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.

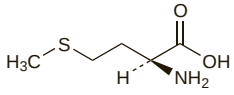
Метионин

$C_5H_{11}NO_2S$ = 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.

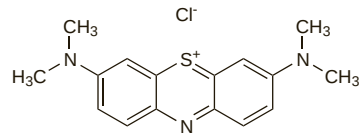
Метилтионина Хлорид

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