Tinnitus, vertigo, deafness, headache, drowsiness, and other neurological symptoms have been reported, as have episodes of jaundice. Skin reactions to chlormethine hydrochloride include maculopapular rashes. Hypersensitivity is frequent when topical preparations are used.

Chlormethine hydrochloride has a powerful vesicant action on the skin and mucous membranes and great care must be taken to avoid contact with the eyes. Thrombophlebitis is a potential hazard of chlormethine particularly if it is not sufficiently diluted. Extravasation of the injection causes severe irritation and even sloughing. If extravasation occurs during injection, it has been suggested that the involved area should be infiltrated with an isotonic 4% solution of sodium thiosulfate, followed by the application of an ice compress intermittently for 6 to 12 hours, although the role of specific antidotes in antineoplastic extravasation is somewhat contentious (see p.640).

Chlormethine hydrochloride may produce temporary or permanent inhibition of fertility. There is some evidence of mutagenicity, teratogenicity, and carcinogenicity.

Effects on the nervous system. Severe immediate neurotoxicity developed[1] in 14 of 21 evaluable patients who underwent bone marrow transplantation after preparation with cytotoxic regimens including chlormethine 0.3 to 2 mg/kg. Symptoms developed a median of 4 days after treatment and included headache, hallucinations, confusion, convulsions, paraplegia, and tremor. Symptoms resolved in most, although in some they had not done so before their death. Six of the patients who recovered from acute toxicity developed a delayed neurotoxicity, beginning a median of 169 days after the first chlormethine injection and characterised by symptoms including confusion, somnolence, personality change, dementia, focal motor seizures, and hydrocephalus. Patients older than 21 years, those who had received CNS irradiation, and those treated concomitantly with other cytotoxic agents were at increased risk of neurotoxicity.

1. Sullivan KM, *et al.* Immediate and delayed neurotoxicity after mechlorethamine preparation for bone marrow transplantation. *Ann Intern Med* 1982; **97:** 182–9.

Handling and disposal. Chlormethine hydrochloride is a strong vesicant; avoid contact with skin and mucous membranes.

The manufacturers state that *unused injection* solutions of chlormethine hydrochloride may be neutralised by mixing with an equal volume of a solution containing sodium thiosulfate 5% and sodium bicarbonate 5% and allowing to stand for 45 minutes. Equipment used in the preparation and administration of such solutions may be treated similarly. Alternatively a solution containing sodium carbonate 2.5% or sodium hydroxide in a mixture of industrial methylated spirit and water has been suggested for the decontamination of equipment.

Urine produced for up to 48 hours after a dose of chlormethine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Pharmacokinetics

On intravenous injection, chlormethine is rapidly converted to a reactive ethyleneimmonium ion. It usually disappears from the blood in a few minutes. A very small proportion is excreted unchanged in the urine.

Uses and Administration

Chlormethine belongs to the group of antineoplastic drugs described as alkylating agents. It also possesses weak immunosuppressant properties.

Chlormethine hydrochloride has been used in the treatment of advanced Hodgkin's disease (p.655), historically with a vinca alkaloid, procarbazine, and prednisone or prednisolone (the MOPP regimen). Chlormethine has also been tried in non-Hodgkin's lymphomas, notably mycosis fungoides (p.657), and some other malignancies including chronic leukaemias, tumours of the breast, ovary, and lung, and in polycythaemia vera. Chlormethine has been used in the management of malignant effusions but is not the agent of choice.

In the MOPP regimen chlormethine hydrochloride has been given in doses of 6 mg/m^2. However, when licensed for use as a single agent, the usual dose of chlormethine hydrochloride is 400 micrograms/kg, preferably as a single dose, although it may be divided into 2 or 4 equal doses on successive days. It is given by intravenous injection in a strength of 1 mg/mL in Water for Injections or sodium chloride 0.9%. Injection over 2 minutes into the tubing of a fast running intravenous infusion of sodium chloride 0.9% or glucose 5% may reduce the incidence of thrombophlebitis and the risk of extravasation.

The response should be assessed by the trend of the blood counts. Treatment with chlormethine may be repeated when the bone-marrow function has recovered.

