5. Yoshizawa K, *et al.* Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst* 1998; **90:** 1219–24.
6. Li H, *et al.* A prospective study of plasma selenium levels and prostate cancer risk. *J Natl Cancer Inst* 2004; **96:** 696–703.
7. Brinkman M, *et al.* Use of selenium in chemoprevention of bladder cancer. *Lancet Oncol* 2006; **7:** 766–74.

Preparations

USP 31: Selenious Acid Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Selebound; ***Austria:*** Selen; Selenase; ***Cz.:*** Selenase; ***Fr.:*** Plexium; Selenion; ***Ger.:*** Cefasel; Seleject; Selemun†; Selen-loges; Selenase; Seltrans; ***Hong Kong:*** Selepen; ***Mex.:*** Selefusin†; ***Neth.:*** Selenase; ***Pol.:*** Cerosel; ***Port.:*** Selenase; ***Switz.:*** Selenase; ***Turk.:*** Selenase; ***UK:*** Selenase; ***USA:*** Sele-Pak; Selepen.

Multi-ingredient: ***Arg.:*** Centella Asiatica Compuesta; ***Canad.:*** Selenium Plus; ***Chile:*** Natursel-C; ***Fr.:*** Bio-Selenium; Phytosolaire; Selenium-ACE; ***Indon.:*** Ekinase; Imulan; Stacare; ***Irl.:*** Antox; ***Ital.:*** Fosfarsile Forte; Influ-Zinc; Longevital; Neomyrt Plus; Selenium-ACE; Tannidin Plus; ***Port.:*** Rilastil Dermo Solar; Selenium-ACE†; ***Thai.:*** Bio-Selenium Zinc; ***UK:*** Se-Power; Selene-Activ; ***Venez.:*** Kalsis.

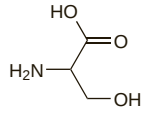
Serine *(USAN, rINN)*

β-Hydroxyalanine; S; Ser; Seriini; Serin; Serina; Serinas; Sérine; L-Serine; Serinum; Seryna; Szerin. L-2-Amino-3-hydroxypropionic acid.

Серин

$C_3H_7NO_3$ = 105.1.

CAS — 56-45-1 (serine); 302-84-1 (DL-serine).



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US.*
Ph. Eur. 6.2 (Serine). White or almost white crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. Protect from light.
USP 31 (Serine). White, odourless crystals. Soluble in water; practically insoluble in dehydrated alcohol and in ether.

Profile

Serine is a non-essential amino acid. It is used as a dietary supplement.

The racemic form (DL-serine) has been included in iron supplements to increase iron absorption.

Preparations

Proprietary Preparations (details are given in Part 3)

Used as an adjunct in: ***Austria:*** Aktiferrin; Aktiferrin Compositum; ***Cz.:*** Aktiferrin; Aktiferrin Compositum; ***Hung.:*** Aktiferrin; ***Israel:*** Aktiferrin-F; ***Malaysia:*** Aktiferrin-F; ***Rus.:*** Aktiferrin (Актиферрин); Aktiferrin Compositum (Актиферрин Композитум); ***Singapore:*** Aktiferrin-F; ***Switz.:*** Actiferrine; Actiferrine-F Nouvelle formule.

Sodium Feredetate *(BAN, rINN)*

Ferédétate de Sodium; Feredetato sódico; Natrii Feredetas; Sodium Ironedetate. The monohydrated iron chelate of the monosodium salt of ethylenediamine-*NNN′N′*-tetra-acetic acid; Iron (III) sodium ethylenediaminetetra-acetate monohydrate.

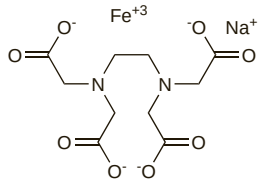
Натрия Фередетат

$C_{10}H_{12}FeN_2NaO_8.H_2O$ = 385.1.

CAS — 15708-41-5 (anhydrous sodium feredetate).

ATC — B03AB03.

ATC Vet — QB03AB03.



(anhydrous sodium feredetate)

Pharmacopoeias. In *Br.*
BP 2008 (Sodium Feredetate). A yellow or yellowish brown, hygroscopic, crystalline powder. A 1% solution in water has a pH of 4.0 to 6.5. Store in airtight containers.

Profile

Sodium feredetate is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given orally in doses of up to 1.42 g daily (equivalent to up to about 205 mg of iron daily).

Preparations

BP 2008: Sodium Feredetate Oral Solution.

