antineoplastic injection; thus the total dose of mesna is equivalent to 60% of the antineoplastic given. This regimen is repeated each time the antineoplastic is used. Each individual dose of mesna may be increased to 40% of the dose of the antineoplastic and given 4 times at intervals of 3 hours for children and patients at high risk of urotoxicity; in such cases the total dose of mesna is equivalent to 160% of the antineoplastic given. The *oral dose of mesna* is 40% of the dose of the antineoplastic given on 3 occasions at intervals of 4 hours beginning 2 hours before the antineoplastic injection; thus a total dose of mesna equivalent to 120% of the antineoplastic is given. Alternatively, the initial dose of mesna may be given *intravenously* (20% of the dose of the antineoplastic), followed by two *oral doses* (each 40% of the dose of the antineoplastic) given 2 and 6 hours after the intravenous dose. Any of these regimens may be used if **cyclophosphamide** is given **orally**.

Intravenous infusion antineoplastic regimens. If the antineoplastic is given as an intravenous infusion over 24 hours, an initial *intravenous injection* of mesna as 20% of the total antineoplastic dose is followed by 100% of the total dose by intravenous infusion concurrently over 24 hours, followed by 60% by intravenous infusion over a further 12 hours (total dose 180% of the antineoplastic). The final 12-hour infusion may be replaced either by 3 intravenous injections each of 20% of the antineoplastic dose at intervals of 4 hours, the first injection being given 4 hours after the infusion has been stopped, or by *oral mesna* given in 3 doses each of 40% of the antineoplastic dose, the first dose being given when the 24-hour infusion is stopped, and the second and third doses being given 2 and 6 hours later.

Mesna is also used as a **mucolytic** in the management of some respiratory-tract disorders. The usual daily dose is 0.6 to 1.2 g given by a nebuliser; it may also be given by direct endotracheal instillation.

◊ General references.

1. Schoenike SE, Dana WJ. Ifosfamide and mesna. *Clin Pharm* 1990; **9:** 179–91.
2. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; **6:** 144–54.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Delinar; Mesnex†; Mestian; Neper; Uromitexan†; Varimesna; ***Austral.:*** Uromitexan; ***Austria:*** Mistabron; Uromitexan; ***Belg.:*** Mistabron; Uromitexan; ***Braz.:*** Mitexan; ***Canad.:*** Uromitexan; ***Chile:*** Mucofluid; Uromitexan; Uroprot; ***Cz.:*** Mistabron; Uromitexan; ***Denm.:*** Uromitexan; ***Fin.:*** Uromitexan; ***Fr.:*** Mucofluid; Uromitexan; ***Ger.:*** Mistabronco†; Uromitexan; ***Gr.:*** Uromitexan; ***Hong Kong:*** Mistabron; Uromitexan; ***Hung.:*** Uromitexan; ***India:*** Uromitexan; ***Indon.:*** Uromitexan; ***Irl.:*** Uromitexan; ***Israel:*** Mexan; ***Ital.:*** Mucofluid†; Mucolene†; Uromitexan; ***Jpn:*** Uromitexan; ***Malaysia:*** Mistabron†; Uromitexan†; ***Mex.:*** Mesnil; Mesodal; Uromes; Uromitexan†; Uroprot; Ziken; ***Neth.:*** Mistabron; Uromitexan; ***Norw.:*** Uromitexan; ***NZ:*** Uromitexan; ***Philipp.:*** Mistabron; Uromitexan; ***Pol.:*** Anti-Uron; Mistabron; Mucofluid; Uromitexan; ***Port.:*** Uromitexan; ***S.Afr.:*** Mistabron; Uromitexan; ***Singapore:*** Mistabron; Uromitexan; ***Spain:*** Mucofluid; Uromitexan; ***Swed.:*** Uromitexan; ***Switz.:*** Mistabron†; Uromitexan; ***Thai.:*** Mistabron†; Uromitexan; ***Turk.:*** Uromitexan; ***UK:*** Uromitexan†; ***USA:*** Mesnex.

Multi-ingredient: ***India:*** Holoxan Uromitexan; Ifex-M; Ipamide with Mesna.

Methionine *(USAN, rINN)*

L-Metionina; M; Methionin; Méthionine; *S*-Methionine; L-Methionine; Methioninum; Metioniini; Metionin; Metionina; Metioninas. L-2-Amino-4-(methylthio)butyric acid.

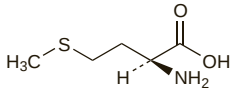
Метионин

$C_5H_{11}NO_2S$ = 149.2.

CAS — 63-68-3.

ATC — V03AB26.

ATC Vet — QA05BA90; QG04BA90; QV03AB26.



