Erythema and focal epidermolysis, progressing to severe radiation dermatitis with necrosis, has been reported in patients given radiation therapy with cetuximab.[14]

1. Busam KJ, *et al.* Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; **144:** 1169–76.
2. Walon L, *et al.* Éruptions acnéiformes induites par le cétuximab. *Ann Dermatol Venereol* 2003; **130:** 443–6.
3. Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. *Arch Dermatol* 2002; **138:** 129–31.
4. Jacot W, *et al.* Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. *Br J Dermatol* 2004; **151:** 238–41.
5. Monti M, *et al.* Cutaneous toxicity induced by cetuximab. *J Clin Oncol* 2003; **21:** 4651–3.
6. Peréz-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol* 2005; **23:** 5235–46.
7. Anonymous. Data support scaling cetuximab dose to provoke rash. *Pharm J* 2006; **277:** 474.
8. Dueland S, *et al.* Epidermal growth factor receptor inhibition induces trichomegaly. *Acta Oncol* 2003; **42:** 345–6.
9. Montagut C, *et al.* Abnormal hair growth in a patient with head and neck cancer treated with the anti-epidermal growth factor receptor monoclonal antibody cetuximab. *J Clin Oncol* 2005; **23:** 5273–5.
10. Boucher KW, *et al.* Paronychia induced by cetuximab, an antiepidermal growth factor receptor antibody. *J Am Acad Dermatol* 2002; **47:** 632–3.
11. Gutzmer R, *et al.* Successful treatment with oral isotretinoin of acneiform skin lesions associated with cetuximab therapy. *Br J Dermatol* 2005; **153:** 849–51.
12. Scope A, *et al.* Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 2007; **25:** 5390–6.
13. Lacouture ME, Lai SE. The PRIDE (Papulopustules and/or paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to Epidermal growth factor receptor inhibitors) syndrome. *Br J Dermatol* 2006; **155:** 852–4.
14. Budach W, *et al.* Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 2007; **357:** 514–5.

Hypomagnesaemia. A patient given cetuximab developed profound hypomagnesaemia, requiring intravenous supplementation with up to 10 g magnesium sulfate daily, throughout the duration of cetuximab therapy. This case prompted a review of 154 patients treated with cetuximab, of whom 34 had their magnesium concentrations measured at least once. Among these 34 patients, 6 had grade 3 and 2 had grade 4 hypomagnesaemia; this equated to an incidence of 24% of grade 3/4 hypomagnesaemia. In each of these cases the need for supplementation subsided after stopping cetuximab, with resolution of the hypomagnesaemia within several weeks.[1] However, it was not clear whether all patients had a normal magnesium concentration before treatment, nor was there any indication of the median time to development of hypomagnesaemia.

Another retrospective review of 114 patients did address these issues.[2] It found 48 patients had normal baseline magnesium concentrations before starting cetuximab. Of these 48 evaluable patients, 13 developed grade 3 or grade 4 hypomagnesaemia (27%); median time to onset of grade 3/4 hypomagnesaemia was 5.5 months. There was a significant association between duration of cetuximab therapy and grade of hypomagnesaemia. Magnesium replacement therapy was given to those patients with grade 3/4 toxicity. Initial attempts at oral replacement with up to 1.6 g magnesium oxide three times daily were ineffective, and intravenous supplementation was needed. However, the effects of infusion did not extend beyond 48 to 72 hours, with some patients requiring daily magnesium sulfate infusions of up to 10 g daily. Furthermore, in some patients, magnesium supplementation became less effective with continued cetuximab treatment. Of 3 patients evaluable for recovery from hypomagnesaemia after stopping cetuximab, 2 were found to correct their magnesium concentrations without supplementation after 1 month. However, 1 patient required prolonged and ongoing supplementation for more than 5 months, at 4 g infused 3 times weekly (having received 8 g daily while on cetuximab).[2] A prospective study[3] found that a progressive decrease in serum magnesium concentrations was seen in 97% of patients after treatment with cetuximab, panitumumab, or matuzumab. The authors concluded that magnesium wasting was specifically due to inhibition of the epidermal growth factor receptor (EGFR), and suggested hypomagnesaemia might be a class effect of the monoclonal antibodies directed against EGFR. However, incidence and severity may vary between products. There was also high interindividual variability; increasing age was associated with more severe hypomagnesaemia.