Proprietary Preparations (details are given in Part 3)
Fr.: Ferrostrane; ***Philipp.:*** Ferrosmate; ***UK:*** Sytron.

Sodium Ferric Gluconate Complex *(USAN)*

Ferric Sodium Gluconate; D-Gluconic acid, iron (3+) sodium salt; Hierro gluconato sódico, complejo de; Iron Gluconate; Natrii ferrigluconas; Sodium Ferric Gluconate; Sodium ferrigluconate; Sodium-Iron(III) Gluconate Complex.

$[NaFe_2O_3(C_6H_{11}O_7)(C_{12}H_{22}O_{11})_5]_x$.

CAS — 34089-81-1.

ATC Vet — QB03AC07.

NOTE. Distinguish from Ferrous Gluconate.

Adverse Effects, Treatment, and Precautions

For parenteral iron, see Iron Dextran, p.1951.

Hypersensitivity. For a discussion as to whether sodium ferric gluconate complex may be a safer alternative to iron dextran, see p.1952.

Pharmacokinetics

Peak concentrations vary with the dose and rate at which sodium ferric gluconate complex is given. The volume of distribution does not appear to vary according to dose or rate. Elimination half-life varies by dose, and has been reported to be 0.85 hours for a dose of 62.5 mg and 1.45 hours for a dose of 125 mg; doses were given by slow intravenous injection.

Uses and Administration

Sodium ferric gluconate complex is used as a source of iron (p.1949) for iron-deficiency anaemia (p.1951). It is given as a solution containing the equivalent of 12.5 mg/mL of elemental iron. The recommended dose for haemodialysis patients who are receiving epoetin therapy is 125 mg iron (10 mL) diluted in 100 mL sodium chloride 0.9%, and given as an intravenous infusion over 1 hour; it may also be given undiluted as a slow intravenous injection (at a rate of 12.5 mg/minute) during dialysis. This dose is usually repeated over 8 dialysis sessions to achieve a favourable response. Children 6 years of age and older may be given 1.5 mg/kg of elemental iron (0.12 mL/kg), diluted in 25 mL sodium chloride 0.9% and infused over 1 hour, up to a maximum of 125 mg per dose.

Anaemia of chronic renal failure. References.

1. Yorgin PD, *et al.* Sodium ferric gluconate therapy in renal transplant and renal failure patients. *Pediatr Nephrol* 2000; **15:** 171–5.
2. Fishbane S, Wagner J. Sodium ferric gluconate complex in the treatment of iron deficiency for patients on dialysis. *Am J Kidney Dis* 2001; **37:** 879–83.
3. Folkert VW, *et al.* Chronic use of sodium ferric gluconate complex in hemodialysis patients: safety of higher dose (> or =250 mg) administration. *Am J Kidney Dis* 2003; **41:** 651–7.
4. Michael B, *et al.* Sodium ferric gluconate complex in haemodialysis patients: a prospective evaluation of long-term safety. *Nephrol Dial Transplant* 2004; **19:** 1576–80.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Pentaferr; ***Cz.:*** Ferrlecit; ***Ger.:*** Ferrlecit; ***Hung.:*** Ferrlecit; ***India:*** Efecient; ***Israel:*** Ferrlecit; ***Ital.:*** Actiferro†; Epaplex 40†; Extrafer; Ferlixit; Ferri-Emina†; Ferritin Oti; Ferrosprint; Fevital Simplex†; Hemocromo; Inferil†; Rossepar; Rubroferrina†; Sanifer; ***USA:*** Ferrlecit.

Multi-ingredient: ***Ital.:*** Ferritin Complex; ***Port.:*** Ferritin Oti.

Sodium Fluoride

Fluorid sodný; Fluoruro sódico; Natrii fluoridum; Natrio fluoridas; Natrium Fluoratum; Natriumfluorid; Nátrium-fluorid; Natriumfluoridi; Sodium, fluorure de; Sodu fluorek; Sodyum Fluorür.

NaF = 41.99.

CAS — 7681-49-4.

ATC — A01AA01; A12CD01.

ATC Vet — QA01AA01; QA12CD01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*
Ph. Eur. 6.2 (Sodium Fluoride). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol.
USP 31 (Sodium Fluoride). A white, odourless powder. Soluble 1 in 25 of water; insoluble in alcohol.

Adverse Effects and Treatment

In the controlled amounts recommended for fluoridation of drinking water and at the recommended doses used in dentistry for caries prophylaxis, sodium fluoride has not been shown to have significant adverse effects.

