Profile

Glucarpidase is a recombinant glutamate carboxypeptidase that hydrolyses methotrexate to inactive metabolites; it is under investigation for the management of methotrexate toxicity.

◊ References.

1. Widemann BC, *et al.* Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. *J Clin Oncol* 1997; **15:** 2125–34.
2. Widemann BC, *et al.* Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. *J Natl Cancer Inst* 2004; **96:** 1557–9.
3. Buchen S, *et al.* Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 2005; **92:** 480–7.

Glutathione *(BAN)*

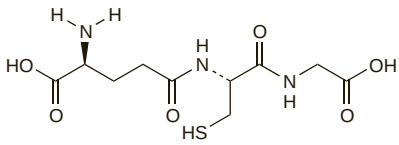
Glutathion; Glutathionum; Glutatión; Glutation; Glutationas; Glutationi; GSH. *N*-(*N*-L-γ-Glutamyl-L-cysteinyl)glycine.

$C_{10}H_{17}N_3O_6S$ = 307.3.

CAS — 70-18-8.

ATC — V03AB32.

ATC Vet — QV03AB32.



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

Ph. Eur. 6.2 (Glutathione). Fermentation product. A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Glutathione is an endogenous peptide with antoxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin or oxaliplatin; they have also been used to prevent other adverse effects of antineoplastic and radiation therapy, as well as in a wide range of other disorders including poisoning with heavy metals and other compounds, liver disorders, corneal disorders, and eczema. Glutathione has also been tried in idiopathic pulmonary fibrosis and peripheral vascular disorders.

Antineoplastic toxicity. Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomised trial[1] in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity. Similar benefit was observed in a randomised, double-blind, placebo-controlled trial involving 52 patients receiving oxaliplatin.[2]

1. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995; **13:** 26–32.
2. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2002; **20:** 3478–83.

Lung disorders. Glutathione is an important extracellular antoxidant in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulised glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis)[1] and in cystic fibrosis,[2] but the clinical effects of these changes are not clear. Another study in cystic fibrosis[3] found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function. Benefit has also been reported[4] in a patient with emphysema. However, in a study[5] of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.

1. Borok Z, *et al.* Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet* 1991; **338:** 215–16.
2. Roum JH, *et al.* Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. *J Appl Physiol* 1999; **87:** 438–43.
3. Griese M, *et al.* Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. *Am J Respir Crit Care Med* 2004; **169:** 822–8.
4. Lamson DW, Brignall MS. The use of nebulized glutathione in the treatment of emphysema: a case report. *Altern Med Rev* 2000; **5:** 429–31.
5. Marrades RM, *et al.* Nebulized glutathione induces bronchoconstriction in patients with mild asthma. *Am J Respir Crit Care Med* 1997; **156:** 425–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Glu-tathion; TAD; ***Ital.:*** Eudon†; Glutanil†; Gluthion; Ipatox†; Maglut†; Reglumax†; Ridutox; Rition; Scavenger†; TAD; Tationil; Thioxene†; ***Jpn:*** Glutathin; ***Rus.:*** Glutoxim (Глутоксим); ***USA:*** Cachexon.

Multi-ingredient: ***Austral.:*** BSS Plus; ***Austria:*** BSS Plus; ***Canad.:*** BSS Plus; ***Fr.:*** BSS Plus; ***Ger.:*** BSS Plus; ***Hong Kong:*** BSS Plus†; ***Hung.:*** BSS Plus; ***Israel:*** BSS Plus; ***Malaysia:*** BSS Plus; ***Philipp.:*** Illumina; ***S.Afr.:*** BSS Plus; ***Singapore:*** BSS Plus; ***Switz.:*** BSS Plus†; ***Thai.:*** BSS Plus; ***USA:*** BSS Plus; Sucrets Defense Kids Formula; ***Venez.:*** BSS Plus†.

Haem Derivatives

Heme Derivatives; Hemo, derivados del grupo.