Intracavitary injections of 200 to 400 micrograms/kg have been given in the treatment of malignant, especially pleural, effusions. In mycosis fungoides with extensive skin involvement, very dilute solutions of chlormethine (e.g. 200 micrograms/mL) have been applied topically.

Histiocytic syndromes. Dilute solutions of chlormethine (200 micrograms/mL) have been applied topically for the cutaneous symptoms of Langerhans-cell histiocytosis (p.650).[1,2] Such therapy was reported to effectively clear skin lesions in most patients, and be well tolerated. However, although no malignant skin disease developed during the follow-up of one group of children, the long-term effects of topical chlormethine are of concern in young patients.[2]

1. Sheehan MP, *et al.* Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; **119:** 317–21.
2. Hoeger PH, *et al.* Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; **82:** 483–7.

Mycosis fungoides. Chlormethine is used topically in the management of mycosis fungoides (p.657). A retrospective cohort analysis[1] of 203 patients treated with chlormethine found a partial response rate of 33% and a complete response rate of 50%. The median time to achieve complete response was 12 months and the time to relapse was also 12 months. Mild disease of limited skin involvement responded better than generalised patch/plaque disease, and more patients with mild disease obtained long-term remission. Maintenance therapy was used in some patients, but on cessation the relapse rate was similar to patients who did not receive maintenance therapy. Treatment had usually been applied as either an aqueous solution or an ointment containing chlormethine 100 to 200 micrograms/mL.

1. Kim YH, *et al.* Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; **139:** 165–73.

Preparations

BP 2008: Chlormethine Injection;
USP 31: Mechlorethamine Hydrochloride for Injection.

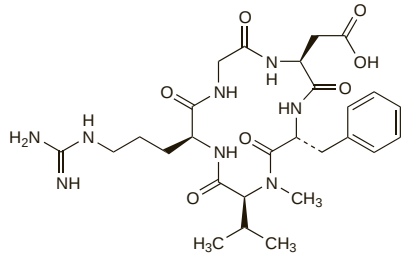
Proprietary Preparations (details are given in Part 3)
Canad.: Mustargen; ***Fr.:*** Caryolysine; ***Gr.:*** Caryolysine; ***Israel:*** Mustargen; ***Switz.:*** Mustargen; ***USA:*** Mustargen.

Cilengitide *(USAN, rINN)*

Cilengitida; Cilengitidum; EMD-121974. Cyclo(L-arginylglycyl-L-α-aspartyl-D-phenylalanyl-*N*-methyl-L-valyl).

Циленгитид

$C_{27}H_{40}N_8O_7$ = 588.7.
CAS — 188968-51-6.



Profile

Cilengitide is an angiogenesis inhibitor under investigation in the treatment of glioma, pancreatic cancer, and non-small cell lung cancer.

◊ References.

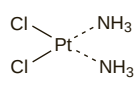
1. Friess H, *et al.* A randomized multi-center phase II trial of the angiogenesis inhibitor cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; **6:** 285.
2. Hariharan S, *et al.* Assessment of the biological and pharmacological effects of the αvβ and αvβ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; **18:** 1400–7.
3. MacDonald TJ, *et al.* Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *J Clin Oncol* 2008; **26:** 919–24.
4. Reardon DA, *et al.* Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. *Expert Opin Invest Drugs* 2008; **17:** 1225–35.

Cisplatin *(BAN, USAN, rINN)*

CDDP; Cisplatina; Cisplatine; Cisplatino; Cisplatinum; Cis-platinum; Ciszplatin; DDP; *cis*-DDP; NSC-119875; Peyrone's Salt; Platinum Diamminodichloride; Sisplatiini; Sisplatin. *cis*-Diamminedichloroplatinum.

Цисплатин

$(NH_3)_2.PtCl_2$ = 300.1.
CAS — 15663-27-1.
ATC — L01XA01.
ATC Vet — QL01XA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Cisplatin). A yellow powder or yellow or orange-yellow crystals. Slightly soluble in water; practically insoluble in alcohol; sparingly soluble in dimethylformamide. A 0.1% solution in sodium chloride 0.9% has a pH of 4.5 to 6.0 immediately after preparation. Store in airtight containers. Protect from light.
USP 31 (Cisplatin). Store in airtight containers. Protect from light.

