Neth.: Xeloda; ***Norw.:*** Xeloda; ***NZ:*** Xeloda; ***Philipp.:*** Xeloda; ***Pol.:*** Xeloda; ***Port.:*** Xeloda; ***Rus.:*** Xeloda (Кселода); ***S.Afr.:*** Xeloda; ***Singapore:*** Xeloda; ***Spain:*** Xeloda; ***Swed.:*** Xeloda; ***Switz.:*** Xeloda; ***Thai.:*** Xeloda; ***Turk.:*** Xeloda; ***UK:*** Xeloda; ***USA:*** Xeloda; ***Venez.:*** Xeloda.

Carboplatin *(BAN, USAN, rINN)*

Carboplatine; Carboplatino; Carboplatinum; CBDCA; JM-8; Karboplatiini; Karboplatin; Karboplatina; NSC-241240. *cis*-Diammine(cyclobutane-1,1-dicarboxylato)platinum.

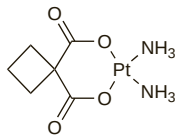
Карбоплатин

$C_6H_{12}N_2O_4Pt$ = 371.3.

CAS — 41575-94-4.

ATC — L01XA02.

ATC Vet — QL01XA02.



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

Ph. Eur. 6.2 (Carboplatin). A colourless, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol and in acetone. Protect from light.

USP 31 (Carboplatin). A 1% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. Carboplatin reacts with aluminium causing loss of potency and forming a precipitate. Needles, syringes, catheters or giving sets that contain aluminium should not be used for preparing or giving carboplatin.

Stability. About 5% of the initial carboplatin concentration was lost over 24 hours when solutions were diluted in sodium chloride 0.9% and stored at 25°; lesser amounts of degradation were seen at lower sodium chloride concentrations, but carboplatin was apparently stable over this period if diluted with glucose 5%.[1] The authors suggested that chloride-containing infusion solutions are not suitable for carboplatin, not only because of the loss of active drug but because of the possibility that conversion to cisplatin may be occurring, with a risk of increased toxicity.[1] This has been contested by the manufacturers (*Bristol-Myers, USA*), who found that only 0.5% or 0.7%, depending on formulation, of a carboplatin solution in sodium chloride 0.9%, had been converted to cisplatin after 24 hours.[2] However, the total degradation of carboplatin was not measured. In another study, the authors calculated the time to 5% degradation of carboplatin at 25° as 29.2 hours in sodium chloride 0.9% compared with 52.7 hours in water.[3] They concluded that carboplatin should not be diluted in sodium chloride 0.9% when intended for continuous infusion over a prolonged period.[3] Carboplatin in glucose 5% was reported to be stable for 7 days at 25° in PVC bags when protected from light.[4]

1. Cheung Y-W, *et al.* Stability of cisplatin, iproplatin, carboplatin, and tetraplatin in commonly used intravenous solutions. *Am J Hosp Pharm* 1987; **44:** 124–30.
2. Perrone RK, *et al.* Extent of cisplatin formation in carboplatin admixtures. *Am J Hosp Pharm* 1989; **46:** 258–9.
3. Allsopp MA, *et al.* The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int J Pharmaceutics* 1991; **69:** 197–210.
4. Diaz Amador F, *et al.* Stability of carboplatin in polyvinyl chloride bags. *Am J Health-Syst Pharm* 1998; **55:** 602, 604.

Adverse Effects, Treatment, and Precautions

As for Cisplatin, p.698; nephrotoxicity and gastrointestinal toxicity are less severe than with cisplatin and reversible myelosuppression is the dose-limiting toxicity; platelet counts reach a nadir between 14 and 21 days after a dose, with recovery within 35 days, but recovery from leucopenia may be slower. Myelosuppression may be more severe and prolonged in patients with impaired renal function. Carboplatin should therefore be given at reduced doses to these patients and should be avoided if creatinine clearance is 20 mL/minute or less. Weekly blood counts and regular renal and hepatic function tests are recommended in all patients during therapy. Neurological function including assessment of hearing should also be monitored.

