upper lobe pulmonary fibrosis occurring in adults given carmustine and high-dose chemotherapy.[3]

1. O'Driscoll BR, *et al.* Late carmustine lung fibrosis: age at treatment may influence severity and survival. *Chest* 1995; **107:** 1355–7.
2. Lohani S, *et al.* 25-year study of lung fibrosis following carmustine therapy for brain tumor in childhood. *Chest* 2004; **126:** 1007.
3. Parish JM, *et al.* Upper lobe pulmonary fibrosis associated with high-dose chemotherapy containing BCNU for bone marrow transplantation. *Mayo Clin Proc* 2003; **78:** 630–4.

Extravasation. For mention of the use of sodium bicarbonate as a specific antidote after carmustine extravasation, see under Treatment of Adverse Effects of Antineoplastics, p.640.

Precautions

For reference to the precautions necessary with antineoplastics, see p.641. Carmustine should be used with extreme caution in children, who are at particular risk of severe delayed pulmonary toxicity. It should also be used with caution in patients with reduced lung function. Lung function should be monitored before and frequently during therapy. Blood counts should be monitored weekly during therapy, and for at least 6 weeks after the last dose. Renal and hepatic function should also be monitored periodically.

Handling and disposal. Carmustine has been shown to permeate latex, PVC, and rubber gloves, the degree of permeation tending to increase with time,[1-3] up to an equilibrium value.[2] The permeation rate appears not to depend solely on glove thickness and material, and may be different for different gloves made from the same material.[2] The time for initial penetration was reported to vary between 4.7 and 66.0 minutes in one study,[2] and gloves could be chosen accordingly depending on the anticipated length of exposure. Double-gloving, particularly with thicker PVC[1] or ethylmethacrylate[3] gloves, may offer some additional protection.

1. Connor TH, *et al.* Permeability of latex and polyvinyl chloride gloves to carmustine. *Am J Hosp Pharm* 1984; **41:** 676–9.
2. Thomas PH, Fenton-May V. Protection offered by various gloves to carmustine exposure. *Pharm J* 1987; **238:** 775–7.
3. Mellström GA, *et al.* Barrier effect of gloves against cytostatic drugs. *Curr Probl Dermatol* 1996; **25:** 163–9.

Interactions

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

Cimetidine. Reductions in white cell counts and platelet counts well below those normally attributed to treatment with carmustine alone were seen in 6 of 8 patients receiving their first course of carmustine and steroids with cimetidine given prophylactically,[1] and in 9 patients in a further study.[2] Cimetidine was also reported to exacerbate the neutropenia and leucopenia in a patient receiving lomustine.[3]

1. Selker RG, *et al.* Bone-marrow depression with cimetidine plus carmustine. *N Engl J Med* 1978; **299:** 834.
2. Volkin RL, *et al.* Potentiation of carmustine-cranial irradiation-induced myelosuppression by cimetidine. *Arch Intern Med* 1982; **142:** 243–5.
3. Hess WA, Kornblith PL. Combination of lomustine and cimetidine in the treatment of a patient with malignant glioblastoma: a case report. *Cancer Treat Rep* 1985; **69:** 733.

Pharmacokinetics

Intravenous carmustine is rapidly metabolised, and no intact drug is detectable after 15 minutes; metabolites have a much longer half-life and are presumed to be responsible for its activity. It is primarily excreted in the urine; some is also excreted as carbon dioxide, via the lungs. Carmustine readily crosses the blood-brain barrier, appearing in CSF in substantial concentrations almost immediately after intravenous injection. Carmustine diffuses from polymer implants into surrounding brain tissue; however, tissue and plasma concentrations after implantation have not been determined.

Uses and Administration

Carmustine is a cell-cycle phase non-specific antineoplastic belonging to the nitrosourea group of compounds, which are considered to function as alkylating agents. It is believed to alkylate DNA and RNA, and may also inhibit enzymatic processes by carbamoylation of amino acids in proteins. Carmustine is used in the treatment of brain tumours, and in combination chemotherapy for multiple myeloma. It may be given as second-line therapy in Hodgkin's disease, non-Hodgkin's lymphoma, and some other malignancies (see below).

Carmustine is licensed for use as a single agent either as a single dose of 150 to 200 mg/m^2 or divided into doses of 75 to 100 mg/m^2 given on 2 successive days. Doses are given by intravenous infusion over 1 to 2 hours in sodium chloride 0.9% or glucose 5%. Lower doses are usually given in combination therapy, except for conditioning before stem-cell transplantation. Doses may be repeated every 6 weeks provided that blood counts have returned to acceptable levels. Subsequent doses must be adjusted according to the haematological response (see also Bone-marrow Depression, p.639).