Incompatibility. Cisplatin is rapidly degraded in the presence of bisulfite or metabisulfite,[1,2] and admixture with preparations containing these as preservatives may result in loss of activity.[2] Sodium bicarbonate may also increase the loss of cisplatin from solution, and in some cases may cause precipitation.[3] The stability of cisplatin when mixed with fluorouracil is reported to be limited, with 10% loss of cisplatin in 1.2 to 1.5 hours.[4] Mixtures with etoposide[5] in sodium chloride 0.9% injection formed a precipitate if mannitol and potassium chloride were present as additives, but not when the diluent was glucose 5% with sodium chloride 0.45%. Turbidity has been reported[6] within 4 hours of mixing 0.1% solutions of cisplatin and thiotepa in glucose 5%. Cisplatin exhibits variable incompatibility with paclitaxel, depending on the paclitaxel concentration and the temperature.[7]

Cisplatin reacts with aluminium causing loss of potency and precipitate formation. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving cisplatin.

1. Hussain AA, *et al.* Reaction of cis-platinum with sodium bisulfite. *J Pharm Sci* 1980; **69:** 364–5.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; **24:** 91–9.
3. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
4. Stewart CF, Fleming RA. Compatibility of cisplatin and fluorouracil in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1990; **47:** 1373–7.
5. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. *Am J Hosp Pharm* 1989; **46:** 1400–4.
6. Trissel LA, Martinez JF. Compatibility of thiotepa (lyophilized) with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1041–5.
7. Zhang Y, *et al.* Compatibility and stability of paclitaxel combined with cisplatin and with carboplatin in infusion solutions. *Ann Pharmacother* 1997; **31:** 1465–70.

Stability. Decomposition of cisplatin in aqueous solutions is primarily due to reversible substitution of water for chloride, and its stability is enhanced in sodium chloride solutions because of the excess of chloride ions available.[1,2] A solution in sodium chloride 0.9% injection has been reported to lose 3% of the drug in less than one hour and to remain stable at this equilibrium value for 24 hours at room temperature.[1] Stability is decreased if exposed to intense light, but the effect of normal lighting conditions is apparently smaller.[1,2] It has been recommended that admixtures of cisplatin with mannitol and magnesium sulfate (in glucose 5% with sodium chloride 0.45%) stored at room temperature in PVC bags should be used within 48 hours, but may be stored for 4 days at 4° or frozen and stored at –15° for up to 30 days.[3] However, solutions containing 600 micrograms/mL or more of cisplatin precipitate out when refrigerated and are slow to redissolve.[1]

1. Greene RF, *et al.* Stability of cisplatin in aqueous solution. *Am J Hosp Pharm* 1979; **36:** 38–43.
2. Hincal AA, *et al.* Cis-platin stability in aqueous parenteral vehicles. *J Parenter Drug Assoc* 1979; **33:** 107–16.
3. LaFollette JM, *et al.* Stability of cisplatin admixtures in polyvinyl chloride bags. *Am J Hosp Pharm* 1985; **42:** 2652.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639.

Severe nausea and vomiting occur in most patients during treatment with cisplatin; nausea may persist for up to a week.

Serious toxic effects on the kidneys, bone marrow, and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative.

Damage to the renal tubules may be evident during the second week after a dose of cisplatin and renal function must return to normal before further cisplatin is given. Adequate hydration, and use of osmotic diuretics such as mannitol to increase urine volume and thus decrease the urinary concentration of platinum, can reduce the incidence of nephrotoxicity. Electrolyte disturbances, particularly hypomagnesaemia and hypocalcaemia, may occur, possibly as a result of renal tubular damage. Hyperuricaemia is also seen.

Bone-marrow depression may be severe with higher doses of cisplatin. Nadirs in platelet and leucocyte counts occur between days 18 and 23 and most patients recover by day 39; anaemia is common and may be