ATC — B06AB01 (Haematin).

ATC Vet — QB06AB01 (haematin).

Profile

Haem is the iron protoporphyrin constituent of haemoglobin and is responsible for its colour and oxygen-carrying capacity. It is used in the management of porphyrias (below). Haem is given intravenously as its derivatives, although there is some confusion over their terminology. The names haematin (hematin) and haemin (hemin) have been used interchangeably although chemically haematin is the hydroxy derivative, formed by the reaction of haemin and sodium carbonate in solution. The arginine salt (haem arginate; haemin arginate; heme arginate) is reported to be more stable.

Haem arginate is used in the treatment of acute hepatic porphyrias, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria. It is given by slow intravenous infusion in a dose of 3 mg/kg daily for 4 days, infused over at least 30 minutes. The maximum recommended dose is 250 mg daily. The course may be repeated, with close monitoring, in patients with an inadequate response.

Haematin is used intravenously for the amelioration of acute intermittent porphyria associated with the menstrual cycle in patients unresponsive to other therapy. It is given in a usual dose of 1 to 4 mg/kg daily for 3 to 14 days as an intravenous infusion over 10 to 15 minutes. In severe cases the dose may be repeated after 12 hours, but no more than 6 mg/kg should be given in any 24 hour period.

Phlebitis may occur after infusion of haem derivatives and they should be given into a large arm vein or central vein. Use of a filter is recommended due to the colour of the infusion.

Porphyrias. The porphyrias are a group of inherited and acquired disorders of haem biosynthesis in which defects in specific enzymes lead to the accumulation of haem precursors, including aminolevulinic acid, porphobilinogen, and porphyrins.[1-11] They are generally classified as acute or non-acute, reflecting their clinical presentation, or as hepatic or erythropoietic, depending on the site of the enzyme defect. The three most common forms are acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria.

ACUTE PORPHYRIAS. These are inherited disorders characterised by the accumulation of porphyrin precursors, leading to acute attacks of neurovisceral symptoms. The most common form is *acute intermittent porphyria* (acute hepatic porphyria); *variegate porphyria* and *hereditary coproporphyria* are generally less common forms in which there is accumulation of both porphyrin precursors and porphyrins, leading to acute attacks with cutaneous symptoms similar to those seen in non-acute porphyrias (see below).

In acute porphyrias, some enzyme activity is present and the defect only becomes apparent when demand for hepatic haem is increased. Attacks are rare before puberty and the disorder may remain latent in many patients. The presenting symptom is most commonly severe abdominal pain; other gastrointestinal symptoms such as nausea and vomiting also occur, along with autonomic effects including hypertension, tachycardia, sweating, pallor, and pyrexia. Convulsions may occur at the peak of an attack and may persist between attacks. Neuropathy leads to weakness and paralysis and may progress rapidly to respiratory distress. Psychiatric symptoms are also common, particularly agitation, anxiety, and behavioural disturbances. Various factors can increase the demand for haem and attacks are usually precipitated by drugs, alcohol, steroid hormones, reduced caloric intake, or infection. They typically last for several days and are followed by complete recovery, although in some patients chronic abdominal pain may persist without other symptoms.