1. Schrag D, *et al.* Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst* 2005; **97:** 1221–4.
2. Fakih MG, *et al.* Cetuximab-induced hypomagnesemia in patients with colorectal cancer. *Clin Colorectal Cancer* 2006; **6:** 152–6.
3. Tejpar S, *et al.* Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 2007; **8:** 387–94.

Pharmacokinetics

The pharmacokinetics of cetuximab have been reported to be non-linear and dose-dependent. Steady-state concentrations are reached after 3 weeks. Cetuximab has a long elimination half-life of about 70 to 100 hours.

Uses and Administration

Cetuximab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in the treatment of EGFR-expressing metastatic colorectal cancer (p.665), either with irinotecan in patients refractory to irinotecan-based chemotherapy, or as monotherapy in patients intolerant to irinotecan. Cetuximab with radiotherapy is also used for the treatment of locally advanced squamous cell cancer of the head and neck (p.666). It is also approved as monotherapy for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. It is under investigation for non-small cell lung cancer and other solid tumours.

Cetuximab 400 mg/m^2 is given as a loading dose by intravenous infusion over 2 hours. This is followed by once weekly maintenance doses of 250 mg/m^2 given over 1 hour. Premedication with a histamine H_1-antagonist is recommended, and patients should be closely monitored for at least 1 hour after the end of the cetuximab infusion. A low-protein-binding 0.22-micrometre in-line filter should be used, and the infusion given via an infusion or syringe pump.

In combined therapy for colorectal cancer, irinotecan should not be given for at least 1 hour after the end of cetuximab infusion. In head and neck carcinoma, cetuximab therapy is started one week before radiation therapy and continued until the end of the radiation therapy period. Cetuximab is usually given 1 hour before radiation therapy. When used as monotherapy, cetuximab is continued until disease progression or unacceptable toxicity occurs.

Cetuximab doses should be permanently halved in patients who have experienced a mild to moderate infusion reaction, and stopped permanently if a severe reaction has occurred (see Adverse Effects and Precautions, above). When a severe acneform rash has occurred, the next dose should be delayed by 1 to 2 weeks. After the first occurrence, the full maintenance dose may be given if there has been improvement in the rash; after a second occurrence the next dose should be delayed and reduced to 200 mg/m^2; after a third occurrence the next dose should be delayed and reduced to 150 mg/m^2. If there is no improvement in the rash when therapy has been delayed, or if the rash has occurred 4 times, cetuximab should be stopped.

◊ References.

1. Cunningham D, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351:** 337–45.
2. Ng M, Cunningham D. Cetuximab (Erbitux)—an emerging targeted therapy for epidermal growth factor receptor-expressing tumours. *Int J Clin Pract* 2004; **58:** 970–6.
3. Wong S-F. Cetuximab: an epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. *Clin Ther* 2005; **27:** 684–94.
4. Chung KY, *et al.* Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol* 2005; **23:** 1803–10.
5. Nygren P, *et al.* Targeted drugs in metastatic colorectal cancer with special emphasis on guidelines for the use of bevacizumab and cetuximab: an Acta Oncologica expert report. *Acta Oncol* 2005; **44:** 203–17.
6. Bonner JA, *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; **354:** 567–78.
7. Frieze DA, McCune JS. Current status of cetuximab for the treatment of patients with solid tumors. *Ann Pharmacother* 2006; **40:** 241–50.
8. Blick SKA, Scott LJ. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck and metastatic colorectal cancer. *Drugs* 2007; **67:** 2585–2607.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Erbitux; ***Austral.:*** Erbitux; ***Belg.:*** Erbitux; ***Chile:*** Erbitux; ***Cz.:*** Erbitux; ***Denm.:*** Erbitux; ***Fin.:*** Erbitux; ***Fr.:*** Erbitux; ***Gr.:*** Erbitux; ***Hong Kong:*** Erbitux; ***Hung.:*** Erbitux; ***Irl.:*** Erbitux; ***Israel:*** Erbitux; ***Ital.:*** Erbitux; ***Malaysia:*** Erbitux; ***Neth.:*** Erbitux; ***Norw.:*** Erbitux; ***NZ:*** Erbitux; ***Philipp.:*** Erbitux; ***Port.:*** Erbitux; ***Singapore:*** Erbitux; ***Spain:*** Erbitux; ***Swed.:*** Erbitux; ***Switz.:*** Erbitux; ***UK:*** Erbitux; ***USA:*** Erbitux.

