NOTE. Prussian blue is available in a number of forms and it is not always clear from the literature which form is being referred to. CI Pigment Blue 27 has been used for both insoluble ferric hexacyanoferrate (II) (Colour Index No. 77510) and the soluble potassium, sodium, or ammonium ferric hexacyanoferrate (II) salts

Profile

Prussian blue is used in the treatment of thallium poisoning (see p.2400) and for known or suspected internal contamination with radiocaesium. When given orally it forms a non-absorbable complex with thallium or caesium in the gastrointestinal tract and increases their elimination from the body; it may also bind other elements and patients should be monitored for electrolyte imbalances. Prussian blue may cause constipation and a fibre-based laxative is recommended.

The usual dose of Prussian blue is 250 to 300 mg/kg daily, or up to 20 g daily for an adult, given in divided doses either by mouth or by nasogastric or duodenal tube. In the USA, a lower dose of 3 g three times daily for adults, or 1 g three times daily for children, has been recommended. For thallium poisoning, treatment should continue until the urinary excretion of thallium falls to 500 micrograms or less per 24 hours, the urine or blood concentration is less than 10 micrograms/L, or no thallium can be detected in the faeces. For radiocaesium contamination, a minimum of 30 days treatment should be given.

◊ References.

1. Thompson DF, Church CO. Prussian blue for treatment of radiocesium poisoning. *Pharmacotherapy* 2001; **21:** 1364–7.
2. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22:** 29–40.
3. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; **38:** 1509–14.

Preparations

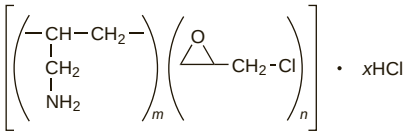
Proprietary Preparations (details are given in Part 3)
Cz.: Radiogardase-Cs; ***Ger.:*** Antidotum Thallii-Heyl; Radiogardase-Cs; ***USA:*** Radiogardase.

Sevelamer *(BAN, rINN)*

Sevelameeri; Sévélamer; Sevelámero; Sevelamerum. Allylamine polymer with 1-chloro-2,3-epoxypropane.

Севеламер

CAS — 52757-95-6.
ATC — V03AE02.
ATC Vet — QV03AE02.



Sevelamer Carbonate *(BANM, USAN, rINNM)*

Carbonato de sevelámero; GT-335-012; Sévélamer Carbonate; Sevelameri Carbonas. Allylamine polymer with 1-chloro-2,3-epoxypropane carbonate.

Севеламера Карбонат

CAS — 845273-93-0.
ATC — V03AE02.
ATC Vet — QV03AE02.

Sevelamer Hydrochloride *(BANM, USAN, rINNM)*

GT16-026A; Hidrocloruro de sevelámero; Sévélamer, Chlorhydrate de; Sevelameri Hydrochloridum. Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride.

Севеламера Гидрохлорид

CAS — 182683-00-7.
ATC — V03AE02.
ATC Vet — QV03AE02.

NOTE. The name sevelamer has been used for both sevelamer and sevelamer hydrochloride.

Adverse Effects and Precautions

The most common adverse effects associated with sevelamer are diarrhoea, nausea and vomiting, constipation, headache, cough and other respiratory symptoms, dizziness, hypotension or hypertension, peripheral oedema, pain, and fever. Flatulence, pharyngitis, skin rashes, and pruritus have also occurred; intestinal obstruction and ileus have been reported.

Sevelamer is contra-indicated in patients with hypophosphataemia and in bowel obstruction. Patients with renal impairment may develop hypocalcaemia or hypercalcaemia, and serum-calcium concentrations should be monitored. Serum-chloride concentrations should also be monitored during treatment with sevelamer.

Interactions

Sevelamer has been reported to reduce the bioavailability of ciprofloxacin and should not be taken at the same time. It may also affect the bioavailability of other drugs and should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

Uses and Administration

Sevelamer is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure on haemodialysis. It is given orally as either the carbonate or the hydrochloride. The initial dose is 0.8 to 1.6 g of sevelamer carbonate or sevelamer hydrochloride three times daily with each meal, depending on the severity of hyperphosphataemia. Doses should then be adjusted according to plasma-phosphate concentrations; the usual maintenance dose is from 0.8 to 4 g with each meal.

◊ References.