Incidence of adverse effects. The manufacturers analysed the adverse effects of carboplatin in studies involving 710 patients.[1] Myelosuppression was the dose-limiting toxicity: leucopenia occurred in 55% of the evaluable patients. Leucopenia and thrombocytopenia result in symptomatic events such as infection or bleeding in a minority of patients. Anaemia was frequent (59%) and required transfusional support in about one-fifth of the patients. Nephrotoxicity and serum electrolyte loss were much less of a problem; no high-volume fluid hydration or electrolyte supplementation was given during treatment. Vomiting occurred in about half the patients, and a further 25% had nausea without vomiting. Peripheral neurotoxicity was reported in 6% of evaluable patients and clinical ototoxicity occurred in only 8 cases or about 1% (but see also Effects on the Ears, below). Increases in liver enzyme values have also been reported, as well as, more rarely, alopecia, skin rash, a flu-like syndrome, and local effects at the injection site.

1. Canetta R, *et al.* Carboplatin: the clinical spectrum to date. *Cancer Treat Rev* 1985; **12** (suppl A): 125–36.

Effects on the ears. Carboplatin is less ototoxic than cisplatin, but ototoxicity is still common with carboplatin when used in high doses, for example, as part of conditioning regimens for bone marrow transplantation.[1,2] There was some evidence that sodium thiosulfate reduced carboplatin-induced hearing loss, when carboplatin was used for CNS malignancy.[3,4]

1. Freilich RJ, *et al.* Hearing loss in children with brain tumors treated with cisplatin and carboplatin-based high-dose chemotherapy with autologous bone marrow rescue. *Med Pediatr Oncol* 1996; **26:** 95–100.
2. Parsons SK, *et al.* Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. *Bone Marrow Transplant* 1998; **22:** 669–74.
3. Neuwelt EA, *et al.* First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. *J Pharmacol Exp Ther* 1998; **286:** 77–84.
4. Doolittle ND, *et al.* Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001; **7:** 493–500.

Effects on the eyes. Cortical blindness developed in 2 patients with impaired renal function receiving high-dose carboplatin;[1] although 10 cases of visual disturbances in patients receiving carboplatin had been reported to the manufacturers, none of these had sudden blindness and it was thought that the effect represented CNS toxicity in the presence of poor renal excretion. It was concluded that it was unwise to give high-dose carboplatin to patients whose glomerular filtration rate is less than 50 mL/minute.

1. O'Brien MER, *et al.* Blindness associated with high-dose carboplatin. *Lancet* 1992; **339:** 558.

Effects on the kidneys. Although carboplatin is reported to be much less nephrotoxic than cisplatin it is not devoid of adverse effects on the kidney.[1-8] Salt wasting nephropathy (similar to that seen with cisplatin),[1] and decreased creatinine clearance[2] and glomerular filtration rate[3] have occurred, as has acute renal failure, including in 2 patients given intraperitoneal carboplatin[4] (although these patients had been heavily pretreated with cisplatin). It has been suggested that renal toxicity may be more likely at cumulative carboplatin doses of about 750 mg/m^2 or more,[3] and there is some evidence to suggest that intensive hydration may ameliorate nephrotoxic effects.[2]

1. Welborn J, *et al.* Renal salt wasting and carboplatinum. *Ann Intern Med* 1988; **108:** 640.
2. Reed E, Jacob J. Carboplatin and renal dysfunction. *Ann Intern Med* 1989; **110:** 409.
3. Smit EF, *et al.* Carboplatin and renal function. *Ann Intern Med* 1989; **110:** 1034.
4. McDonald BR, *et al.* Acute renal failure associated with the use of intraperitoneal carboplatin: a report of two cases and review of the literature. *Am J Med* 1991; **90:** 386–91.
5. Frenkel J, *et al.* Acute renal failure in high dose carboplatin chemotherapy. *Med Pediatr Oncol* 1995; **25:** 473–4.
6. Agraharkar M, *et al.* Carboplatin-related hematuria and acute renal failure. *Am J Kidney Dis* 1998; **32:** E5.
7. Butani L, *et al.* End-stage renal disease after high-dose carboplatinum in preparation of autologous stem cell transplantation. *Pediatr Transplant* 2003; **7:** 408–12.
8. Tarrass F, *et al.* End-stage renal disease following carboplatin chemotherapy for a nasopharyngeal carcinoma. *Ren Fail* 2007; **29:** 1049–51.