Chlorambucil *(BAN, rINN)*

CB-1348; Chlorambucilis; Chlorambucilum; Chlorambucyl; Chloraminophene; Chlorbutinum; Clorambucilo; Klórambucil; Klorambucil; Klorambusiili; Klorambusil; NSC-3088; WR-139013.
4-[4-Bis(2-chloroethyl)aminophenyl]butyric acid.

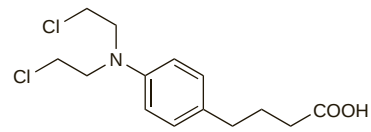
Хлорамбуцил

$C_{14}H_{19}Cl_2NO_2$ = 304.2.

CAS — 305-03-3.

ATC — L01AA02.

ATC Vet — QL01AA02.



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

Ph. Eur. 6.2 (Chlorambucil). A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone. Protect from light.

USP 31 (Chlorambucil). An off-white, slightly granular powder. M.p. 65° to 69°. Very slightly soluble in water; soluble 1 in 2 of acetone; soluble in dilute alkali. Store in airtight containers. Protect from light.

Storage. The manufacturers recommend that tablets of chlorambucil should be stored at 2° to 8° and kept dry.

Adverse Effects and Treatment

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

A reversible progressive lymphocytopenia tends to develop during treatment with chlorambucil. Neutropenia may continue to develop up to 10 days after the last dose. Irreversible bone-marrow depression can occur particularly when the total dosage for the course approaches 6.5 mg/kg.

Other reported adverse effects include gastrointestinal disturbances, hepatotoxicity, skin rashes (rarely Stevens-Johnson syndrome or toxic epidermal necrolysis), peripheral neuropathy, and central neurotoxicity, including seizures. Interstitial pneumonia and pulmonary fibrosis have occurred; the latter is usually reversible but fatalities have been recorded. Chlorambucil in high doses may produce azoospermia and amenorrhoea; sterility has developed particularly when chlorambucil has been given to boys at or before puberty.

Overdosage may result in pancytopenia and in neurotoxicity, including agitation, ataxia, and grand mal seizures.

Like other alkylating agents, chlorambucil is potentially mutagenic, teratogenic, and carcinogenic, and an increased incidence of acute leukaemias and other secondary malignancies has been reported in patients who have received the drug.

Effects on the bladder. Chlorambucil-induced cystitis was reported in a 73-year-old woman given 2 mg daily for over 2 years for the treatment of lymphocytic lymphoma.[1]

1. Daoud D, *et al.* Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; **11:** 491.

Effects on the eyes. Visual impairment and optic atrophy in a patient who had been receiving chlorambucil for 5 years to control non-Hodgkin's lymphoma were thought to be due to the drug,[1] although ocular effects are extremely rare with chlorambucil.

1. Yiannakis PH, Larner AJ. Visual failure and optic atrophy associated with chlorambucil therapy. *BMJ* 1993; **306:** 109.

Effects on the nervous system. There have been a small number of reports of seizures in patients given chlorambucil. A review[1] of these suggested that in adults, patients with a history of seizures, or those given high doses of chlorambucil may be at increased risk. The reports in children consisted mainly of patients being treated for nephrotic syndrome, possibly because the condition may alter the pharmacokinetics of chlorambucil.

1. Salloum E, *et al.* Chlorambucil-induced seizures. *Cancer* 1997; **79:** 1009–13.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Chlorambucil should be avoided, or given with great care and at reduced doses, for at least 4 weeks after treatment with radiotherapy or other

antineoplastics (unless only low doses of radiation have been given to parts remote from the bone marrow and the neutrophil and platelet counts are not depressed). The dose should be reduced if there is lymphocytic involvement of the bone marrow or if it is hypoplastic. Chlorambucil should be given with care to patients with impaired renal function; consideration should also be given to dose reduction in patients with gross hepatic dysfunction. Children with nephrotic syndrome, patients receiving high-dose pulse therapy with chlorambucil, and those with a history of seizures, may be at increased risk of seizures. Regular blood counts are required during therapy.

