excreted in the urine. Sodium thiosulfate provides an additional source of sulfur for this reaction and this accelerates the process.

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 nitrite has also been suggested in the treatment of hydrogen sulfide poisoning (see p.1690).

Sodium nitrite has been used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats but should not be used in food for infants under the age of 3 months due to the risk of methaemoglobinaemia. Potassium nitrite is also used as a food preservative.

### Preparations

***USP 31:*** Sodium Nitrite Injection.

**Proprietary Preparations** (details are given in Part 3)
***Austral.:*** O A R†.

**Multi-ingredient:** ***Ital.:*** Citrosil Alcolico Azzuro; ***S.Afr.:*** Tripac-Cyano; ***USA:*** Cyanide Antidote Package.

## Sodium Polystyrene Sulfonate

Natrii polystyrenesulfonas; Natrii Polystyrensulfonas; Natrio polistirensulfonatas; Natriumpolystyreenisulfonaatti; Natriumpolystyrensulfonat; Natrium-polystyrensulfonát; Poliestirenosulfonato sódico; Polystyrène sulfonate sodique; Sodium Polystyrene Sulphonate.

*CAS — 9003-59-2; 9080-79-9; 25704-18-1.*

*ATC — V03AE01.*

*ATC Vet — QV03AE01.*

**Pharmacopoeias.** In *Eur.* (see p.vii), *Jpn*, and *US*.
**Ph. Eur. 6.2** (Sodium Polystyrene Sulphonate). An almost white to light brown powder. It contains 9.4 to 11.0% of sodium, calculated with reference to the dried substance. Each g exchanges 2.8 mmol to 3.4 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in dichloromethane. Store in airtight containers.
**USP 31** (Sodium Polystyrene Sulfonate). A golden brown, fine, odourless powder containing not more than 10% of water. The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis. Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis. Insoluble in water.

### Adverse Effects

Anorexia, nausea, vomiting, constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate. Constipation may be severe; large doses in elderly patients and in children may result in faecal impaction and gastrointestinal concretions have occurred after oral use in neonates. If necessary a mild laxative may be used to prevent or treat constipation (but see Precautions, below, for laxatives that should be avoided).

Serious potassium deficiency can occur with sodium polystyrene sulfonate and signs of severe hypokalaemia may include irritability, confusion, ECG abnormalities, cardiac arrhythmias, and severe muscle weakness. Like other cation-exchange resins, sodium polystyrene sulfonate is not totally selective and its use may result in other electrolyte disturbances such as hypocalcaemia. Significant sodium retention may also occur, especially in patients with renal impairment, and may lead to heart failure.

**Effects on the gastrointestinal tract.** Colonic necrosis, including some fatalities, has been reported[1-3] after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in *animals*[1] suggested that the use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested[4,5] as a possible cause. Both colonic[6] and upper gastrointestinal necrosis[7] have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there has also been a report[8] of colonic necrosis with oral sodium polystyrene sulfonate alone.


1. Lillemoe KD, *et al.* Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; **101:** 267–72.
2. Wootton FT, *et al.* Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; **111:** 947–9.
3. Rogers FB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* 2001; **51:** 395–7.
4. Burnett RJ. Sodium polystyrene-sorbitol enemas. *Ann Intern Med* 1990; **112:** 311–12.
5. Shepard KV. Cleansing enemas after sodium polystyrene sulfonate enemas. *Ann Intern Med* 1990; **112:** 711.
6. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997; **21:** 60–9.
7. Abraham SC, *et al.* Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; **25:** 637–44.
8. Cheng ES, *et al.* Colonic necrosis and perforation following oral sodium polystyrene sulfonate (Resonium A /Kayexelate ) in a burn patient. *Burns* 2002; **28:** 189–90.


**Effects on the lungs.** Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of 3 patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in 2 and with early bronchitis in the third.[1] It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.


1. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; **142:** 379–81.


### Precautions

Sodium polystyrene sulfonate should not be given orally to neonates, and is contra-indicated by any route in neonates with reduced gut motility or in any patient with obstructive bowel disease. Care is also needed with rectal use in neonates and children in order to avoid impaction of the resin. Treatment should be discontinued if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis in patients receiving this combination (see Effects on the Gastrointestinal Tract, above) and licensed product information advises against the use of sorbitol with polystyrene sulfonates. Magnesium-containing laxatives are also contra-indicated (see Interactions, below).