1. Burke SK. Renagel : reducing serum phosphorus in haemodialysis patients. *Hosp Med* 2000; **61:** 622–7.
2. Qunibi WY, *et al.* Treatment of hyperphosphatemia in hemodialysis patients: The Calcium Acetate Renagel Evaluation (CARE Study). *Kidney Int* 2004; **65:** 1914–26.
3. Almirall J, *et al.* Safety and efficacy of sevelamer in the treatment of uncontrolled hyperphosphataemia of haemodialysis patients. *Nephron Clin Pract* 2004; **97:** c17–c22.
4. Duggal A, *et al.* Novel dosage forms and regimens for sevelamer-based phosphate binders. *J Ren Nutr* 2006; **16:** 248–52.
5. Fischer D, *et al.* Results of a randomized crossover study comparing once-daily and thrice-daily sevelamer dosing. *Am J Kidney Dis* 2006; **48:** 437–44.
6. Suki WN, *et al.* Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007; **72:** 1130–7.
7. Tonelli M, *et al.* Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; **22:** 2856–66.
8. Ramos R, *et al.* The Catalano–Balear Peritoneal Dialysis Study Group. Sevelamer hydrochloride in peritoneal dialysis patients: results of a multicenter cross-sectional study. *Perit Dial Int* 2007; **27:** 697–701.
9. Delmez J, *et al.* A randomized, double-blind, crossover design study of sevelamer hydrochloride and sevelamer carbonate in patients on hemodialysis. *Clin Nephrol* 2007; **68:** 386–91.
10. Suki WN. Dialysis Clinical Outcomes Revisited Investigators. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. *J Ren Nutr* 2008; **18:** 91–8.
11. Goldsmith DR, *et al.* Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. *Drugs* 2008; **68:** 85–104.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Renagel; ***Belg.:*** Renagel; ***Canad.:*** Renagel; ***Cz.:*** Renagel; ***Denm.:*** Renagel; ***Fin.:*** Renagel; ***Fr.:*** Renagel; ***Ger.:*** Renagel; ***Gr.:*** Renagel; ***Hong Kong:*** Renagel; ***Hung.:*** Renagel; ***Irl.:*** Renagel; ***Israel:*** Renagel; ***Ital.:*** Renagel; ***Jpn:*** Renagel; ***Neth.:*** Renagel; ***Norw.:*** Renagel; ***Pol.:*** Renagel; ***Port.:*** Renagel; ***Spain:*** Renagel; ***Swed.:*** Renagel; ***Switz.:*** Renagel; ***Turk.:*** Renagel; ***UK:*** Renagel; ***USA:*** Renagel; Renvela.

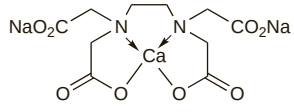
Sodium Calcium Edetate *(BAN, rINN)*

Calcioedetato de sodio; Calcium Disodium Edathamil; Calcium Disodium Edetate; Calcium Disodium Ethylenediaminetetra-acetate; Calcium Disodium Versenate; Calcium édétate de sodium; Calcium EDTA; Disodium Calcium Tetracemate; E385; Edetan sodno-vápenatý hydrát; Edetate Calcium Disodium *(USAN)*; Kalcium-nátrium-edetát; Natrii calcii edetas; Natrii Calcii Edetas Hydricus; Natrio-kalcio edetatas; Natriumkalciumedetat; Natriumkalsiumedetaatti; Sodium, calcium édétate de; Sodium Calciumedetate; Sodu wapnia edetynian; Sodyum Kalsiyum Edetat; Wapniowo-disodowy edetynian. The calcium chelate of disodium ethylenediaminetetra-acetate; Disodium[(ethylenedinitrilo)tetraacetato]calciate(2–) hydrate.

Натрия Кальция Эдетат

$C_{10}H_{12}CaN_2Na_2O_8.xH_2O$ = 374.3 (anhydrous).

CAS — 62-33-9 (anhydrous sodium calcium edetate); 23411-34-9 (sodium calcium edetate hydrate).



NOTE. Do not confuse with sodium edetate; see Inappropriate Administration under Sodium Edetate, p.1464.

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

Ph. Eur. 6.2 (Sodium Calcium Edetate). A white or almost white, hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 6.5 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Edetate Calcium Disodium). White, slightly hygroscopic, odourless, crystalline powder or granules. Freely soluble in water. pH of a 20% solution in water is between 6.5 and 8.0. Store in airtight containers.

Adverse Effects

Sodium calcium edetate is nephrotoxic and may cause renal tubular necrosis. Nausea, diarrhoea, and abdominal cramp may also occur. Thrombophlebitis has followed intravenous infusion and may be related to the concentration of the injection. Pain at the intramuscular injection site has been reported. Other adverse effects that have been reported include fever, malaise, headache, myalgia, histamine-like responses such as sneezing, nasal congestion, and lachrymation, skin eruptions, transient hypotension, and ECG abnormalities.