Handling and disposal. Chlorambucil is irritant; avoid contact with skin and mucous membranes.

Urine produced for up to 48 hours after a dose of chlorambucil 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.

Porphyria. Chlorambucil is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For a general outline of antineoplastic drug interactions, see p.642.

Pharmacokinetics

Chlorambucil is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses and is reported to have a terminal half-life in plasma of about 1.5 hours. It is extensively metabolised in the liver, primarily to active phenylacetic acid mustard, which has a slightly longer plasma half-life of about 1.8 to 2.5 hours, and which like chlorambucil also undergoes some spontaneous degradation to further derivatives. Chlorambucil and its metabolites are extensively protein bound. It is excreted in the urine almost entirely as metabolites with less than 1% unchanged.

Uses and Administration

Chlorambucil is an antineoplastic derived from chlormethine (p.697) and has a similar mode of action. It acts on lymphocytes and to a lesser extent on neutrophils and platelets. Chlorambucil is most valuable in those conditions associated with the proliferation of white blood cells, especially lymphocytes, and is used in the treatment of chronic lymphocytic leukaemia and lymphomas, including Hodgkin's disease. It is also used in Waldenström's macroglobulinaemia and has been given in gestational trophoblastic tumours. Although formerly widely used in the management of polycythaemia vera it has largely been superseded.

Chlorambucil also has immunosuppressant properties and has been given in auto-immune disorders including amyloidosis, Behçet's syndrome, glomerular kidney disease, primary biliary cirrhosis, polymyositis, rheumatoid arthritis, and sarcoidosis.

The use of chlorambucil in these disorders is discussed further elsewhere, as indicated by the cross-references given below.

Chlorambucil is better tolerated than chlormethine hydrochloride and serious bone-marrow toxicity is not usually a problem with normal doses. When used as a single-agent antineoplastic for chronic lymphocytic leukaemia and lymphomas, chlorambucil is licensed for oral use in usual initial doses of 100 to 200 micrograms/kg daily (usually 4 to 10 mg once daily), for 3 to 8 weeks. A dose of 100 micrograms/kg daily may be adequate for the treatment of non-Hodgkin's lymphoma; 150 micrograms/kg daily until the total leukocyte count falls below 10 000 cells/mm^3 may be used in chronic lymphocytic leukaemia; and in Hodgkin's disease, 200 micrograms/kg daily is usually required. Lower doses may be given as part of a combination regimen. If lymphocytic infiltration of the bone marrow is present or if the bone marrow is hypoplastic, the daily dose should not exceed 100 micrograms/kg. Alternatively, high-dose chlorambucil may be given intermittently. For example, in chronic lymphocytic leukaemia it may be given in an initial single dose of 400 micrograms/kg increased by 100 micrograms/kg at each 2- or 4-week dose interval until control of lymphocytosis is achieved or toxicity occurs.

Once a remission has been established the patient may receive continuous maintenance with 30 to 100 micrograms/kg daily. However, short intermittent courses appear to be safer and are generally preferred for maintenance.

In patients with Waldenström's macroglobulinaemia chlorambucil is licensed in an initial oral dose of 6 to 12 mg daily until leucopenia develops. Maintenance therapy with doses of 2 to 8 mg daily may then be given indefinitely.

Total and differential white cell counts and haemoglobin and platelet examinations are recommended each week during treatment with chlorambucil.

Amyloidosis. Chlorambucil may be of use in preserving kidney function and improving survival in patients with amyloidosis secondary to rheumatic disease,[1-4] the management of which is discussed in more detail on p.743.

1. Berglund K, *et al.* Alkylating cytostatic treatment in renal amyloidosis secondary to rheumatic disease. *Ann Rheum Dis* 1987; **46:** 757–62.
2. Berglund K, *et al.* Results, principles and pitfalls in the management of renal AA-amyloidosis; a 10-21 year followup of 16 patients with rheumatic disease treated with alkylating cytostatics. *J Rheumatol* 1993; **20:** 2051–7.
3. David J, *et al.* Amyloidosis in juvenile chronic arthritis: a morbidity and mortality study. *Clin Exp Rheumatol* 1993; **11:** 85–90.
4. Savolainen HA. Chlorambucil in severe juvenile chronic arthritis: longterm followup with special reference to amyloidosis. *J Rheumatol* 1999; **26:** 898–903.