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

Ph. Eur. 6.2 (Methionine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. A 2.5% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 31 (Methionine). White crystals having a characteristic odour. Soluble in water, in warm dilute alcohol, and in dilute mineral acids; insoluble in dehydrated alcohol, in acetone, in ether, and in benzene. pH of a 1% solution in water is between 5.6 and 6.1.

DL-Methionine

DL-Metionina; Methionin racemický; DL-Méthionine; DL-Methioninum; Methioninum Racemicum; DL-Metioniini; DL-Metionin; DL-Metionina; DL-Metioninas; Racemethionine *(USAN)*. DL-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$ = 149.2.

CAS — 59-51-8.

ATC — V03AB26.

ATC Vet — QV03AB26.

NOTE. The name methionine is often applied to DL-methionine. Compounded preparations of DL-methionine may be represented by the following names:

- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol respectively.

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

Ph. Eur. 6.2 (DL-Methionine). An almost white crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol; dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 5.4 to 6.1. Protect from light.

Adverse Effects and Precautions

Methionine may cause nausea, vomiting, drowsiness, and irritability. It should not be used in patients with acidosis. Methionine may aggravate hepatic encephalopathy in patients with established liver damage; it should be used with caution in patients with severe liver disease.

Interactions

Methionine may be adsorbed by activated charcoal and the effect of oral methionine may be reduced if they are given together.

Dopaminergics. For reference to the antagonism of the antiparkinsonian effect of *levodopa* by methionine, see Nutritional Agents, under Interactions of Levodopa, p.808.

Pharmacokinetics

Methionine is absorbed from the gastrointestinal tract. It is extensively metabolised to *S*-adenosylmethionine (ademetionine, p.2247), homocysteine, and other metabolites, and is excreted in the urine as an inorganic sulfate.

Uses and Administration

L-Methionine is an essential amino acid and is therefore included in amino-acid solutions used for parenteral nutrition (p.1923).

Methionine also enhances the synthesis of glutathione and is used as an alternative to acetylcysteine in the treatment of paracetamol poisoning to prevent hepatotoxicity (see p.108). The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the usual dose of DL-methionine is 2.5 g by mouth every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. Children under 6 years old may be given 1 g every 4 hours for 4 doses. Methionine has also been given intravenously. Preparations containing both methionine and paracetamol have been formulated for use in situations where overdosage may occur. However, the issue of whether methionine should be routinely added to paracetamol preparations is contentious for medical and ethical reasons.

Methionine has also been given orally to lower urinary pH and as an adjunct in the treatment of liver disorders. It has also been used in the assessment of hyperhomocysteinaemia.

Acetylmethionine has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Neutrodor†; ***Austral.:*** Methnine; ***Austria:*** Acimethin; ***Ger.:*** Acimethin; Acimol; Methio; Methiotrans; Urol methin; Uromethin†; ***Switz.:*** Acimethin; ***USA:*** M-Caps; Pedameth†; Uracid.

Multi-ingredient: ***Austral.:*** Berberis Complex; Liv-Detox†; ***Braz.:*** Aminotox†; Anekron; Betaliver†; Biohepax; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Extrato Hepatico Vitaminado†; Hecrosine B12†; Hepacitron†; Hepalin; Hepatogenol†; Hepatotris†; Hepatox; Hormo Hepatico†; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B-6; Panvitrop; Regenom; Silimalon; Xantina B12†; Xantinon B12; Xantinon Complex; ***Canad.:*** Amino-Cerv; Selenium Plus; ***Cz.:*** Lipovitan†; ***Fr.:*** Cysti-Z†; Lobamine-Cysteine; Nivabetol; Verrulyse-Methionine; ***Ger.:*** Lipovitan†; ***Hong Kong:*** Bilsan; Lipochol; ***India:*** Neutrosec; ***Indon.:*** BIO-EPL; Lipagent; Methicol; Methioson; Naturica DFM; Vionin NF; ***Irl.:*** Antox; ***Ital.:*** Agedin Plus; Detoxicon; Meziv†; ***Mex.:*** Lipovitasi-Or; ***S.Afr.:*** Hepavite; ***Spain:*** Dertrase; Epitelizante; ***Switz.:*** Mechovit; ***Thai.:*** Bio-Vitas†; Lipochol; Liporon; ***UK:*** Lipotropic Factors; Paradote; ***USA:*** Amino-Cerv.