The primary management of an attack is to remove precipitants and to provide intensive support. *Symptomatic treatment* is complicated by the wide range of drugs that may precipitate porphyria. High doses of parenteral opioids may be required for pain; there is a danger of addiction occurring, but this is rare unless attacks are frequent or pain persists between attacks. Phenothiazines such as chlorpromazine are useful to control nausea and agitation and their sedative effect may also be beneficial. High doses of propranolol may be required for cardiovascular symptoms. Assisted ventilation may be necessary. Convulsions usually disappear as the attack resolves; management of patients who experience convulsions between attacks is a therapeutic problem since many antiepileptics are porphyrinogenic (see Porphyria, p.471). *Specific therapy* is aimed at suppressing the haem biosynthetic pathway, to prevent further accumulation of precursors. Haem, given as either haematin or haem arginate, is the most effective treatment and should be given as soon as possible after onset of the attack; it produces feedback suppression of the biosynthetic pathway. Tin-protoporphyrin, a haem oxygenase inhibitor, has been given with haem to prolong its action but is not commercially available. A high carbohydrate intake may also suppress haem precursor production and should be ensured in all patients, especially if haem is not immediately available; it is usually given orally to prevent fluid overload and exacerbation of hyponatraemia, but intravenous glucose may be required in patients who are vomiting. *Prevention* of attacks involves avoiding drugs that precipitate porphyria and maintaining an adequate carbohydrate intake. Gonadorelin analogues, such as buserelin, may have a role in preventing attacks related to the menstrual cycle. Long-term treatment with haem has been tried in patients with frequent attacks, although such use is not established.

NON-ACUTE PORPHYRIAS. These are characterised by the accumulation of porphyrins and usually present with cutaneous symptoms, although porphyrins also accumulate in the liver and liver damage commonly occurs. *Porphyria cutanea tarda* (cutaneous hepatic porphyria) is the most common form of porphyria. It is usually an acquired disorder and in most cases there is a history of moderate or heavy alcohol intake. There is usually a raised serum-iron concentration and use of oestrogen has also been implicated. The main clinical symptom is cutaneous photosensitivity leading to bullous dermatosis, pruritus, and skin fragility, in areas exposed to sunlight. *Management* involves protecting the skin from sunlight and trauma and avoiding causative agents such as alcohol and iron. Sunscreen preparations must be based on zinc oxide or titanium dioxide to be effective. Reduction of serum-iron concentrations by phlebotomy restores enzyme function and is effective in most patients; it should be carried out every 1 to 2 weeks until remission occurs, and may be required periodically for maintenance. Chloroquine and hydroxychloroquine have also been used and may be effective where phlebotomy is contra-indicated; they appear to act by complexing with porphyrins and increasing their excretion, but low doses are necessary to avoid exacerbating the condition. An alternative method of reducing serum-iron is with the iron chelator desferrioxamine, although it may be less effective than phlebotomy; it is usually reserved for patients unable to tolerate phlebotomy. In patients with renal failure who are too anaemic for phlebotomy and who cannot excrete chloroquine, erythropoietin may be used, and may be combined with desferrioxamine or low-volume phlebotomy.

Erythropoietic protoporphyria is a less common non-acute porphyria and is an inherited disorder leading to accumulation of protoporphyrin. Symptoms are cutaneous and there is an acute reaction to sunlight leading to urticaria, pruritus, swelling, redness, and a severe burning sensation; liver damage may also occur. *Management* involves protection of the skin, as for porphyria cutanea tarda. Betacarotene is widely used to increase tolerance to sunlight, although its efficacy is not established; canthaxanthin, another carotenoid, has also been used. Haem administration, as haematin or haem arginate, may be beneficial in suppressing protoporphyrin production. Colestyramine and activated charcoal reduce protoporphyrin levels by interrupting enterohepatic recycling; they also bind other porphyrins and may have a role in rare forms of porphyria such as *congenital erythropoietic porphyria*.

1. Murphy GM. The cutaneous porphyrias: a review. *Br J Dermatol* 1999; **140:** 573–81.
2. Thadani H, *et al.* Diagnosis and management of porphyria. *BMJ* 2000; **320:** 1647–51.
3. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; **26:** 225–32.
4. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002; **56:** 272–8.
5. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003; **16:** 57–64.
6. Lecha M, *et al.* Diagnosis and treatment of the hepatic porphyrias. *Dermatol Ther* 2003; **16:** 65–72.
7. Kauppinen R. Porphyrias. *Lancet* 2005; **365:** 241–52.
8. Anderson KE, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; **142:** 439–50. Correction. *ibid.*; **143:** 316.
9. European Porphyria Initiative. Information available at: http://www.porphyria-europe.com (accessed 04/10/05)
10. University of Cape Town Porphyria Service. Information available at: http://www.porphyria.uct.ac.za (accessed 04/10/05)
11. University of Queensland Porphyria Research Unit. Information available at: http://www.uq.edu.au/porphyria (accessed 04/10/05)

