Sodium Thiosulfate

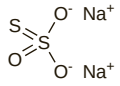
Disodium Thiosulfate Pentahydrate; Hiposulfito sódico; Natrii thiosulfas; Natrii Thiosulfas Pentahydricus; Natrio tiosulfatas; Natrium Thiosulfuricum; Natriumtiosulfaatti; Natriumtiosulfat; Nátrium-tioszulfát; Sodium Hyposulphite; Sodium, thiosulfate de; Sodium Thiosulphate; Sodu tiosiarczan; Sodyum Tiyosülfat; Thiosíran sodný pentahydrát; Tiosulfato sódico.

$Na_2S_2O_3,5H_2O$ = 248.2.

CAS — 7772-98-7 (anhydrous sodium thiosulfate); 10102-17-7 (sodium thiosulfate pentahydrate).

ATC — V03AB06.

ATC Vet — QV03AB06.



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

Ph. Eur. 6.2 (Sodium Thiosulphate). Colourless transparent crystals; efflorescent in dry air. It dissolves in its own water of crystallisation at about 49°. Very soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH of 6.0 to 8.4. Store in airtight containers.

USP 31 (Sodium Thiosulfate). Large, colourless crystals, or a coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33°. Soluble 1 in 0.5 of water; insoluble in alcohol. Its solutions are neutral or faintly alkaline to litmus. Store in airtight containers.

Incompatibility. Sodium thiosulfate may reduce the activity of some preservatives, including bronopol (p.1633), phenylmercuric salts (see Phenylmercuric Nitrate, p.1657), and thiomersal (p.1664).

Stability. Solutions of sodium thiosulfate 50% stored in air developed cloudiness or a deposit after autoclaving.[1] Addition of sodium phosphate 0.5% or 1.2% improved stability but solutions became cloudy or developed a deposit after 12 and 6 weeks respectively at 25°. Solutions containing sodium bicarbonate 0.5% became cloudy or developed a deposit after 12 weeks at 25°. No significant improvement in stability was obtained when the concentration of sodium thiosulfate was reduced to 30% or 15%, or when the injection was sealed under nitrogen.

1. Anonymous. Sodium thiosulphate injection–effect of additives on stability. *PSGB Lab Rep* P/75/3 1975.

Adverse Effects

Apart from osmotic disturbances sodium thiosulfate is relatively non-toxic. Large oral doses have a cathartic action.

Pharmacokinetics

Sodium thiosulfate is poorly absorbed from the gastrointestinal tract. After intravenous injection it is distributed throughout the extracellular fluid and rapidly excreted in the urine.

◊ An intravenous infusion of sodium thiosulfate 12 g/m^2 was given over 6 hours to 8 patients receiving intraperitoneal antineoplastic therapy.[1] The thiosulfate was rapidly eliminated, 95% being excreted within 4 hours of stopping the infusion; on average only 28.5% of the dose was recovered unchanged in the urine. The mean plasma elimination half-life was 80 minutes.

1. Shea M, *et al*. Kinetics of sodium thiosulfate, a cisplatin neutralizer. *Clin Pharmacol Ther* 1984; **35:** 419–25.

Uses and Administration

Sodium thiosulfate is used in the treatment of cyanide poisoning (p.2045). Sodium thiosulfate may be effective alone in less severe cases of cyanide poisoning, but it is often used with sodium nitrite (p.1464).

Sodium thiosulfate acts as a sulfur-donating substrate for the enzyme rhodanese, which catalyses the conversion of cyanide to relatively non-toxic thiocyanate, and thus accelerates the detoxification of cyanide.

The usual dosage regimen in adults is 300 mg of *sodium nitrite* (10 mL of a 3% solution) given intravenously over 5 to 20 minutes followed by 12.5 g of *sodium thiosulfate* (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over a period of about 10 minutes. A suggested dosage regimen in children is about 4 to 10 mg/kg of *sodium nitrite*, given as a 3% solution (0.13 to 0.33 mL/kg) to a maximum of 300 mg (10 mL), followed by about 400 mg/kg of *sodium thiosulfate*, as a 25 or 50% solution (1.65 mL/kg of a 25% solution) to a maximum of 12.5 g (50 mL of a 25% solution). The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses.

Sodium thiosulfate is used as an isotonic 4% solution in the management of extravasation of chlormethine and has been tried in the management of extravasation of some other antineoplastics (but see below).

Sodium thiosulfate has been used for its antifungal properties. Sodium thiosulfate and magnesium thiosulfate are included in mixed preparations for a variety of disorders.

Antineoplastic toxicity. Sodium thiosulfate may be used in the management of extravasation of chlormethine and some other antineoplastics (although this is a contentious area, see p.640). It is also used to inactivate some antineoplastics before disposal.

Sodium thiosulfate, given by intravenous infusion, has also been investigated for reducing the systemic toxicity of some antineoplastics. It has been reported to reduce the incidence of nephrotoxicity associated with intraperitoneal cisplatin (see Prophylaxis under Effects on the Kidneys, p.699) and to reduce hearing loss associated with carboplatin (see Effects on the Ears, p.693).