Methylthioninium Chloride *(BAN, rINN)*

Azul de Metileno; Błękit metylenowy; Blu di Metilene; CI Basic Blue 9; Cloruro de metiltioninio; Colour Index No. 52015; Methylene Blue; Methylenii Caeruleum; Methylthioninii chloridum; Methylthioninii Chloridum Hydricum; Méthylthioninium, chlorure de; Methylthioninium-chlorid hydrát; Metilen Mavisi; Metiltioninio chloridas; Metiltionin-klorid; Metylotioniniowy chlorek; Metyltioniniumklorid; Metyylitioniniumkloridi; Schultz No. 1038; Tetramethylthionine Chloride Trihydrate. 3,7-Bis(dimethylamino)phenazathionium chloride trihydrate.

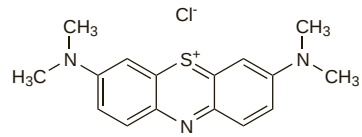
Метилтионина Хлорид

$C_{16}H_{18}ClN_3S,3H_2O$ = 373.9.

CAS — 61-73-4 (anhydrous methylthioninium chloride); 7220-79-3 (methylthioninium chloride trihydrate).

ATC — V03AB17; V04CG05.

ATC Vet — QV03AB17; QV04CG05.



NOTE. *Commercial methylthioninium chloride may consist of the double chloride of tetramethylthionine and zinc, and is not suitable for medicinal use.*

Pharmacopoeias. In *Chin.* and *US*; in *Eur.* (see p.vii) (as xH_2O); in *Int.* (as anhydrous or $3H_2O$).

Ph. Eur. 6.2 (Methylthioninium Chloride). A dark blue, crystalline powder with a copper-coloured sheen, or green crystals with a bronze-coloured sheen. Soluble in water; slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 31 (Methylene Blue). Dark green crystals or crystalline powder with a bronze-like lustre. Is odourless or practically so. Solutions in water or alcohol are deep blue in colour. Soluble 1 in 25 of water and 1 in 65 of alcohol; soluble in chloroform. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

After high intravenous doses, methylthioninium chloride may cause nausea, vomiting, abdominal and chest pain, headache, dizziness, mental confusion, profuse sweating, dyspnoea, and hypertension; methaemoglobinaemia and haemolysis may occur. Haemolytic anaemia and hyperbilirubinaemia have been reported in neonates after intra-amniotic injection. Oral use may cause gastrointestinal disturbances and dysuria.

Methylthioninium chloride should not be injected subcutaneously as it has been associated with isolated cases of necrotic abscesses. It should not be given by intrathecal injection as neural damage has occurred. Methylthioninium chloride should be used with caution in patients with severe renal impairment and is contra-indicated in patients with G6PD deficiency (see Uses, below). Methylthioninium chloride is used to treat methaemoglobinaemia but in large doses it can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride should not be used to treat methaemoglobinaemia induced by sodium nitrite during the treatment of cyanide poisoning, since cyanide binding will be reduced with resultant increased toxicity. It has also been contra-indicated in methaemoglobinaemia due to chlorate poisoning because of the risk that the more toxic hypochlorite may be formed, although several authorities consider its use to treat methaemoglobinaemia in severe chlorate poisoning appropriate.

Methylthioninium chloride imparts a blue colour to saliva, urine, faeces, and skin, which may hinder a diagnosis of cyanosis.

Aniline poisoning. It has been suggested[1] that methylthioninium chloride should be used with caution in the treatment of aniline-induced methaemoglobinaemia since it may precipitate Heinz body formation and haemolytic anaemia. Methylthioninium chloride may reduce methaemoglobin concentrations, but repeated doses could aggravate haemolysis without further reducing methaemoglobinaemia.

1. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. *Br J Haematol* 1983; **54:** 29–41.

Pregnancy. Although intra-amniotic injection of methylthioninium chloride has been used to diagnose premature rupture of fetal membranes or to identify separate amniotic sacs in twin pregnancies, there have been several reports of haemolytic anaemia (Heinz-body anaemia) and hyperbilirubinaemia in neonates who had been exposed to methylthioninium chloride in the amniotic cavity.[1-5] In most cases, exchange transfusions and/or phototherapy were required to control the jaundice; in 1 case phototherapy led to a phototoxic reaction.[5] It has therefore been suggested[3,6] that the use of methylthioninium chloride for detecting premature rupture of the membranes should be avoided.

Multiple ileal occlusions have been reported in babies born to mothers who had twin pregnancies and who had received methylthioninium chloride by amniocentesis;[4,7,8] in some cases it was possible to determine that methylthioninium chloride had been injected into the amniotic sac of the affected twin. Analysis of data from the EUROCAT registries[9] for 1980 to 1988, which surveyed pregnancy outcomes in 11 countries, found a slightly higher risk of ileal and jejunal atresia or stenosis in twins regardless of whether they had received methylthioninium chloride, but the use of methylthioninium chloride was rare and no increased risk could be shown in babies exposed to it. A subsequent review[6] from the Centers for Disease Control and Prevention concluded that the epidemiological evidence for the teratogenicity of methylthioninium chloride was quite strong and advised that it should not be used for midtrimester amniocentesis.