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Panhematin†; ***Denm.:*** Normosang; ***Fin.:*** Normosang; ***Fr.:*** Normosang; ***Ger.:*** Normosang; ***Ital.:*** Normosang; ***Neth.:*** Normosang; ***Port.:*** Normosang; ***Spain:*** Normosang; ***Swed.:*** Normosang; ***Switz.:*** Normosang; ***UK:*** Normosang; ***USA:*** Panhematin.

Multi-ingredient: ***Cz.:*** Normosang.

Lanthanum Carbonate *(USAN)*

Lanthanum carbonate (2:3) hydrate.
$La_2(CO_3)_3.xH_2O$ = 457.8 (anhydrous lanthanum carbonate).
CAS — 54451-24-0.
ATC — V03AE03.
ATC Vet — QV03AE03.

Adverse Effects and Precautions

The most common adverse effects with lanthanum carbonate are gastrointestinal disturbances, including nausea, vomiting, constipation, diarrhoea, dyspepsia, and abdominal pain. Only small amounts of lanthanum are absorbed from the gastrointestinal tract but some accumulation of lanthanum in bone has been reported; the clinical significance of this is unknown.

Ingestion of lanthanum carbonate may produce a radio-opaque appearance on abdominal radiography.

Uses and Administration

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia (p.1669) in patients with chronic renal failure. It is given orally as the hydrate, but doses are expressed in terms of elemental lanthanum. The usual initial daily dose is 0.75 to 2.25 g of elemental lanthanum, given in divided doses with meals. The dose should be adjusted every 2 to 3 weeks until an acceptable serum-phosphate concentration is achieved; the usual maintenance dose is 1.5 to 3 g daily in divided doses, but up to 3.75 g daily has been given. The tablets should be chewed thoroughly before swallowing.

◊ Reviews.

1. Swainston Harrison T, Scott LJ. Lanthanum carbonate. *Drugs* 2004; **64:** 985–96.
2. Joy MS, *et al.* Lanthanum carbonate. *Ann Pharmacother* 2006; **40:** 234–40.

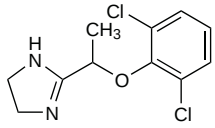
Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Fosrenol; ***Cz.:*** Fosrenol; ***Fr.:*** Fosrenol; ***Gr.:*** Fosrenol; ***Irl.:*** Foznol; ***Port.:*** Fosrenol; ***Swed.:*** Fosrenol; ***UK:*** Fosrenol; ***USA:*** Fosrenol.

Lofexidine Hydrochloride *(BANM, USAN, rINNM)*

Ba-168; Hidrocloruro de lofexidina; Lofeksidin Hidroklorür; Lofexidine, Chlorhydrate de; Lofexidini Hydrochloridum; MDL-14042; MDL-14042A; RMI-14042A. 2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride.

Лофексидина Гидрохлорид
$C_{11}H_{12}Cl_2N_2O,HCl$ = 295.6.
CAS — 31036-80-3 (lofexidine); 21498-08-8 (lofexidine hydrochloride).
ATC — N07BC04.
ATC Vet — QN07BC04.



(lofexidine)

Pharmacopoeias. In *Chin.*

Adverse Effects

Lofexidine has central alpha-adrenergic effects and may cause drowsiness, dryness of the mouth, throat, and nose, hypotension, and bradycardia; prolongation of the QT interval has also been reported. Sedation may occur following overdosage.

Sudden withdrawal of lofexidine may produce rebound hypertension.