Bromate poisoning. Sodium thiosulfate has been used in the treatment of bromate poisoning[1,2] although its clinical efficacy is unclear;[3] it is thought to act by reducing bromate to the less toxic bromide ion, but evidence is lacking.[3,4] Although it has been given orally, this is no longer recommended since toxic sulfide may be formed.[4] However, intravenous sodium thiosulfate may have a role in some clinical circumstances.[4,5]

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; **7:** 66–70.
2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; **114:** 891–4.
3. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 570, 572.
4. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; **12:** 204–9.
5. Johnson CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; **7:** 572.

Preparations

BP 2008: Sodium Thiosulphate Injection;
USP 31: Sodium Thiosulfate Injection.

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Azufracid; ***Austria:*** Schwefelbad Dr Klopfer; ***Braz.:*** Dessensibilizante Chauvin†; ***Canad.:*** Adasept; ***Cz.:*** Carbotox; ***Fr.:*** Desintex; Desintex Infantile; Desintex-Choline; Rhino-Sulfuryl; Vagostabyl; ***Ger.:*** Corti Jaikal†; Jaikal†; Schwefelbad Dr Klopfer; Sulfuretten†; ***Hung.:*** Schwefelbad Dr Klopfer; ***Ital.:*** Antimicotica Solforata; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package; Tinver; Versiclear.

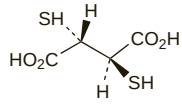
Succimer *(BAN, USAN, rINN)*

DIM-SA; DMSA; Succimère; Succímero; Succimero; Succimerum; Suksimeeri. *meso*-2,3-Dimercaptosuccinic acid; (*R**,*S**)-2,3-Dimercapto-butanedioic acid.

Сукцимер

$C_4H_6O_4S_2$ = 182.2.

CAS — 304-55-2.



Pharmacopoeias. In *Chin.*

Adverse Effects and Precautions

Succimer may cause gastrointestinal disorders, skin rashes, increases in serum transaminase, flu-like symptoms, drowsiness, and dizziness. Mild to moderate neutropenia has been reported in some patients and regular full blood counts are recommended during therapy. Succimer should be used with caution in patients with renal impairment or a history of hepatic disease.

Pharmacokinetics

Succimer is rapidly but incompletely absorbed after oral doses. It undergoes rapid and extensive metabolism and is excreted mainly in the urine with small amounts excreted in the bile and via the lungs.

◊ References.

1. Dart RC, *et al.* Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; **125:** 309–16.

Uses and Administration

Succimer is a chelator structurally related to dimercaprol (p.1444). It forms water-soluble chelates with heavy metals and is used in the treatment of lead poisoning. It has also been used in the treatment of poisoning with arsenic or mercury.

Succimer, labelled with a radionuclide, is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given orally in a dose of 10 mg/kg or 350 mg/m^2 every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks.

Lead poisoning. Succimer is an effective lead chelator[1] and is used in the management of lead poisoning (see Treatment of Adverse Effects under Lead, p.2332). Succimer is also used in children with chronic lead exposure, and various dosage regimens have been studied.[2] It is generally only indicated if blood-lead concentrations are greater than 45 micrograms per 100 mL;[3] although short-term studies[4] in children with lower concentrations have shown effective reduction of blood lead, no effect on neurodevelopmental outcome has been shown in follow-up studies[5,6] and treatment of such children remains controversial.

1. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; **10:** 914–22.
2. Farrar HC, *et al.* A comparison of two dosing regimens of succimer in children with chronic lead poisoning. *J Clin Pharmacol* 1999; **39:** 180–3.
3. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; **116:** 1036–46. Also available at: http://pediatrics.aappublications.org/cgi/reprint/116/4/1036 (accessed 11/10/05)
4. Besunder JB, *et al.* Short-term efficacy of oral dimercaptosuccinic acid in children with low to moderate lead intoxication. *Pediatrics* 1995; **96:** 683–7.
5. Rogan WJ, *et al.* The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; **344:** 1421–6.
6. Dietrich KN, *et al.* Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. *Pediatrics* 2004; **114:** 19–26.

Mercury poisoning. Succimer, given orally, increases the renal excretion of mercury and may be used in mercury poisoning (see Treatment of Adverse Effects under Mercury, p.2342). In patients with renal impairment, the succimer-mercury chelate may accumulate, and alternative methods have been tried. Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.[1] Clearance was about ten times greater than that achieved with haemodialysis after intramuscular dimercaprol.

1. Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; **9:** 137–41.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Succicaptal; ***USA:*** Chemet.

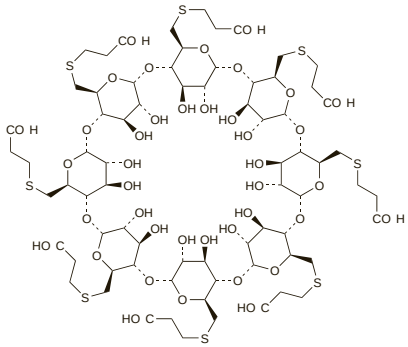
Sugammadex Sodium *(USAN, rINNM)*

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.

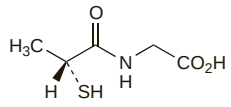
Тиопронин

$C_5H_9NO_3S$ = 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.

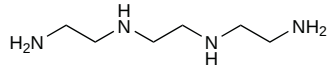
Trientine Dihydrochloride *(BAN, rINNM)*

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.

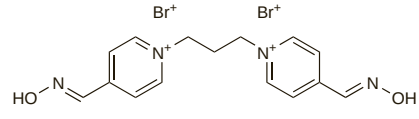
Trimedoxime Bromide *(rINN)*

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.