2. Drake MV, *et al*. Levobunolol compared to dipivefrin in African American patients with open angle glaucoma. *J Ocul Pharmacol* 1993; **9:** 91–5. Correction. *ibid*.; 385.
3. Albracht DC, *et al*. A double-masked comparison of betaxolol and dipivefrin for the treatment of increased intraocular pressure. *Am J Ophthalmol* 1993; **116:** 307–13.
4. Widengard I, *et al*. Effects of latanoprost and dipivefrin, alone or combined, on intraocular pressure and on blood-aqueous barrier permeability. *Br J Ophthalmol* 1998; **82:** 404–6.

Preparations

BP 2008: Dipivefrine Eye Drops;
USP 31: Dipivefrin Hydrochloride Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Propine†; ***Austral.:*** Dipoquin; Propine; ***Austria:*** Glaucothil†; ***Belg.:*** Propine; ***Braz.:*** Propine; ***Canad.:*** Propine†; ***Cz.:*** d Epifrin†; Oftanex†; ***Denm.:*** Oftapinex†; Propine; ***Fin.:*** Oftapinex†; Propine; ***Fr.:*** Propine; ***Ger.:*** d Epifrin; Glaucothil; ***Gr.:*** Diopine†; Glaucodose; Prodren†; Thilodrin; ***Hong Kong:*** Propine; ***Irl.:*** Propine; ***Israel:*** Difrin; ***Ital.:*** Propine; ***Jpn:*** Pivalephrine; ***Malaysia:*** Propine†; ***Mex.:*** Diopine†; ***Neth.:*** Diopine; ***Norw.:*** Oftapinex†; Propine; ***NZ:*** Dipoquin†; Propine; ***Port.:*** Propine†; ***S.Afr.:*** Propine†; ***Singapore:*** Propine†; ***Spain:*** Diopine; Glaudrops†; ***Swed.:*** Oftapinex†; Propine; ***Switz.:*** Diopine†; ***Thai.:*** Propine†; ***UK:*** Propine; ***USA:*** AkPro; Propine.

Multi-ingredient: ***Austria:*** Thiloadren; Thilodigon†; ***Canad.:*** Probeta†; ***Ger.:*** Thiloadren N; Thilodigon; ***Gr.:*** Ryvina†; Thilocombin†.

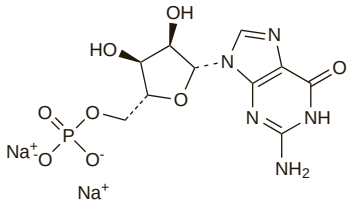
Disodium Guanylate

Disodium Guanosine-5′-monophosphate; E627; Guanilato disódico; Sodium 5′-Guanylate. Guanosine 5′-(disodium phosphate).

Гуанилат Натрия Двузамещенный

$C_{10}H_{12}N_5Na_2O_8P,xH_2O$ = 407.2 (anhydrous).

CAS — 5550-12-9 (anhydrous disodium guanylate).



Profile

Disodium guanylate is used in preparations containing other nucleosides in the treatment of corneal damage. Disodium guanylate has been used as a flavour enhancer in foods. The term sodium 5′-ribonucleotide (disodium 5′-ribonucleotide) has been used to refer to a mixture of disodium guanylate with disodium inosinate (see below).

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Belg.:*** Vitacic; ***Cz.:*** Laevadosin†; ***Hung.:*** Vitacic†; ***Mon.:*** Vitacic; ***Rus.:*** Vitacic (Витасик)†.

Disodium Inosinate

Disodium Inosine-5′-monophosphate; E631; Inosinato disódico; Sodium 5′-Inosinate. Inosine 5′-(disodium phosphate).

$C_{10}H_{11}N_4Na_2O_8P,xH_2O$ = 392.2 (anhydrous).

CAS — 4691-65-0 (anhydrous disodium inosinate).

Profile

Disodium inosinate has been used as a flavour enhancer in foods. It has also been given by mouth and been applied topically in the treatment of visual disturbance. The term sodium 5′-ribonucleotide has been used to refer to a mixture of disodium inosinate with disodium guanylate (above).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Lumiclar; Opacout; ***Fr.:*** Catacol; Correctol; ***Ger.:*** Antikataraktikum N.

Multi-ingredient: ***Arg.:*** Antikatarata†.