Sodium calcium edetate chelates zinc within the body and zinc deficiency has been reported. Displacement of calcium from sodium calcium edetate may lead to hypercalcaemia.

Effects on the kidneys. Of 130 children with lead poisoning who received chelation therapy with sodium calcium edetate (25 mg/kg intramuscularly every 12 hours) and dimercaprol (3 mg/kg intramuscularly every 4 hours) for a total of 5 days, 21 developed clinical evidence of nephrotoxicity and in 4 severe oliguric acute renal failure began 1 or 2 days after chelation therapy was discontinued.[1] Nephrotoxicity was probably attributable to the use of sodium calcium edetate.

1. Moel DI, Kumar K. Reversible nephrotic reactions to a combined 2,3-dimercapto-l-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics* 1982; **70:** 259–62.

Precautions

Sodium calcium edetate should be used with caution, if at all, in patients with renal impairment. Daily urinalysis to monitor proteinuria and haematuria and regular monitoring of renal and hepatic function has been recommended.

Sodium calcium edetate can chelate several endogenous metals, including zinc, and may increase their excretion; therapy should be intermittent to prevent severe deficiency developing and monitoring of zinc levels may be required (see below).

Sodium calcium edetate should not be given orally in the treatment of lead poisoning as it has been suggested that absorption of lead may be increased as a result.

◊ Sodium calcium edetate 500 mg/m^2 was given by deep intramuscular injection every 12 hours for 5 days to 10 children with asymptomatic lead poisoning.[1] Blood-lead concentrations decreased to about 58% of the pretreatment values after 5 days and were essentially unchanged for up to 60 hours after the last dose. Sodium calcium edetate also produced a marked fall in the mean plasma-zinc concentration but this rebounded rapidly after the end of treatment. Mean urinary-lead excretion increased about 21-fold during the first 24 hours of therapy and urinary-zinc excretion increased about 17-fold. Sodium calcium edetate had little effect on the plasma concentrations or urinary excretion of copper. The results suggested that careful monitoring of zinc was required during treatment with sodium calcium edetate.

1. Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium disodium ethylenediamine tetraacetate treatment of lead-poisoned children. *J Pharmacol Exp Ther* 1986; **239:** 829–35.

Pharmacokinetics

Sodium calcium edetate is poorly absorbed from the gastrointestinal tract. It distributes primarily to the extracellular fluid and does not penetrate cells. It is not significantly metabolised; after intravenous injection about 50% of a dose is excreted in the urine in 1 hour and over 95% in 24 hours.

Uses and Administration

Sodium calcium edetate is the calcium chelate of disodium edetate and is a chelator used in the treatment of lead poisoning (see Treatment of Adverse Effects under Lead, p.2332). It mobilises lead from bone and tissues and aids elimination from the body by forming a stable, water-soluble, lead complex which is readily

excreted by the kidneys. It may be used as a diagnostic test for lead poisoning but measurement of blood-lead concentrations is generally preferred.

Sodium calcium edetate is also a chelator of other heavy-metal polyvalent ions, including chromium. A cream containing sodium calcium edetate 10% has been used in the treatment of chrome ulcers and skin sensitivity reactions due to contact with heavy metals.

Sodium calcium edetate is also used as a pharmaceutical excipient and as a food additive.

In the treatment of lead poisoning, sodium calcium edetate may be given by intramuscular injection or by intravenous infusion. The intramuscular route may be preferred in patients with lead encephalopathy and increased intracranial pressure in whom excess fluids must be avoided, and also in children, who have an increased risk of incipient encephalopathy. Sodium calcium edetate may initially aggravate the symptoms of lead toxicity due to mobilisation of stored lead and it has often been given with dimercaprol (p.1444) in patients who are symptomatic; the first dose of dimercaprol should preferably be given at least 4 hours before the sodium calcium edetate.

For intravenous infusion, 1 g of sodium calcium edetate should be diluted with 250 to 500 mL of glucose 5% or sodium chloride 0.9%; a concentration of 3% should not be exceeded. The infusion should be given over a period of at least 1 hour. In the UK, the usual dose is 60 to 80 mg/kg daily given in two divided doses. In the USA, a dose of 1000 mg/m^2 daily is suggested for asymptomatic adults and children; a daily dose of 1500 mg/m^2 may be used in patients with symptomatic poisoning. Treatment is given for up to 5 days, repeated if necessary after an interval of at least 2 days. Any further treatment with sodium calcium edetate should then not be given for at least 7 days.