A further difficulty in using methylthioninium chloride by amniocentesis for the diagnosis of premature rupture of the membranes is that the resultant staining of the skin and mucous membranes of the neonate hinders assessment of hypoxia, including the use of pulse oximetry.[10]

1. Cowett RM, *et al.* Untoward neonatal effect of intraamniotic administration of methylene blue. *Obstet Gynecol* 1976; **48** (suppl): 74s–75s.
2. Serota FT, *et al.* The methylene-blue baby. *Lancet* 1979; **ii:** 1142–3.
3. Crooks J. Haemolytic jaundice in a neonate after intra-amniotic injection of methylene blue. *Arch Dis Child* 1982; **57:** 872–3.
4. Nicolini V, Monni G. Intestinal obstruction in babies exposed in utero to methylene blue. *Lancet* 1990; **336:** 1258–9.
5. Porat R, *et al.* Methylene blue-induced phototoxicity: an unrecognized complication. *Pediatrics* 1996; **97:** 717–21.
6. Cragan JD. Teratogen update: methylene blue. *Teratology* 1999; **60:** 42–8.
7. van der Pol JG, *et al.* Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. *Br J Obstet Gynaecol* 1992; **99:** 141–3.
8. Lancaster PAL, *et al.* Intra-amniotic methylene blue and intestinal atresia in twins. *J Perinat Med* 1992; **20** (suppl 1): 262.
9. Dolk H. Methylene blue and atresia or stenosis of ileum and jejunum. *Lancet* 1991; **338:** 1021–2.
10. Troche BT. The methylene blue baby. *N Engl J Med* 1989; **320:** 1756–7.

Interactions

Serotonergic drugs. Methylthioninium chloride has been associated with CNS toxicity when given intravenously as a visualising agent for thyroid or parathyroid surgery in patients who had recently received serotonergic drugs such as *bupropion*, *buspirone*, *clomipramine*, *mirtazapine*, *SSRIs*, or *venlafaxine*.[1] The MHRA in the UK therefore recommends that methylthioninium chloride should be avoided in patients recently treated with such drugs.

1. MHRA/CHM. Methylthioninium chloride (methylene blue): CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; **1** (6): 5–6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2033510&RevisionSelectionMethod=LatestReleased (accessed 19/07/08)

Pharmacokinetics

Methylthioninium chloride is absorbed from the gastrointestinal tract. It is believed to be reduced in the tissues to leucomethylene blue, which is slowly excreted, mainly in the urine, with some unchanged drug.

◊ References.

1. Peter C, *et al.* Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; **56:** 247–50.

Uses and Administration

Methylthioninium chloride is a thiazine dye that is used in the treatment of methaemoglobinaemia; it is also used as an antiseptic and in diagnostic procedures.

In patients with methaemoglobinaemia, therapeutic doses of methylthioninium chloride can lower the levels of methaemoglobin in the red blood cells. It activates a normally dormant reductase enzyme system, which reduces the methylthioninium chloride to leucomethylene blue and in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses methylthioninium chloride can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency as these patients have a diminished capacity to reduce methylthioninium chloride to leucomethylene blue; it is also potentially harmful as patients with G6PD deficiency are particularly susceptible to the haemolytic anaemias induced by methylthioninium chloride.

In the treatment of acute methaemoglobinaemia, such as in nitrite poisoning, methylthioninium chloride is given intravenously as a 1% solution in doses of 1 to 2 mg/kg injected over a period of several minutes. A repeat dose may be given after one hour if required. It may be of some value in inherited methaemoglobinaemia; doses of up to 300 mg daily by mouth have been used.

Methylthioninium chloride has a mildly antiseptic action and has been given orally in doses of 65 to 130 mg three times daily in minor urinary-tract infections and to prevent the formation of urinary oxalate stones. It is also included in some preparations intended for application to the eye, mouth and pharynx, and skin.

Methylthioninium chloride is also used as a bacteriological stain, as a dye in diagnostic procedures such as fistula detection and the diagnosis of ruptured amniotic membranes (but see Pregnancy under Adverse Effects and Precautions, above), and for the delineation of certain body tissues during surgery, in particular the parathyroid glands. It is also used for viral photoinactivation in some plasma products. The blue colour can be removed from the skin with hypochlorite solution. Methylthioninium chloride was formerly used in a renal-function test.