Precautions

Lofexidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including recent myocardial infarction, bradycardia, renal impairment, or a history of depression.

It may cause drowsiness and if affected, patients should not drive or operate machinery.

Withdrawal of lofexidine therapy should be gradual over 2 to 4 days or more to reduce the risk of rebound hypertension.

Interactions

Lofexidine may enhance the central depressant effects of sedatives, including alcohol. It may also enhance the effects of antihypertensives. Tricyclic antidepressants may reduce the efficacy of lofexidine.

Methadone. A 44-year-old opioid-dependent female receiving methadone had prolongation of the QT interval after a single 400-microgram dose of lofexidine.[1] The patient had previously had a normal QT while receiving methadone and it was suggested the effect might have been caused by the combination of the 2 drugs.

1. Schmittner J, *et al.* QT interval increased after single dose of lofexidine. *BMJ* 2004; **329:** 1075.

Pharmacokinetics

Lofexidine is absorbed from the gastrointestinal tract with peak plasma concentrations occurring after about 3 hours. It is extensively metabolised in the liver and excreted mainly in the urine. The elimination half-life is 11 hours.

Uses and Administration

Lofexidine is an alpha$_2$-adrenoceptor agonist structurally related to clonidine (p.1247). It has antihypertensive activity, but is used mainly in the control of opioid withdrawal symptoms.

In opioid withdrawal, lofexidine is given as the hydrochloride in an initial oral dose of 800 micrograms daily in divided doses. The dose may be increased gradually by 400 to 800 micrograms daily to a maximum of 2.4 mg daily; the maximum single dose should not exceed 800 micrograms. After 7 to 10 days, or longer in some cases, treatment is withdrawn gradually over at least 2 to 4 days.

Opioid dependence. A systematic review[1] of the use of alpha$_2$-adrenoceptor agonists in the management of opioid dependence (p.101) concluded that they were as effective as methadone, although patients stayed in treatment for longer with methadone and there were fewer adverse effects with methadone than with clonidine. Lofexidine was associated with less hypotension than clonidine and may therefore be preferred, particularly for outpatient treatment.

1. Gowing L, *et al.* Alpha2 adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 04/10/05).

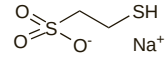
Preparations

Proprietary Preparations (details are given in Part 3)
UK: Britlofex.

Mesna *(BAN, USAN, rINN)*

D-7093; Mesnum; NSC-113891; UCB-3983. Sodium 2-mercaptoethanesulphonate.

Месна
$C_2H_5NaO_3S_2$ = 164.2.
CAS — 19767-45-4.
ATC — R05CB05; V03AF01.
ATC Vet — QR05CB05; QV03AF01.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Mesna). A white or slightly yellow, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

Incompatibility and stability. There was no evidence of degradation of mesna when stored in solution with ifosfamide in polyethylene infusion bags at room temperature for 7 hours[1] or in polypropylene syringes at room temperature or at 4° for 4 weeks.[2] However, in the latter study ifosfamide concentrations fell by about 3% after 7 days and 12% after 4 weeks at both temperatures. Another study[3] found that mixtures of mesna with cyclophosphamide in polyethylene infusion bags were stable for 48 hours at 4° and for 6 hours at room temperature.

Mesna has been reported to be incompatible with platinum compounds such as carboplatin and cisplatin.

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; **i:** 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; **ii:** 468.
3. Menard C, *et al.* Stability of cyclophosphamide and mesna admixtures in polyethylene infusion bags. *Ann Pharmacother* 2003; **37:** 1789–92.

Adverse Effects and Precautions

Adverse effects that may occur after use of mesna include gastrointestinal effects, headache, fatigue, limb pains, depression, irritability, hypotension (but see below), tachycardia, and skin rash. Bronchospasm has been reported after nebulisation.

Mesna may produce a false positive result in diagnostic tests for urinary ketones and may produce a false positive or false negative result in diagnostic tests for urinary erythrocytes.