Blood disorders, non-malignant. Chlorambucil may produce a response in cold auto-immune haemolytic anaemia (p.1043).

Connective tissue and muscular disorders. Chlorambucil has been used as a corticosteroid-sparing agent in patients with Behçet's syndrome (p.1499). It has occasionally been tried in polymyositis (p.1510). In both these conditions, the potential benefits must be weighed against the possibility of toxicity.

Kidney disorders, non-malignant. Chlorambucil has been used in some forms of glomerular kidney disease (p.1504). In minimal change nephropathy, in which cytotoxics are reserved for the most severe cases because of fears about toxicity, cyclophosphamide is generally preferred to chlorambucil because it is perceived as entailing somewhat less risk; chlorambucil has been used with corticosteroids in patients with membranous nephropathy,[1-3] but again cyclophosphamide may be better tolerated.

1. Ponticelli C, *et al.* Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous nephropathy. *N Engl J Med* 1992; **327:** 599–603.
2. Reichert LJM, *et al.* Preserving renal function in patients with membranous nephropathy: daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 1994; **121:** 328–33.
3. Ponticelli C, *et al.* A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 1995; **48:** 1600–4.

Liver disorders, non-malignant. No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p.2408). Chlorambucil is one of a number of drugs for which reports of benefit exist.[1]

1. Hoofnagle JH, *et al.* Randomized trial of chlorambucil for primary biliary cirrhosis. *Gastroenterology* 1986; **91:** 1327–34.

Malignant neoplasms. Chlorambucil is used in the management of a number of haematological malignancies including chronic lymphocytic leukaemia (p.653), Hodgkin's disease (p.655), indolent low-grade non-Hodgkin's lymphomas (p.656), and Waldenström's macroglobulinaemia (p.658). It was formerly used in polycythaemia vera (p.654) but is now largely superseded.

Ocular disorders, non-malignant. Chlorambucil is one of the immunosuppressants that may be considered for patients with uveitis (p.1515) unresponsive to corticosteroids in tolerable doses.[1-3]

1. Mudun AB, *et al.* Short-term chlorambucil for refractory uveitis in Behcet's disease. *Ocul Immunol Inflamm* 2001; **9:** 219–29.
2. Miserocchi E, *et al.* Efficacy and safety of chlorambucil in intractable noninfectious uveitis. *Ophthalmology* 2002; **109:** 137–42.
3. Goldstein DA, *et al.* Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. *Ophthalmology* 2002; **109:** 370–7.

Pemphigus and pemphigoid. Chlorambucil with prednisone or prednisolone has been reported[1,2] to be effective in the treatment of pemphigus and pemphigoid (p.1582).

1. Shah N, *et al.* The use of chlorambucil with prednisone in the treatment of pemphigus. *J Am Acad Dermatol* 2000; **42:** 85–8.
2. Chave TA, *et al.* Chlorambucil as a steroid-sparing agent in bullous pemphigoid. *Br J Dermatol* 2004; **151:** 1107–8.

Rheumatoid arthritis. Chlorambucil has been used for its immunosuppressant properties in a few patients with severe rheumatoid arthritis (p.11), especially with vasculitis, who have failed to respond to other drugs. However, the use of cytotoxic immunosuppressants other than methotrexate is considered debatable.

Sarcoidosis. Where drug therapy is required for sarcoidosis (p.1512), corticosteroids are the usual treatment. Chlorambucil is one of a number of cytotoxic immunosuppressants that have been tried, with variable results, as a second-line therapy.

Preparations

BP 2008: Chlorambucil Tablets;
USP 31: Chlorambucil Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Leukeran; ***Austral.:*** Leukeran; ***Austria:*** Leukeran; ***Belg.:*** Leukeran; ***Braz.:*** Leukeran; ***Canad.:*** Leukeran; ***Chile:*** Leukeran; ***Cz.:*** Leukeran; ***Denm.:*** Leukeran; ***Fin.:*** Leukeran; ***Ger.:*** Leukeran; ***Gr.:*** Leukeran; ***Hong Kong:*** Leukeran; ***India:*** Leukeran; ***Irl.:*** Leukeran; ***Israel:*** Leukeran; ***Ital.:*** Leukeran; ***Malaysia:*** Leukeran; ***Mex.:*** Leukeran; ***Neth.:*** Leukeran; ***Norw.:*** Leukeran; ***NZ:*** Leukeran; ***Philipp.:*** Leukeran; ***Pol.:*** Leukeran; ***Port.:*** Leukeran; ***Rus.:*** Leukeran (Лейкеран); ***S.Afr.:*** Leukeran; ***Singapore:*** Leukeran; ***Spain:*** Leukeran; ***Swed.:*** Leukeran; ***Switz.:*** Leukeran; ***Thai.:*** Leukeran; ***Turk.:*** Leukeran; ***UK:*** Leukeran.