Dementia. The aggregation of tau protein filaments in the brain is believed to be associated with the development of cognitive symptoms in Alzheimer's disease (see Dementia, p.362). Methylthioninium chloride, which is thought to dissolve and prevent such aggregations, is under investigation in the management of Alzheimer's disease.

Glutaric aciduria. Glutaric aciduria type II is a metabolic disorder associated with a deficiency of electron-transferring flavoproteins involved in the metabolism of amino acids and fatty acids. Treatment may involve diets low in fats and protein, and some success has been reported with riboflavin. Methylthioninium chloride may also be of benefit since it may act as an electron acceptor, and a response has been seen in an infant[1] with neonatal glutaric aciduria type II. An association has also been noted between encephalopathy due to ifosfamide neurotoxicity (see Effects on the Nervous System under Adverse Effects of Ifosfamide, p.732) and glutaric aciduria, possibly due to inhibition of electron transport by a metabolite of ifosfamide. Methylthioninium chloride has therefore been tried for both treatment and prevention of ifosfamide neurotoxicity, and successful results have been reported;[2-4] however, its role remains unclear.[5]

1. Harpey J-P, *et al.* Methylene-blue for riboflavine-unresponsive glutaricaciduria type II. *Lancet* 1986; **i:** 391.
2. Küpfer A, *et al.* Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet* 1994; **343:** 763–4.
3. Zulian GB, *et al.* Methylene blue for ifosfamide-associated encephalopathy. *N Engl J Med* 1995; **332**: 1239–40.
4. Pelgrims J, *et al.* Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer* 2000; **82:** 291–4.
5. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother* 2006; **40:** 299–303.

Hypotension. Excess nitric oxide production leading to peripheral vasodilatation may be involved in the pathogenesis of hypotension associated with a number of conditions and it has been suggested that methylthioninium chloride, which is a guanylate cyclase inhibitor, may block the effects of nitric oxide and increase blood pressure in such cases. Studies[1,2] in patients with septic shock, including 5 neonates[3] with refractory hypotension assumed to be due to sepsis, have suggested that methylthioninium chloride increases blood pressure and improves tissue oxygenation, although no mortality benefit has been demonstrated.

There have also been reports of the successful use of methylthioninium chloride in patients with anaphylactic shock,[4] hypotension associated with haemodialysis,[5] vasoplegia after cardiac surgery,[6] and severe hepatopulmonary syndrome,[7] all of which may involve increased nitric oxide production. However, the role of methylthioninium chloride in these conditions is not established.

The usual management of shock is discussed on p.1183; anaphylactic shock should be treated with adrenaline, as discussed on p.1205.

1. Preiser J-C, *et al.* Methylene blue administration in septic shock: a clinical trial. *Crit Care Med* 1995; **23:** 259–64.
2. Kirov MY, *et al.* Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001; **29:** 1860–7.
3. Driscoll W, *et al.* Effect of methylene blue on refractory neonatal hypotension. *J Pediatr* 1996; **129:** 904–8.
4. Oliviera Neto AM, *et al.* Methylene blue: an effective treatment for contrast medium-induced anaphylaxis. *Med Sci Monit* 2003; **9:** CS102–CS106.
5. Peer G, *et al.* Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. *Nephrol Dial Transplant* 2001; **16:** 1436–41.
6. Levin RL, *et al.* Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg* 2004; **77:** 496–9.
7. Schenk P, *et al.* Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; **133:** 701–6.

Ifosfamide encephalopathy. See Glutaric Aciduria, above.

Methaemoglobinaemia. Methaemoglobinaemia is a rare disorder of the blood in which there is an increase in the proportion of haemoglobin present in the oxidised form. Inherited methaemoglobinaemia may be due either to a deficiency of methaemoglobin reductase or to a structural abnormality of haemoglobin. Acquired methaemoglobinaemia may be caused by drugs[1] or chemicals that oxidise haemoglobin, including nitrates and nitrites, sodium nitroprusside, dapsone, sulfonamides, phenacetin, and some local anaesthetics such as prilocaine; it may occur as a result of direct administration or occupational[2] or environmental exposure. Exposure to low doses over long periods may lead to chronic methaemoglobinaemia whereas large doses may lead to an acute effect.

Methaemoglobinaemia has a profound effect on oxygen transport by the blood; there is an increase in oxygen affinity leading to reduced tissue delivery and varying degrees of cyanosis. The presence of symptoms depends upon the degree and rapidity of methaemoglobin formation. Chronic mild methaemoglobinaemia is generally well tolerated although patients may appear cyanotic. Acute methaemoglobinaemia, particularly where methaemoglobin levels exceed 20%, is associated with dyspnoea, headache, malaise, giddiness, and altered mental state; methaemoglobin levels above 50% may lead to vascular collapse, coma, and death.