Hypersensitivity. In one series, 12% of 205 patients treated with carboplatin developed a hypersensitivity reaction after a median of 8 courses of platinum therapy.[1] Symptoms were at least moderately severe in half of the patients. Reactions to cisplatin would be anticipated in patients who have been previously sensitised to carboplatin—for 1 such case see p.699. In another study,[2] patients receiving more than 7 courses of carboplatin therapy were given a skin test before each course in an attempt to identify patients at risk for hypersensitivity reactions. The test consisted of 0.02 mL of an undiluted aliquot of their planned infusion, injected intradermally 1 hour before the dose. A negative skin test accurately predicted the absence of a hypersensitivity reaction. In a further extended report[3] by the same group, the skin test had been given about 30 minutes before carboplatin doses in 126 women who had already received at least 6 courses of a platinum-based regimen for a gynaecological cancer. Of 668 negative skin tests, a hypersensitivity reaction developed on 10 occasions (in 7 patients), giving a false-negative rate of 1.5%. None of the reactions were severe. Of the 39 patients who had a positive skin test, 7 elected to receive the dose of carboplatin; 6 of these developed a hypersensitivity reaction but none were severe.

The use of a desensitisation regimen has been successful in a small number of patients,[4] although others have not found it useful.[5]

1. Markman M, *et al.* Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol* 1999; **17:** 1141–5.
2. Zanotti KM, *et al.* Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol* 2001; **19:** 3126–9.
3. Markman M, *et al.* Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 2003; **21:** 4611–14.
4. Markman M, *et al.* Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. *J Cancer Res Clin Oncol* 2004; **130:** 25–8.
5. Lafay-Cousin L, *et al.* Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer* 2008; **112:** 892–9.

Pregnancy. For a report of the successful use of carboplatin-based chemotherapy during pregnancy, with no adverse effects on the infant, see Pregnancy, under Cisplatin, p.699.

Interactions

As for Cisplatin, p.700.

Pharmacokinetics

Intravenous carboplatin exhibits a biphasic elimination and is excreted primarily in the urine, about 70% of a dose being excreted within 24 hours, almost all unchanged. The terminal half-life of intact carboplatin is reported to be about 1.5 to 6 hours. Platinum from carboplatin slowly becomes protein bound, and is subsequently excreted with a half-life of 5 days or more.

◊ References.

1. van der Vijgh WJF. Clinical pharmacokinetics of carboplatin. *Clin Pharmacokinet* 1991; **21:** 242–61.

Uses and Administration

Carboplatin is an analogue of cisplatin with similar actions and uses (see p.700). It is used in the treatment of advanced ovarian cancers and of small-cell lung cancer, both alone and combined with other antineoplastics. It has also been tried as an alternative to cisplatin in other solid tumours (see below).

Carboplatin is given by intravenous infusion over 15 minutes to 1 hour. In the UK an initial dose of 400 mg/m^2 is licensed for use as a single agent in previously untreated patients with normal renal function, reduced by 20 to 25% (300 to 320 mg/m^2) in patients who have previously been treated with myelosuppressive therapy or who have poor performance status. In the USA an initial dose of 360 mg/m^2 is licensed as a single agent in previously treated patients with recurrent disease, and an initial dose of 300 mg/m^2 when used with cyclophosphamide in previously untreated patients.

Dosage adjustments are necessary in patients with renal impairment (see below) and when carboplatin is given as part of a combination regimen. The dose in mg may be calculated using the Calvert formula as described under Administration, below. Subsequent doses should be adjusted according to the nadir of the white cell and platelet counts (see also Bone-marrow Depression, p.639), and should not be given more frequently than every 4 weeks.

Administration. Pharmacokinetic studies by Calvert and colleagues[1] have indicated that the dose of carboplatin to produce a desired area under the concentration-time curve (AUC) could be calculated, based on the patient's glomerular filtration rate (GFR), as:

$$\text{Dose in mg} = \text{target AUC} \times (\text{GFR} + 25)$$

It should be noted that the resultant dose is given in mg and not in mg/m^2. This formula was found to be useful in patients with higher than normal as well as reduced GFR. Suggested target AUCs were 5 mg/mL per minute in previously treated patients and 7 mg/mL per minute in those who had not previously received chemotherapy. In combination therapy the appropriate AUC value depended on the other drugs used: an AUC of 4.5 mg/mL per minute gave acceptable results when carboplatin was used with bleomycin and etoposide for testicular teratoma.