Alternatively, the same daily dose of sodium calcium edetate may be given intramuscularly in 2 to 4 divided doses as a 20% solution. Intramuscular injection of sodium calcium edetate is painful and it is recommended that preservative-free procaine hydrochloride should be added to a concentration of 0.5 to 1.5% to minimise pain; alternatively, lidocaine may be added to a concentration of 0.5%.

As excretion is mainly renal, an adequate urinary flow must be established and maintained during treatment. Doses should be reduced in patients with renal impairment (see below).

Administration in renal impairment. The dose of sodium calcium edetate should be reduced in patients with renal impairment. It has been suggested that the dose is halved and given once daily in moderate impairment, and that smaller and less frequent doses are given if renal impairment is severe.

Preparations

BP 2008: Sodium Calcium Edetate Intravenous Infusion;
USP 31: Edetate Calcium Disodium Injection.

Proprietary Preparations (details are given in Part 3)

Ger.: Calcium Vitis†; ***Gr.:*** Ledclair; ***Irl.:*** Ledclair; ***Switz.:*** Chelintox†; ***Turk.:*** Libenta; ***UK:*** Ledclair.

Multi-ingredient: ***Arg.:*** Calcium C.

Sodium Cellulose Phosphate

Cellulose Sodium Phosphate *(USAN)*; Celulosa, fosfato sódico de.

CAS — 9038-41-9; 68444-58-6.

ATC — V03AG01.

ATC Vet — QV03AG01.

Pharmacopoeias. In *US*.

USP 31 (Cellulose Sodium Phosphate). It is prepared by the phosphorylation of alpha cellulose. A free-flowing, cream-coloured, odourless, powder. Insoluble in water, in dilute acids, and in most organic solvents. The pH of a filtrate of a 5% mixture in water is between 6.0 and 9.0. The inorganic bound phosphate content is not less than 31.0% and not more than 36.0%; the free phosphate content is not more than 3.5%; and the sodium content is not less than 9.5% and not more than 13.0%, all calculated on the dried basis. The calcium binding capacity, calculated on the dried basis, is not less than 1.8 mmol per g.

Adverse Effects and Precautions

Diarrhoea and other gastrointestinal disturbances have been reported.

Sodium cellulose phosphate should not be given to patients with primary or secondary hyperparathyroidism, hypomagnesaemia, hypocalcaemia, bone disease, or enteric hyperoxaluria. It should be used cautiously in pregnant women and children, since they have high calcium requirements.

Patients should be monitored for electrolyte disturbances. Uptake of sodium and phosphate may increase and sodium cellulose phosphate should not be given to patients with renal failure or conditions requiring a restricted sodium intake such as heart failure. Theoretically, long-term treatment could result in calcium deficiency; regular monitoring of calcium and parathyroid hormone has therefore been recommended. Sodium cellulose phosphate is not a totally selective exchange resin and the intestinal absorption of other dietary cations may be reduced; magnesium deficiency has been reported but may be corrected by dosage reduction or oral magnesium supplements. Urinary excretion of oxalate may increase and dietary restriction of oxalate intake may be necessary.

◊ Potential complications of long-term sodium cellulose phosphate therapy include secondary hyperparathyroidism and bone disease; deficiency of magnesium, copper, zinc, and iron; and hyperoxaluria. A study in 18 patients[1] with absorptive hypercalciuria and recurrent renal stones indicated that these complications could largely be avoided if use was confined to those with absorptive hypercalciuria (hypercalciuria, intestinal hyperabsorption of calcium, and normal or suppressed parathyroid function), if the dose was adjusted so as not to reduce intestinal calcium absorption or urinary calcium subnormally (the optimal maintenance dose in most patients was 10 g daily), if oral magnesium supplements were provided, and if a moderate dietary restriction of calcium and oxalate was imposed. There was no evidence of zinc, copper, or iron deficiency.

1. Pak CYC. Clinical pharmacology of sodium cellulose phosphate. *J Clin Pharmacol* 1979; **19:** 451–7.

Interactions

Sodium cellulose phosphate binds with calcium and other cations. Use with calcium or magnesium salts, including cation-donating antacids or laxatives, may reduce its efficacy. Magnesium supplements are often required in patients receiving sodium cellulose phosphate but should be given at least one hour before or after any dose of the resin since the absorption of the magnesium may otherwise be impaired.