Effects on blood pressure. Hypotension may occur with mesna; however, severe hypertension has also been reported[1] after use of mesna, either alone or with ifosfamide.

1. Gilleece MH, Davies JM. Mesna therapy and hypertension. *DICP Ann Pharmacother* 1991; **25:** 867.

Effects on the nervous system. For reports of severe encephalopathy in patients receiving mesna and ifosfamide, see p.732.

Hypersensitivity. Hypersensitivity reactions including rash, fever, nausea, facial and periorbital oedema, ulceration of mucous membranes, and tachycardia have been attributed to mesna.[1-4] Reactions may be more common in patients with autoimmune disorders; drug eruptions developed in 7 of 16 patients receiving mesna and cyclophosphamide for auto-immune disorders.[5] Five of these patients had a rash, with angioedema in 2 cases, and a pseudo-hypersensitivity reaction was diagnosed.

1. Lang E, Goos M. Hypersensitivity to mesna. *Lancet* 1985; **ii:** 329.
2. Seidel A, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 381.
3. Gross WL, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 381–2.
4. D'Cruz D, *et al.* Allergic reactions to mesna. *Lancet* 1991; **338:** 705–6.
5. Zonzits E, *et al.* Drug eruptions from mesna: after cyclophosphamide treatment of patients with systemic lupus erythematosus and dermatomyositis. *Arch Dermatol* 1992; **128:** 80–2.

Pharmacokinetics

Mesna is absorbed from the gastrointestinal tract. It is rapidly metabolised after oral or intravenous dosage to mesna disulfide (dimesna) and is excreted in the urine as both metabolite and unchanged drug; dimesna is reduced back to mesna, which is the active form, in the kidney. The half-lives of mesna and dimesna are reported to be about 20 minutes and 70 minutes respectively. After intravenous use, most of the dose is excreted in the urine within 4 hours. Mesna is about 70% bound to plasma proteins.

◊ References.

1. Burkert H, *et al.* Bioavailability of orally administered mesna. *Arzneimittelforschung* 1984; **34:** 1597–1600.
2. James CA, *et al.* Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects. *Br J Clin Pharmacol* 1987; **23:** 561–8.
3. El-Yazigi A, *et al.* Pharmacokinetics of mesna and dimesna after simultaneous intravenous bolus and infusion administration in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1997; **37:** 618–24.

Uses and Administration

Mesna is used for the prevention of urothelial toxicity in patients being treated with the antineoplastics ifosfamide or cyclophosphamide. In the kidney, dimesna, the inactive metabolite of mesna, is reduced to free mesna. This has thiol groups that react with the metabolites of ifosfamide and cyclophosphamide, including acrolein, which are considered to be responsible for the toxic effects on the bladder.

The aim of mesna therapy is to ensure adequate levels of mesna in the urine throughout the period during which these toxic metabolites are present. The duration of mesna treatment should therefore equal that of the antineoplastic treatment plus the time taken for the concentration of antineoplastic metabolites in the urine to fall to non-toxic concentrations. Urinary output should be maintained and the urine monitored for haematuria and proteinuria throughout the treatment period. However, frequent emptying of the bladder should be avoided.

Mesna may be given intravenously or orally for the prevention of urothelial toxicity, the dosage and frequency depending on the antineoplastic regimen used. After oral use, availability of mesna in urine is about 50% of that after intravenous use and excretion in urine is delayed up to 2 hours and is more prolonged. The intravenous preparation may be given orally added to a flavoured drink; this mixture may be stored in a sealed container in a refrigerator for up to 24 hours. Alternatively, tablets are available.

Intravenous bolus antineoplastic regimens. If ifosfamide or cyclophosphamide is given as an intravenous bolus, the *intravenous dose of mesna* is 20% of the dose of the antineoplastic on a weight for weight basis given on 3 occasions over 15 to 30 minutes at intervals of 4 hours beginning at the same time as the