Patients with inherited methaemoglobinaemia are usually asymptomatic but treatment may be given for cosmetic purposes to reduce the cyanotic skin colour. Patients with reductase deficiency generally respond to oral therapy with drugs that promote the reduction of methaemoglobin to haemoglobin, such as ascorbic acid, riboflavin, or methylthioninium chloride; methylthioninium chloride may also be given intravenously. Patients with structural abnormalities of haemoglobin do not respond. In acquired methaemoglobinaemia the causative agent should be identified and removed. Chronic or mild cases may not require treatment but acute symptomatic methaemoglobinaemia may be life-threatening and patients should be given intravenous methylthioninium chloride, along with oxygen and other supportive therapy as required. Toxicity is uncommon with methylthioninium chloride but it should not be used for methaemoglobinaemia due to the use of nitrites for cyanide poisoning since increased toxicity may result (for debate about its use after chlorate poisoning, see Adverse Effects and Precautions, above). Severe methaemoglobinaemia may require exchange transfusion; exchange transfusion with haemodialysis is the treatment of choice in patients with acute methaemoglobinaemia and haemolysis. Hyperbaric oxygen therapy has also been suggested in severe cases. Ascorbic acid is not useful in the acute situation since it acts too slowly but it may be of benefit where maintenance therapy is required.

1. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia: treatment issues. *Drug Safety* 1996; **14:** 394–405.
2. Bradberry SM. Occupational methaemoglobinaemia: mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev* 2003; **22:** 13–27.

ADMINISTRATION. In acute methaemoglobinaemia, methylthioninium chloride is usually given by intravenous bolus injection, but repeated doses may be needed and continuous intravenous infusion has also been used. Methylthioninium chloride was given at a dose of 7.5 to 10 mg/hour for 43 hours to control methaemoglobinaemia after dapsone poisoning.[1] The patient had responded to two bolus doses of 100 mg but methaemoglobinaemia had subsequently increased again owing to the long half-life of dapsone. Additional therapy included repeated doses of activated charcoal. A dosing schedule for methylthioninium chloride of 1 to 2 mg/kg as a bolus followed by a continuous infusion at an initial rate of 100 to 150 micrograms/kg per hour was suggested.

1. Dawson AH, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; **4:** 387–92.

Priapism. Priapism is usually treated with corporal aspiration or intracavernosal vasoconstrictors (see under Uses of Metaraminol, p.1333). There have been reports[1-4] of the successful use of

intracavernosal methylthioninium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred[5] after the use of methylthioninium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthioninium chloride about 5 minutes after injection has been suggested.[2,3]

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; **146:** 1361–3.
2. deHoll JD, *et al.* Alternative approaches to the management of priapism. *Int J Impot Res* 1998; **10:** 11–14.
3. Martínez Portillo FJ, *et al.* Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; **39:** 20–3.
4. Hübler J, *et al.* Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; **35:** 519–21.
5. Mejean A, *et al.* Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; **149:** 1149.

Preparations

BP 2008: Methylthioninium Injection;
USP 31: Methylene Blue Injection.

Proprietary Preparations (details are given in Part 3)
Hung.: Metilenkek; ***USA:*** Urolene Blue.

Multi-ingredient: ***Arg.:*** Lagrimas de Santa Lucia†; Mictasol Azul; Muelita; Visubril; ***Austria:*** Methyment; ***Braz.:*** Acridin; Cystex; Lisian†; Pilulas De Witt's†; Sepurin; Vislin; Visodin; Visolux†; ***Canad.:*** Collyre Bleu†; ***Fr.:*** Collyre Bleu; Pastilles Monleon; ***Hong Kong:*** Clear Blue; ***Israel:*** Pronestin; ***Ital.:*** Mictasol Bleu†; Visustrin; ***NZ:*** De Witts Pills†; ***Pol.:*** Ginjal; Mibalin; ***Rus.:*** Neo-Anusol (Нео-анузол); ***Spain:*** Argentofenol†; Centilux; Tivitis; ***Switz.:*** Collyre Bleu Laiter; ***Turk.:*** Buco Bleu; Helmobleu; ***USA:*** Atrosept; Dolsed†; MHP-A; MSP-Blu; Prosed/DS; Trac Tabs 2X†; UAA; Urelle; Uretron; Uridon Modified†; Urimar-T; Urimax; Urised; Uriseptic; UriSym†; Uritact; Uro Blue; Urogesic Blue; Utira.

Milk Thistle

Cardo mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainių vaisiai (milk-thistle fruit); Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Plod ostropestřece mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle.
CAS — 84604-20-6 (milk thistle extract).