Uses and Administration

Sodium cellulose phosphate, the sodium salt of the phosphate ester of cellulose, is a cation-exchange resin that exchanges sodium ions for calcium and other divalent cations. When given orally, it binds calcium ions within the stomach and intestine to form a non-absorbable complex which is excreted in the faeces. Theoretically a 5-g dose will bind about 350 mg calcium. It is used in the treatment of absorptive hypercalciuria type I with recurrent formation of calcium-containing renal calculi (p.2181), usually with a moderate dietary calcium restriction. Sodium cellulose phosphate is also used in the treatment of hypercalcaemia associated with osteopetrosis, sarcoidosis, and vitamin D intoxication, and in idiopathic hypercalcaemia of infancy, although other more effective agents are usually used (see Vitamin D-mediated Hypercalcaemia, p.1668).

The usual initial dose is 15 g daily by mouth in 3 divided doses with meals reducing to 10 g daily for maintenance. A suggested dose for children is 10 g daily (but see Adverse Effects and Precautions, above). The powder may be taken dispersed in water or sprinkled onto food. Oral magnesium supplements equivalent to about 60 or 90 mg (about 2.4 or 3.6 mmol) of elemental magnesium twice daily have been recommended for patients taking daily doses of sodium cellulose phosphate 10 or 15 g respectively. The magnesium supplement should not be given simultaneously with sodium cellulose phosphate.

Sodium cellulose phosphate has also been used for the investigation of calcium absorption.

Preparations

USP 31: Cellulose Sodium Phosphate for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Spain: Anacalcit; ***USA:*** Calcibind.

Sodium Edetate

Sodu edetynian.

Эдетат Натрия

CAS — 17421-79-3 (monosodium edetate).

ATC — S01XA05.

ATC Vet — QS01XA05.

NOTE. The name sodium edetate has been used in the literature for various sodium salts of edetic acid. Do not confuse with sodium calcium edetate (p.1462) or etomidate (p.1783); see also Inappropriate Administration, below.

Disodium Edetate *(BAN)*

Dinatrii edetas; Dinatrii Edetas Dihydricus; Dinatrio edetatas; Dinatriumedetaatti; Dinatriumedetat; Disodium Edathamil; Disodium EDTA; Disodium Tetracemate; Disodu edetynian; Edetan disodný dihydrát; Édétate disodique; Edetate Disodium; Edetato disódico; Edetynian disodu; Natrii Edetas; Nátrium-edetát; Sodium Versenate. Disodium dihydrogen ethylenediaminetetra-acetate dihydrate .

$C_{10}H_{14}N_2Na_2O_8,2H_2O$ = 372.2.

CAS — 139-33-3 (anhydrous disodium edetate); 6381-92-6 (disodium edetate dihydrate).

ATC — S01XA05.

ATC Vet — QS01XA05.

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

Ph. Eur. 6.2 (Disodium Edetate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 31 (Edetate Disodium). A white crystalline powder. Soluble in water. pH of a 5% solution in water is between 4.0 and 6.0.

Trisodium Edetate

Edetate Trisodium *(USAN)*; Edetato trisódico. Trisodium hydrogen ethylenediaminetetra-acetate .

$C_{10}H_{13}N_2Na_3O_8$ = 358.2.

CAS — 150-38-9.

ATC — S01XA05.

ATC Vet — QS01XA05.

Tetrasodium Edetate

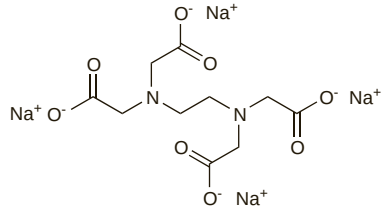
Edetate Sodium *(USAN)*.

$C_{10}H_{12}N_2Na_4O_8$ = 380.2.

CAS — 64-02-8.

ATC — S01XA05.

ATC Vet — QS01XA05.



Incompatibility. See under Edetic Acid, p.1445.

Adverse Effects and Treatment

In common with other edetates (see Sodium Calcium Edetate, p.1462), sodium edetate may cause gastrointestinal effects such as nausea, vomiting, and diarrhoea. Pain at the site of injection and thrombophlebitis may also occur. Other adverse effects include fever, headache, skin rashes, hypotension, and hyperuricaemia; nephrotoxicity has also been reported, particularly following overdosage.

Hypocalcaemia can occur, particularly if sodium edetate is infused too rapidly or in too concentrated a solution and tetany, convulsions, respiratory arrest, and cardiac arrhythmias may result.

The rate of infusion should be decreased if signs of muscle reactivity occur. The infusion should be discon-