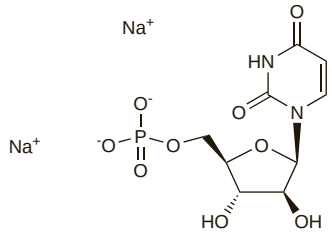
Disodium Uridine Monophosphate

Disodium UMP. 5′-Uridylic acid, disodium salt; disodium 5′ uridylate.

Уридин Монофосфат Динатрия

$C_9H_{11}N_2O_9PNa_2$ = 368.1.

CAS — 3387-36-8.



Profile

Uridine monophosphate is an endogenous uracil nucleotide involved in many biological processes. Disodium uridine monophosphate is included in preparations for neuralgia, neuritis, and myopathies and has also been used for peripheral and cerebral vascular disorders; disodium uridine diphosphate has also been used.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Cz.:*** Laevadosin†; ***Ger.:*** Keltican N; ***Spain:*** Nucleo CMP.

Disulfiram *(BAN, rINN)*

Dissulfiramo; Disulfiraami; Disulfiramas; Disulfirame; Disulfiramum; Diszulfirám; Éthyldithiourame; TTD. Tetraethylthiuram disulphide; Bis(diethylthiocarbamoyl) disulfide.

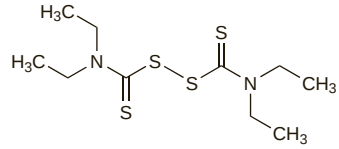
Дисульфирам

$C_{10}H_{20}N_2S_4$ = 296.5.

CAS — 97-77-8.

ATC — N07BB01; P03AA04.

ATC Vet — QN07BB01; QV03AA01.



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

Ph. Eur. 6.2 (Disulfiram). A white or almost white, crystalline powder. M.p. 70° to 73°. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Disulfiram). A white to off-white, odourless crystalline powder. M.p. 69° to 72°. Very slightly soluble in water; soluble 1 in 30 of alcohol and 1 in 15 of ether; soluble in acetone, in carbon disulfide, and in chloroform. Store in airtight containers. Protect from light.

Stability. Studies[1,2] on the stability of disulfiram preparations.

1. Gupta VD. Stability of aqueous suspensions of disulfiram. *Am J Hosp Pharm* 1981; **38:** 363–4.
2. Philips M, *et al*. Stability of an injectable disulfiram formulation sterilized by gamma irradiation. *Am J Hosp Pharm* 1985; **42:** 343–5.

Adverse Effects and Treatment

Drowsiness and fatigue are common during initial treatment with disulfiram. Other adverse effects reported include a garlic-like or metallic aftertaste, gastrointestinal upsets, body odour, bad breath, headache, impotence, and allergic dermatitis. Peripheral and optic neuropathies, psychotic reactions, and hepatotoxicity may occur.

Disulfiram-alcohol reaction. The use of disulfiram in the management of alcoholism is based on the extremely unpleasant, but generally self-limiting, systemic effects which occur when a patient receiving the drug ingests alcohol. These effects begin with flushing of the face and, as vasodilatation spreads, throbbing in the head and neck and a pulsating headache may develop. Respiratory difficulties, nausea, copious vomiting, sweating, thirst, chest pain, tachycardia, palpitations, marked hypotension, giddiness, weakness, blurred vision, and confusion may follow. The intensity and duration of symptoms is very variable and even small quantities of alcohol may result in alarming reactions. In addition to the above effects, severe reactions have included respiratory depression, cardiovascular collapse, cardiac arrhythmias, myocardial infarction, acute heart failure, unconsciousness, convulsions, and sudden death.

Severe reactions require intensive supportive therapy; oxygen and intravenous fluids may be necessary. Potassium concentrations should be monitored. Giving intravenous ascorbic acid, ephedrine sulfate, or antihistamines has been suggested.

◊ Reviews.

1. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety* 1999; **20:** 427–35.

Effects on the blood. There were isolated reports of blood dyscrasias associated with disulfiram in the 1960s. US licensed product information recommends that blood counts should be performed during treatment.

Effects on the liver. A review of 18 cases of hepatitis in patients receiving disulfiram.[1] Symptoms have appeared between 10 days and 6 months after starting disulfiram, and clinical improvement has been seen within 2 weeks of stopping the drug, although liver enzyme values may not return to normal for several months. Fatal hepatic coma had been reported in 7 patients. The clinical picture of disulfiram-induced hepatitis is consistent with a hypersensitivity reaction. Another review[2] evaluated 82 cases of liver injury thought to be due to disulfiram and reported to the Swedish Adverse Drug Reactions Advisory Committee between 1966 and 2002. All but one of the cases were of hepatocellular liver damage, and 4 patients died and 4 underwent liver transplantation. Although there was some evidence that hypersensitivity played a role, it might not be the only mechanism of disulfiram-induced liver disease.