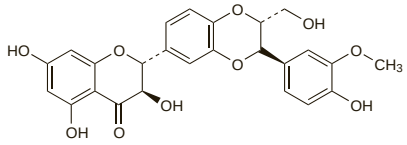
Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug). Protect from light.
USP 31 (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin *(rINN)*

Silibinina; Silibinine; Silibininum; Silybin; Silybum Substance E_6; Sylibinina. 3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.

Силибинин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 22888-70-6.



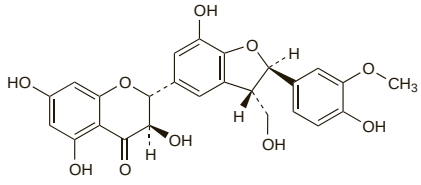
NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin *(rINN)*

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin. 2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuranyl]-3,5,7-trihydroxy-4-chromanone.

Силикристин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 33889-69-9.

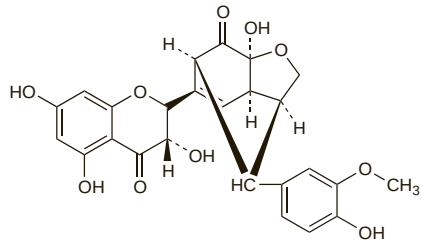


Silidianin *(rINN)*

Silidianina; Silidianine; Silidianinum; Silydianin. (+)-2,3α,3aα,7a-Tetrahydro-7aα-hydroxy-8(*R*")-(4-hydroxy-3-methoxyphenyl)-4-(3α,5,7-trihydroxy-4-oxo-2β-chromanyl)-3,6-methanobenzofuran-7(6α*H*)-one.

Силидианин

$C_{25}H_{22}O_{10}$ = 482.4.
CAS — 29782-68-1.



Silymarin

Silimarina; Silymarinum. A mixture of the isomers silibinin, silicristin, and silidianin.
CAS — 65666-07-1.
ATC — A05BA03.
ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum*; *Carduus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotectant properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* poisoning (p.2349) both silymarin and silibinin (as the disodium dihemisuccinate salt) have been used.

Milk thistle is usually given as a standardised extract containing mainly silymarin, although the herb and fruit have also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; the usual dose in *Amanita phalloides* poisoning is equivalent to silibinin 20 mg/kg daily, given by intravenous infusion in 4 divided doses.

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.[1-3]

1. Lorenz D. Über die anwending von silibinin bei der knollenblätterpilzvergiftung. *Dtsch Arzt* 1982; **79:** 43–5.
2. Hruby K, *et al.* Chemotherapy of Amanita phalloides poisoning with intravenous silibinin. *Hum Toxicol* 1983; **2:** 183–90.
3. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; **40:** 715–57.

Liver disorders. References to the use of milk thistle or silymarin in patients with liver disorders.

1. Saller R, *et al.* The use of silymarin in the treatment of liver diseases. *Drugs* 2001; **61:** 2035–63.
2. Jacobs BP, *et al.* Milk thistle for the treatment of liver disease: a systematic review and meta-analysis. *Am J Med* 2002; **113:** 506–15.

Preparations

USP 31: Milk Thistle Capsules; Milk Thistle Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Benevolus†; Laragon; ***Austral.:*** Bioglan Liver-Vite; Herbal Liver Formula†; Prol†; Silymarin Phytosome†; ***Austria:*** Apihepar; Ardeyhepan; Legalon; Silyhexal; ***Belg.:*** Legalon; Legalon SIL; ***Braz.:*** Eleparon†; Legalon; Silliver; ***Chile:*** Legalon; ***Cz.:*** Flavobion; Lagosa; Legalon; Nat Cubetu Benediktu†; Silygal; ***Fr.:*** Legalon; ***Ger.:*** Alepa; Ardeyhepan; Cefasliymarin; durasilymarin; Hegrimarin; Hepa-Loges; Hepa-Merz Sil†; HepaBesch; Hepaduran V†; Hepar-Pasc; Heparsyx N†; Hepatos; Heplant; Lagosa; Legalon; Legalon SIL; Lomacholan†; Phytohepar; Poikicholan†; Silibene; Silicur; Silimarit; Silmar†; Silvaysan; Sily-Sabona†; ***Gr.:*** Legalon; ***Hong Kong:*** Legalon; ***Hung.:*** Hegrimarin; Legalon; Legalon SIL; Silegon; ***India:*** Limarin; Silybon; ***Ital.:*** Legalon; Silimarin; Silirex; Silliver†; ***Mex.:*** Etagerin; Legalon; ***Philipp.:*** Hepavit; Legalon; Liveraide; ***Pol.:*** Flexiderm; Lagosa; Legalon; Silimax; Sylicaps; Sylimarol; Syliverin; ***Port.:*** Legalon; Legalon SIL; ***Rus.:*** Carsil (Карсил); ***S.Afr.:*** Legalon; ***Spain:*** Legalon; Legalon SIL; Silarine; Silimazu†; ***Switz.:*** Legalon; Legalon SIL; ***Thai.:*** Legalon; Leveron; Marina; Samarin; Sivylar; ***Venez.:*** Legalon.

