientine, Dichlorhydrate de; Trientine Hydrochloride *(USAN)*; Trientini Dihydrochloridum; Triethylenetetramine Dihydrochloride. 2,2′-Ethylenedi-iminobis(ethylamine) dihydrochloride; *N,N′*-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

Триентина Дигидрохлорид

$C_6H_{18}N_4,2HCl$ = 219.2.

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).



(trientine)

Pharmacopoeias. In *US*.

USP 31 (Trientine Hydrochloride). A white to pale yellow crystalline powder. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store under an inert gas in airtight containers at 2° to 8°. Protect from light.

Adverse Effects and Precautions

Trientine may cause nausea and skin rashes; duodenitis and colitis have also been reported. Iron deficiency may occur; if iron supplements are given an interval of at least 2 hours between the doses of trientine and iron has been recommended. Recurrence of symptoms of SLE has been reported in a patient who had previously reacted to penicillamine.

Interactions

Chelation of trientine with metal ions in the diet or in mineral supplements may impair the absorption of both. Trientine should not be taken with mineral supplements and should be taken at least 1 hour apart from food, other drugs, or milk, to reduce the likelihood of absorption being affected. Iron supplements should be taken at least 2 hours before or after trientine.

Uses and Administration

Trientine is a copper chelator used in a similar way to penicillamine in the treatment of Wilson's disease (p.1459). It tends to be used in patients intolerant of penicillamine.

Trientine dihydrochloride is given orally, preferably on an empty stomach. In the USA, the usual initial dose for adults is 0.75 to 1.25 g daily in 2 to 4 divided doses; this may be increased to a maximum of 2 g daily if required. In children, the usual initial dose is 500 to 750 mg daily, increased if necessary to a maximum dose of 1.5 g daily. In the UK, a dose of 1.2 to 2.4 g daily, in 2 to 4 divided doses, has been recommended for adults; children may be given an initial dose of 0.6 to 1.5 g daily.

Preparations

USP 31: Trientine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
USA: Syprine.

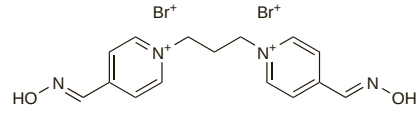
Trimedoxime Bromide *(rINN)*

Bromuro de trimedoxima; Dipyroxime; TMB-4; Trimédoxime, Bromure de; Trimedoximi Bromidum. 1,1′- Trimethylenebis[4-formylpyridinium bromide]dioxime.

Тримедоксима Бромид

$C_{15}H_{18}Br_2N_4O_2$ = 446.1.

CAS — 56-97-3.



NOTE. Do not confuse with Trimedoxine, a range of veterinary antibacterial preparations.

Profile

Trimedoxime bromide is a cholinesterase reactivator given with atropine in the treatment of organophosphorus poisoning.

◊ References.

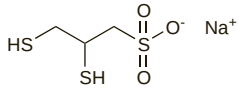
1. Kozer E, *et al.* Pediatric poisoning from trimedoxime (TMB4) and atropine automatic injectors. *J Pediatr* 2005; **146**: 41–4.

Unithiol

DMPS; Unithiolum; Unitiol; Unitioli. Sodium 2,3-dimercaptopropanesulfonate .

$C_3H_7NaO_3S_3$ = 210.3.

CAS — 4076-02-2.



Profile

Unithiol is a chelator structurally related to dimercaprol (p.1444). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds; it has also been used in poisoning with chromium or cadmium, although its efficacy is not established.

Unithiol is given orally in doses of 100 mg three or four times daily in chronic poisoning. In acute poisoning, a dose of 1.2 to 2.4 g by mouth, in divided doses over 24 hours, has been suggested. It may also be given parenterally in patients with severe toxicity; a suggested intravenous dose is 3 to 5 mg/kg every 4 hours, reducing the frequency after 1 to 2 days and then changing to oral therapy.

◊ Reviews.

1. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; **2:** 317–23.
2. Aposhian HV, *et al.* Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology* 1995; **97:** 23–38.

Arsenic poisoning. Complete recovery, without renal or neurological sequelae, has been reported[1,2] following the use of unithiol in patients with potentially lethal acute arsenic poisoning; haemodialysis was also used in 1 patient.[2] Increased urinary arsenic excretion, with some improvement in clinical symptoms, has also been reported[3,4] with unithiol in chronic arsenic toxicity.

1. Moore DF, *et al.* Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). *J Neurol Neurosurg Psychiatry* 1994; **57:** 1133–5.
2. Kruszewska S, *et al.* The use of haemodialysis and 2,3 propanesulphonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide. *Int J Occup Med Environ Health* 1996; **9:** 111–115.
3. Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. *J Toxicol Clin Toxicol* 2000; **38:** 777–80.
4. Guha Mazumder DN, *et al.* Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *J Toxicol Clin Toxicol* 2001; **39:** 665–74.

Lead poisoning. Unithiol may be used in lead poisoning, although other chelators are generally preferred (see Treatment of Adverse Effects under Lead, p.2332). In a study of 12 children[1] it reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.

1. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; **235:** 665–9.

Mercury poisoning. Unithiol is used in poisoning with mercury and mercury salts (see Treatment of Adverse Effects under Mercury, p.2342) and has been given by various routes. In 7 patients with poisoning due to mercury vapour or mercuric oxide, unithiol 100 mg given twice daily by mouth for up to 15 days enhanced urinary elimination of mercury;[1] the urinary elimination of copper and zinc was also increased in most patients and 2 developed skin rashes. A dose of 5 mg/kg intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[2] A patient with severe mercuric chloride poisoning was treated successfully with unithiol given intravenously for 4 weeks, then orally for 3 weeks.[3] Unithiol has also been used with haemofiltration in patients with inorganic mercury poisoning and acute renal failure.[4,5]

1. Mant TGK. Clinical studies with dimercaptopropane sulphonate in mercury poisoning. *Hum Toxicol* 1985; **4:** 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; **218:** 74–83.
3. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13:** 11–16.
4. Pai P, *et al.* Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulphonate [sic]) and continuous haemofiltration. *Nephrol Dial Transplant* 2000; **15:** 1889–90.
5. Dargan PI, *et al.* Case report: severe mercuric sulphate poisoning treated with 2,3-dimercaptopropane-1-sulphonate and haemodiafiltration. *Crit Care* 2003; **7:** R1–R6.

Wilson's disease. Unithiol 200 mg twice daily[1] was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease (p.1459) after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride. Unithiol was started in 2 similar patients[1] but both withdrew from treatment, one because of fever and a fall in leucocyte count after a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *BMJ* 1985; **290:** 673–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dimaval; ***Ger.:*** Dimaval; Mercuval.