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Use of sodium polystyrene sulfonate can result in sodium overloading and it should be used cautiously in patients with renal failure or conditions requiring a restricted sodium intake, such as heart failure and severe hypertension; calcium polystyrene sulfonate (p.1438) may be preferred in these patients.

The possible effects of sodium polystyrene sulfonate on serum electrolytes should be considered when interpreting diagnostic measurements.

After use of sodium polystyrene sulfonate retention enemas, the colon should be irrigated to ensure removal of the resin.

### Interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, particularly in patients with renal impairment, metabolic alkalosis may develop due to binding of the cation by the resin; this prevents neutralisation of bicarbonate ions in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine (see p.2173) and lithium salts.

Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

### Uses and Administration

Sodium polystyrene sulfonate, the sodium salt of sulfonated styrene copolymer with divinylbenzene, is a cation-exchange resin that exchanges sodium ions for potassium ions and other cations in the gastrointestinal tract when given orally or rectally. The exchanged resin is then excreted in the faeces. Each gram of resin exchanges about 3 mmol of potassium *in vitro*, and about 1 mmol *in vivo*.

Sodium polystyrene sulfonate is used to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria (caution is required due to the sodium content). An effect may not be evident for several hours or longer, and in severe hyperkalaemia, where a rapid effect is required, other measures must also be considered (see p.1669).

Serum-electrolyte concentrations should be monitored throughout treatment and doses given according to response.

The usual oral dose is 15 g up to 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 suggested oral dose for children is 1 g/kg daily in divided doses for acute hyperkalaemia, reduced to a maintenance dose of 500 mg/kg daily; the oral route is not recommended for neonates.

When oral use is difficult, sodium 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; higher doses, shorter retention times, and alternative vehicles have also been used. After retention of the enema the colon should be irrigated to remove the resin. Initial therapy may involve both oral and rectal routes. Children and neonates may be given rectal doses similar to the oral doses suggested for children; particular care is needed with rectal use in children as excessive dosage or inadequate dilution could result in impaction of resin.

Other polystyrene sulfonate resins include calcium polystyrene sulfonate (p.1438), which is used similarly to the sodium resin and potassium polystyrene sulfonate (p.1460), which has been used in the treatment of hypercalciuria. Aluminium polystyrene sulfonate, ammonium polystyrene sulfonate, and magnesium polystyrene sulfonate have all occasionally been used.

### Preparations

***USP 31:*** Sodium Polystyrene Sulfonate Suspension.

**Proprietary Preparations** (details are given in Part 3)
***Austral.:*** Resonium A; ***Austria:*** Resonium A; ***Belg.:*** Kayexalate; ***Canad.:*** K-Exit; Kayexalate; ***Denm.:*** Resonium; ***Fin.:*** Resonium; ***Fr.:*** Kayexalate; ***Ger.:*** Elutit-Natrium; Resonium A; ***Gr.:*** Kayexalate; ***Hong Kong:*** Resonium A; ***Hung.:*** Resonium A; ***Irl.:*** Resonium A†; ***Israel:*** Kayexalate; ***Ital.:*** Kayexalate; ***Malaysia:*** Resonium A†; ***Neth.:*** Resonium A; ***NZ:*** Resonium A; ***Pol.:*** Resonium A; ***Port.:*** Resonium; ***S.Afr.:*** Kexelate; ***Singapore:*** Resinsodio; ***Spain:*** Resinsodio; ***Swed.:*** Resonium; ***Switz.:*** Resonium A; ***Thai.:*** Kayexalate; Resinsodio; Resonium A; ***UK:*** Resonium A; ***USA:*** Kayexalate; Kionex; SPS; ***Venez.:*** Kayexalate.

**Multi-ingredient:** ***Ger.:*** Ujostabil†.

## Sodium Thiosulfate

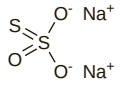
Disodium Thiosulfate Pentahydrate; Hiposulfito sódico; Natrii thiosulfas; Natrii Thiosulfas Pentahydricus; Natrio tiosulfatas; Natrium Thiosulfuricum; Natriumtiosulfaatti; Natriumtiosulfat; Nátrium-tioszulfát; Sodium Hyposulphite; Sodium, thiosulfate de; Sodium Thiosulphate; Sodu tiosiarczan; Sodyum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

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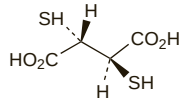
## Succimer *(BAN, USAN, rINN)*

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.