1. Mason NA. Disulfiram-induced hepatitis: case report and review of the literature. *DICP Ann Pharmacother* 1989; **23:** 872–4.
2. Björnsson E, *et al*. Clinical characteristics and prognostic markers in disulfiram-induced liver injury. *J Hepatol* 2006; **44:** 791–7.

Effects on the nervous system. ***ENCEPHALOPATHY.*** A 2% incidence of reversible toxic encephalopathy has been reported in patients receiving disulfiram.[1] Onset varies from days to months following the start of therapy and early signs include impaired concentration, memory deficits, anxiety, depression, and somnolence. Confusion and disorientation follow, often accompanied by paranoid delusions and sometimes hallucinations. Other symptoms may include ataxia, loss of fine motor coordination, slurred speech, and intention tremor. The encephalopathy usually resolves within 3 days to 2 weeks of stopping disulfiram, although symptoms may persist for 6 weeks. There are conflicting opinions on whether this psychosis is a toxic reaction to disulfiram or a response to abstinence from alcohol, but the authors suspected that most cases represent a toxic encephalopathy. However, psychosis without any suggestion of encephalopathy has been reported.[2]

1. Hotson JR, Langston JW. Disulfiram-induced encephalopathy. *Arch Neurol* 1976; **33:** 141–2.
2. Rossiter SK. Psychosis with disulfiram prescribed under probation order. *BMJ* 1992; **305:** 763.

PERIPHERAL NEUROPATHY. Reports of peripheral neuropathy associated with disulfiram and reference to previously reported cases.[1,2] Onset of neuropathy varied from days to months after starting disulfiram treatment and could develop with doses of 250 or 500 mg daily. The most common symptom reported was pins and needles, but numbness, pain/burning, and weakness were frequently described; usually both muscle weakness and sensory loss were noted. Optic atrophy has also been described. Although there might be some improvement immediately after disulfiram withdrawal, the neurological deficit only improved slowly and symptoms might persist for as long as 2 years.[1]

1. Watson CP, *et al*. Disulfiram neuropathy. *Can Med Assoc J* 1980; **123:** 123–6.
2. Frisoni GB, Di Monda V. Disulfiram neuropathy: a review (1971-1988) and report of a case. *Alcohol Alcohol* 1989; **24:** 429–37.

Effects on the respiratory tract. Bronchospasm and hypertension were observed in an asthmatic patient taking disulfiram after an alcohol challenge test.[1]

1. Zapata E, Orwin A. Severe hypertension and bronchospasm during disulfiram-ethanol test reaction. *BMJ* 1992; **305:** 870.

Effects on the skin. Orange-coloured palms and soles, provoking an initial diagnosis of jaundice, developed in a 55-year-old man who had been taking disulfiram for about 2 months.[1] It was postulated that the discoloration was due to accumulation of carotenes in the skin as a result of inhibition of vitamin A metabolism by disulfiram. The discoloration disappeared soon after disulfiram was stopped.

1. Santonastaso M, *et al*. Yellow palms with disulfiram. *Lancet* 1997; **350:** 266.

Overdosage. There has been a report of a 6-year-old boy who experienced disulfiram intoxication after receiving disulfiram 250 mg four times daily to a total of 13 doses but who later recovered.[1] Of 6 previous reports one child died and 3 had moderate or severe brain damage. The syndrome of disulfiram intoxication in children is distinct from the disulfiram-alcohol interaction or acute disulfiram intoxication in adults. It is characterised by lethargy or somnolence, weakness, hypotonia, and vomiting, beginning about 12 hours after ingestion and progressing to stupor or coma. Dehydration, moderate tachycardia, and marked tachypnoea occur frequently, muscle tone is greatly decreased, and deep-tendon reflexes may be weak or absent.

Severe neurological damage has also been reported[2] in a 5-year-old girl after acute disulfiram intoxication which was initially diagnosed as diabetic ketoacidosis.

1. Benitz WE, Tatro DS. Disulfiram intoxication in a child. *J Pediatr* 1984; **105:** 487–9.
2. Mahajan P, *et al*. Basal ganglion infarction in a child with disulfiram poisoning. *Pediatrics* 1997; **99:** 605–8.