Polymer implants containing carmustine have been developed for implantation into the brain in the localised treatment of high-grade malignant glioma or recurrent glioblastoma multiforme. Each implant contains 7.7 mg of carmustine: up to 8 such implants are inserted into the cavity left by surgical removal of the tumour.

Amyloidosis. For mention of chemotherapy with epirubicin, cyclophosphamide, and carmustine to suppress amyloidosis after cardiac transplantation, see p.743.

Malignant neoplasms. Carmustine has been used in chemotherapeutic regimens for a number of malignancies. Because of its ability to pass the blood-brain barrier it has been extensively used in malignant neoplasms of the brain (p.660). As an extension of such use, carmustine-releasing wafers have been implanted directly into the brain.[1] In a multicentre study[2] in patients with recurrent malignant glioma, biodegradable poly(carboxyphenoxypropane/sebacic acid)anhydride polymer wafers containing carmustine implanted into the brain after tumour resection produced a median survival of 31 weeks compared with 23 weeks for placebo. A subsequent small cohort study[3] failed to find a clear survival benefit associated with wafer implantation in recurrent glioma, and reported a higher rate of complications including seizures, cerebral oedema, CSF leaks, sepsis, and wound infections. The limitations of this small study were acknowledged by the authors, and a review[4] that included these studies concluded that despite limited data, carmustine wafers do provide some survival benefit. A randomised trial in 240 patients found that treatment with carmustine wafers reduced the risk of death by 28% compared with placebo;[5] this survival advantage was maintained at 1, 2, and 3 years, with statistical significance at 3 years.[6] The adverse effect profile was similar for carmustine and placebo groups,[5] and a retrospective review[7] found carmustine wafers to be well tolerated with a low incidence of surgical complications such as infection. However, it was noted that, in some patients, neurological symptoms developed during an attempted tapering of dexamethasone dosage after carmustine with radiotherapy and that close supervision of patients is warranted. Treatment effects or necrosis can radiographically mimic recurrent tumour in a proportion of patients;[7] implantation of wafers caused morphological changes of the brain immediately adjacent to the implants.[8]

Other conditions in which carmustine has been employed, include malignant melanoma (p.673), Hodgkin's disease (p.655), and multiple myeloma (p.658).

1. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther* 2008; **8:** 343–59.
2. Brem H, *et al.* Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. *Lancet* 1995; **345:** 1008–12.
3. Subach BR, *et al.* Morbidity and survival after 1,3-bis(2-chloroethyl)-1-nitrosourea wafer implantation for recurrent glioblastoma: a retrospective case-matched cohort series. *Neurosurgery* 1999; **45:** 17–23.
4. Engelhard HH. The role of interstitial BCNU chemotherapy in the treatment of malignant glioma. *Surg Neurol* 2000; **53:** 458–64.
5. Westphal M, *et al.* A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncol* 2003; **5:** 79–88.
6. Westphal M, *et al.* Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148:** 269–75.
7. Kleinberg LR, *et al.* Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest* 2004; **22:** 1–9.
8. Giese A, *et al.* Pattern of recurrence following local chemotherapy with biodegradable carmustine (BCNU) implants in patients with glioblastoma. *J Neurooncol* 2004; **66:** 351–60.

Mycosis fungoides. Topical application of carmustine has been used successfully[1-5] in early mycosis fungoides (p.657). Erythema and telangiectasia were the most frequent adverse effects.