In **acute** poisoning, sodium fluoride taken by mouth is corrosive, forming hydrofluoric acid in the stomach. Adverse effects include a salty or soapy taste, increased salivation, gastrointestinal disturbances, abdominal pain, weakness, drowsiness, faintness, and shallow breathing; more serious effects include hypocalcaemia, hypomagnesaemia, hyperkalaemia, tremors, hyperreflexia, tetany, convulsions, cardiac arrhythmias, shock, respiratory arrest, and cardiac failure. Death may occur within 2 to 4 hours. Although there is much interindividual variation, a single oral dose of 5 to 10 g of sodium fluoride would be considered lethal in an untreated adult by most authorities. However, severe poisoning has been reported after oral doses of less than 1 g, and the minimum dose that can cause possibly fatal toxicity in children has been suggested to be 5 mg/kg of fluoride ion.

Treatment of acute poisoning involves gastric lavage with lime water or a weak solution of another calcium salt to precipitate fluoride, maintenance of high urine output, slow intravenous injections of calcium gluconate 10% for hypocalcaemia and tetany, and symptomatic and supportive measures. Magnesium sulfate may be given to correct hypomagnesaemia, and aluminium hydroxide may also reduce fluoride absorption. Haemodialysis may be considered.

Chronic fluoride poisoning may result in skeletal fluorosis, manifestations of which include increased density and coarsened trabeculation of bone and calcification in ligaments, tendons, and muscle insertions. Clinical signs are bone pain, stiffness, limited movement, and in severe cases, crippling deformities. Prolonged excessive intake by children during the period of tooth development before eruption can result in dental fluorosis characterised by mottled enamel. At fluoride concentrations in drinking water of 1 to 2 ppm (1 to 2 mg/litre) dental fluorosis is mild with white opaque flecks on the teeth. At higher concentrations, enamel defects become more severe with brown to black staining and the teeth have a pitted corroded appearance.

The **fluoridation** of water (below) has been a subject of considerable controversy. Suggestions that it increases the incidence of thyroid disorders, chromosome aberrations, and cancer have not been substantiated.

◊ Reviews of the toxic effects of fluoride salts.

1. WHO. Fluorine and Fluorides. *Environmental Health Criteria 36*. Geneva: WHO, 1984. Available at: http://www.inchem.org/documents/ehc/ehc/ehc36.htm (accessed 08/11/05)
2. Whitford GM. The physiological and toxicological characteristics of fluoride. *J Dent Res* 1990; **69** (Spec Iss): 539–49.
3. Whitford GM. The metabolism and toxicity of fluoride. *Monogr Oral Sci* 1996; **16:** 1–153.
4. WHO. Fluorides. *Environmental Health Criteria 227*. Geneva: WHO, 2002. Available at: http://www.inchem.org/documents/ehc/ehc/ehc227.htm (accessed 08/11/05)

Carcinogenicity. Based on comparisons of cancer mortality rates for communities residing in fluoridated and non-fluoridated cities, it was alleged that artificial fluoridation of water might be associated with an increased risk of cancer.[1] Re-examination of these data by others did not confirm the relationship, nor did further studies in a number of countries.[2] In Great Britain, the Working Party on Fluoridation of Water and Cancer[3] found nothing that could lead them to conclude that either fluoride occurring naturally in water, or fluoride added to water supplies, was capable of inducing cancer, or of increasing the mortality from cancer. In this respect, fluoridation of drinking water was considered safe. Further study in *animal* models by the USA National Toxicology Programme[4] found no evidence of carcinogenicity in female *rats* or in *mice* of either sex. A small number of osteosarcomas was found in male *rats* in the medium- and high-dose groups, although the association between sodium fluoride and the tumour was uncertain. A review of epidemiological evidence of possible carcinogens in drinking water stated that additional data gathered since 1990 did not support an association between the risk of osteosarcoma, or any other cancer, and the fluoride in drinking water.[5]

A cohort study of workers exposed to high levels of fluoride dust reported excess incidences of primary lung cancer and bladder tumours.[6]

1. Yiamouyiannis J, Burk D. Fluoridation and cancer: age-dependence of cancer mortality related to artificial fluoridation. *Fluoride* 1977; **10**: 102–25S.
2. Clemmesen J. The alleged association between artificial fluoridation of water supplies and cancer: a review. *Bull WHO* 1983; **61:** 871–83.