Chlormethine Hydrochloride *(BANM, rINNM)*

Chlorethazine Hydrochloride; Chlorméthine, Chlorhydrate de; Chlormethini Hydrochloridum; Hidrocloruro de clormetina; HN2 (chlormethine); Klormetin Hidroklorür; Mechlorethamine Hydrochloride; Mustin Hidroklorür; Mustine Hydrochloride; Nitrogen Mustard (chlormethine); NSC-762; WR-147650. Bis(2-chloroethyl)methylamine hydrochloride; 2,2′-Dichloro-*N*-methyldiethylamine hydrochloride.

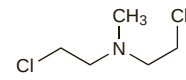
Хлорметина Гидрохлорид

$C_5H_{11}Cl_2N,HCl$ = 192.5.

CAS — 51-75-2 (chlormethine); 55-86-7 (chlormethine hydrochloride).

ATC — L01AA05.

ATC Vet — QL01AA05.



(chlormethine)

Pharmacopoeias. In *Br.*, *Chin.*, *Int.*, and *US.*

BP 2008 (Chlormethine Hydrochloride). A white or almost white, hygroscopic, vesicant, crystalline powder or mass. Very soluble in water. Store at a temperature of 8° to 15°.

USP 31 (Mechlorethamine Hydrochloride). A white, hygroscopic, crystalline powder. A 0.2% solution in water has a pH of 3.0 to 5.0. Store in airtight containers. Protect from light.

Stability. Solutions of chlormethine hydrochloride lose their activity very rapidly, particularly at neutral or alkaline pH.

A study[1] using an assay specific for chlormethine found that a 0.1% solution in Water for Injections or sodium chloride 0.9% injection underwent a loss of about 10% when stored for 6 hours at room temperature, and of about 4 to 6% when stored for the same period at 4°; similar results were obtained whether the solution was stored in glass vials or plastic syringes. Solutions in 500 mL of sodium chloride or glucose 5% injection and stored in PVC infusion bags were still less stable, with 15% and 10% degradation respectively after 6 hours at room temperature.

Chlormethine hydrochloride has been used in extemporaneous ointment preparations in the treatment of mycosis fungoides.[2] One formulation of chlormethine hydrochloride, dissolved in acetone and worked into white soft paraffin, was reported[3] to be stable for at least 84 days when stored at 4°, and for at least 40 days at 37°.

1. Kirk B. Stability of reconstituted Mustine Injection BP during storage. *Br J Parenter Ther* 1986; **7:** 86–92.
2. Price NM, *et al.* Ointment-based mechlorethamine treatment for mycosis fungoides. *Cancer* 1983; **52:** 2214–19.
3. Cummings J, *et al.* The long term stability of mechlorethamine hydrochloride (nitrogen mustard) ointment measured by HPLC. *J Pharm Pharmacol* 1993; **45:** 6–9.

Adverse Effects, Treatment, and Precautions

For general discussions see Antineoplastics, p.635, p.639, and p.641.

Chlormethine hydrochloride is extremely toxic and its use is invariably accompanied by adverse effects. Severe nausea and vomiting may begin within an hour of injection of the drug and last for some hours; antiemetics should be given before treatment. It causes varying degrees of bone-marrow depression depending on the dose. In heavily pretreated patients, or when the total dose for a single course exceeds 400 micrograms/kg, there is a risk of severe and possibly fatal depression with anaemia, lymphocytopenia, granulocytopenia, and thrombocytopenia with consequent haemorrhage. Depression of lymphocytes may be apparent within 24 hours of a dose and maximum suppression of granulocytes and platelets occurs within 7 to 21 days; haematological recovery may be adequate after 4 weeks.