1. Zackheim HS, *et al.* Topical carmustine (BCNU) for mycosis fungoides and related disorders: a 10-year experience. *J Am Acad Dermatol* 1983; **9:** 363–74.
2. Zackheim HS, *et al.* Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; **22:** 802–10.
3. Zackheim HS. Topical carmustine (BCNU) for patch/plaque mycosis fungoides. *Semin Dermatol* 1994; **13:** 202–6.
4. Heald PW, Glusac EJ. Unilesional cutaneous T-cell lymphoma: clinical features, therapy, and follow-up of 10 patients with a treatment-responsive mycosis fungoides variant. *J Am Acad Dermatol* 2000; **42:** 283–5.
5. Zackheim HS. Topical carmustine (BCNU) in the treatment of mycosis fungoides. *Dermatol Ther* 2003; **16:** 299–302.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: BiCNU; ***Austral.:*** BiCNU; Gliadel; ***Austria:*** Carmubris; ***Belg.:*** Nitrumon†; ***Braz.:*** Becenun; ***Canad.:*** BiCNU; ***Chile:*** BiCNU; Gliadel†; ***Cz.:*** BiCNU; ***Fr.:*** BiCNU; Gliadel; ***Ger.:*** Carmubris; ***Gr.:*** Carmubris; Gliadel; Nitrumon†; ***Hong Kong:*** BiCNU; ***Hung.:*** BiCNU; ***Irl.:*** BiCNU; ***Israel:*** BiCNU†; Gliadel; ***Ital.:*** Gliadel; ***Malaysia:*** BiCNU†; Gliadel; ***Mex.:*** BiCNU; ***Neth.:*** Gliadel; ***NZ:*** BiCNU; ***Philipp.:*** BiCNU; ***Port.:*** Gliadel; ***S.Afr.:*** BiCNU; Gliadel; ***Singapore:*** BiCNU; ***Spain:*** Gliadel; ***Turk.:*** Nitrumon; ***UK:*** BiCNU†; Gliadel; ***USA:*** BiCNU; Gliadel.

Cetuximab *(USAN, rINN)*

C-225; Cétuximab; Cetuximabum. Immunoglobulin G1 (human-mouse monoclonal C225 γ1-chain anti-human epidermal growth factor receptor), disulfide with human-mouse monoclonal C225 κ-chain, dimer.

Цетуксимаб

CAS — 205923-56-4.

ATC — L01XC06.

ATC Vet — QL01XC06.

Adverse Effects, Treatment, and Precautions

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

Adverse effects associated with cetuximab include skin reactions, asthenia, and gastrointestinal disturbances. Skin reactions present mainly as an acneform rash, and, if severe, require dosage adjustment (see Uses and Administration, below). Infusion reactions suggestive of a cytokine release syndrome can occur, usually with the first dose. Mild reactions include chills, fever, and dyspnoea; severe reactions include bronchospasm, urticaria, hypotension, and loss of consciousness, and fatalities have occurred. Premedication with a histamine H_1-antagonist is recommended, and dose adjustment may be necessary (see below). Cardiopulmonary arrest and/or sudden death has been reported in patients treated with cetuximab and radiation therapy, and cetuximab should be given with caution in head and neck cancer patients with coronary artery disease, congestive cardiac failure, or arrhythmias. Hypomagnesaemia can occur; patients should be monitored for this and accompanying hypocalcaemia and hypokalaemia both during, and for up to 8 weeks after stopping, cetuximab therapy. Interstitial lung disease and pneumonitis have been reported rarely.

Effects on the skin, hair, and nails. Acneform follicular rashes have been reported with cetuximab therapy;[1,2] lesions were pustular and papular,[2-4] and commonly occurred on the face, scalp, chest, and upper back.[1-5] It has been suggested that there is a relationship between rash and response to therapy or survival, i.e. that rash might be a surrogate marker of cetuximab activity;[6] doubling the cetuximab dose in patients without severe initial skin reactions is reported to increase their response rate to therapy.[7] A few cases of lengthening eyelash and eyebrow hair[8] and abnormal growth of chest hair[9] have been described. Paronychia has also been reported,[1,5,10] as have intraoral aphthous ulcers.[1]

Treatment with oral isotretinoin 500 micrograms/kg daily has been reported to successfully clear acneform skin lesions in 2 patients; topical therapy with metronidazole 0.75% gel or erythromycin 1% was also used.[11] Prophylactic oral minocycline 100 mg daily, started on the same day as cetuximab and given for 8 weeks, significantly reduced total facial lesion counts in the first 4 weeks when compared with placebo; this difference tapered by the end of 8 weeks of treatment. Topical tazarotene showed no clinical benefit and caused local irritation that forced tazarotene to be stopped in many patients.[12]

Some have suggested that the clinical findings of papulopustular rash, nail and periungual abnormalities, alterations in hair texture and growth, and dry skin and pruritus, constitute a syndrome unique to the epidermal growth factor receptor (EGFR) inhibitors, believed to be due to EGFR inhibition in the epidermis, hair follicle, and nail matrix.[13]

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.

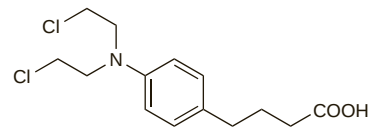
Хлорамбуцил

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