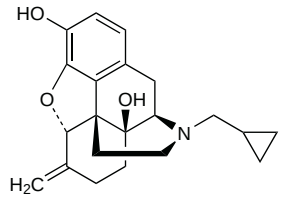
Multi-ingredient: ***Arg.:*** Bibol Leloup; Hepadigenor†; Quelodin F; ***Austral.:*** Antioxidant Forte Tablets; Bupleurum Complex; Bupleurum Compound; Digest; Extralife Liva-Care; Herbal Cleanse†; Lifesystem Herbal Formula 7 Liver Tonic†; Liver Tonic Herbal Formula 6†; Livstim†; Livton Complex†; Silybum Complex†; St Mary's Thistle Plus; ***Austria:*** Hepabene; ***Braz.:*** Silimalon; ***Canad.:*** Milk Thistle; Milk Thistle Extract Formula†; ***Cz.:*** Hepabene†; Iberogast; Naturland Grosser Swedenbitter†; Simepar; Ungolen†; ***Ger.:*** Bilisan Duo; Cheirantho†; Cholhepan N; Cholosom-Tee; Gallexier; Galloselect M†; Hepaticum-Medice H†; Heumann Leber- und Gallentee Solu-Hepar S†; Heumann Verdauungstee Solu-Lipar; Heusin†; Iberogast; Marianon†; Pankreaplex Neu†; Pascopankreat novo†; Presselin Hepaticum P†; Schwohepan S†; Venacton†; ***Hong Kong:*** Hepatofalk Planta; Simepar; ***Hung.:*** Hepabene; ***India:*** Livosil-B; ***Indon.:*** Aptivium Liver Support; Curliv Plus; Hepa-Q; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta; Verona; Vionin NF; ***Ital.:*** Depatox; Epagest†; Liverton; Tarassaco (Specie Composta)†; Venoplus†; ***Malaysia:*** Hepavite; Simepar; ***Philipp.:*** Liverine; Livermin; ***Pol.:*** Artecholin; Artecholwex; Gastrobonisol; Sylicynar; Sylivit; Tabletki Przeciw Niestrawnosci; ***Port.:*** Cholagutt†; Synchrorose; ***Rus.:*** Hepabene (Гепабене); Sibectan (Сибектан); ***Singapore:*** Hepatofalk Planta; Hepavite; Noricaven†; Simepar; ***Switz.:*** Demonatur Gouttes pour le foie et la bile; Iberogast; Phytomed Hepato†; Simepar†; Tisane hepatique et biliaire.

Nalmefene *(BAN, USAN, rINN)*

6-Desoxy-6-methylene-naltrexone; JF-1; Nalméfène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676. 17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol.

Налмефен

$C_{21}H_{25}NO_3$ = 339.4.
CAS — 55096-26-9.



Nalmefene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalmefeno; Nalméfène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmetrene Hydrochloride.

Налмефена Гидрохлорид

$C_{21}H_{25}NO_3$,HCl = 375.9.
CAS — 58895-64-0.

Adverse Effects

Nausea, vomiting, tachycardia, hypertension, fever, and dizziness have been reported with therapeutic doses of nalmefene. At higher doses or in patients later found to be physically dependent on opioids, symptoms suggestive of opioid withdrawal have been noted; these have included abdominal cramps, chills, dysphoria, myalgia, and joint pain.

Precautions

As for Naloxone, p.1453.

Incremental doses of nalmefene should be given slowly in patients with renal impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is not complete owing to significant first-pass metabolism. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The plasma elimination half-life is reported to be about 10 hours.

◊ References.

1. Dixon R, *et al.* Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; **39:** 49–53.
2. Dixon R, *et al.* Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; **27:** 233–9.
3. Frye RF, *et al.* The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; **42:** 301–6.
4. Frye RF, *et al.* Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; **61:** 15–23.

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions and uses similar to those of naloxone (p.1454), but with a longer duration of action. It is given as the hydrochloride but doses are expressed in terms of the base. Nalmefene hydrochloride 111 micrograms is equivalent to about 100 micrograms of nalmefene. It is usually given intravenously for a rapid onset of action; subcutaneous or intramuscular administration is also effective but has a slower onset. Nalmefene has also been given orally.

For the reversal of postoperative central depression due to the use of opioids, nalmefene is given intravenously,