However, determination of GFR may be a problem: clearance of technetium-99m-labelled diethylenetriamine penta-acetic acid (DTPA) or chromium-51-labelled edetic acid is more accurate than 24-hour creatinine clearance, with the first of these more convenient than the second.[2] (It has been suggested that creatinine clearance should not be used to estimate GFR for the Calvert equation.[3]) Nonetheless, radioisotopic determination of

GFR is still an elaborate procedure, and may be less accurate in children than adults.[4] Chatelut and colleagues have proposed formulae for determining clearance of carboplatin in both adults[5] and children.[4]

It has been suggested that the Calvert and Chatelut formulae are not sufficiently accurate for use in children, or in adults with very severe renal impairment. Bayesian methods are the technique of choice where serum carboplatin concentrations can be monitored.[3] However, a study in children showed that dosage based on determination of the GFR results in more consistent carboplatin exposure than dosage based on body-surface area.[6]

1. Calvert AH, *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7:** 1748–56.
2. Millward MJ, *et al.* Carboplatin dosing based on measurement of renal function—experience at the Peter MacCallum Cancer Institute. *Aust N Z J Med* 1996; **26:** 372–9.
3. Duffull SB, Robinson BA. Clinical pharmacokinetics and dose optimisation of carboplatin. *Clin Pharmacokinet* 1997; **33:** 161–83.
4. Chatelut E, *et al.* Population pharmacokinetics of carboplatin in children. *Clin Pharmacol Ther* 1996; **59:** 436–43.
5. Chatelut E, *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; **87:** 573–80.
6. Thomas H, *et al.* Prospective validation of renal-function-based carboplatin dosing in children with cancer: a United Kingdom Children's Cancer Study Group Trial. *J Clin Oncol* 2000; **18:** 3614–21.

Administration in renal impairment. The initial dose of carboplatin is usually determined using a formula (see Administration, above). If this approach is not adopted, the UK licensed product information recommends the following doses based on the patient's creatinine clearance (CC):

- CC 40 mL/minute or more: 400 mg/m^2
- CC 20 to 39 mL/minute: 250 mg/m^2

However, in the USA, the licensed information recommends:

- CC 41 to 59 mL/minute: 250 mg/m^2
- CC 16 to 40 mL/minute: 200 mg/m^2

Malignant neoplasms. A preliminary review[1] of carboplatin, concluded that it was active in ovarian cancer (p.670), with similar responses to those seen with cisplatin; its activity in small-cell lung cancer (p.668), seminoma, and squamous cell carcinomas of the head and neck seemed likely to be comparable, whereas results in gastrointestinal and breast cancers, lymphomas and leukaemias, melanoma, mesothelioma, renal carcinoma, and sarcoma were, generally unimpressive. A subsequent review[2] suggested that in testicular cancer, where there was a prospect of cure, cisplatin, which appeared to give better results in some studies should be preferred. However, in ovarian cancer, where treatment was largely palliative, carboplatin had the advantage of being better tolerated. A further review[3] of randomised studies concurred that carboplatin was equivalent to cisplatin in suboptimally debulked ovarian cancer and extensive-stage small-cell lung cancer, and was inferior to cisplatin in testicular cancer. It was also concluded that carboplatin was inferior to cisplatin in head and neck and oesophageal cancers. There was insufficient comparative evidence for other cancers for which cisplatin has a role.

1. Wagstaff AJ, *et al.* Carboplatin: a preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Drugs* 1989; **37:** 162–90.
2. Anonymous. Cisplatin or carboplatin for ovarian and testicular cancer? *Drug Ther Bull* 1994; **32:** 62–3.
3. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; **17:** 409–22.

Preparations

BP 2008: Carboplatin Injection;
USP 31: Carboplatin for Injection.

Proprietary Preparations (details are given in Part 3)

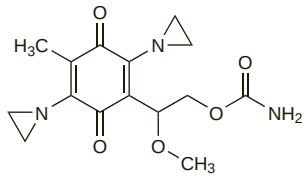
Arg.: Carbokebir; Carboplat; Carboxtie; Omilipis; Paraplatin†; ***Austria:*** Carbosol; Paraplatin; ***Belg.:*** Carbosin; Paraplatin; ***Braz.:*** B-Platin; Biocarbo; Displata†; Evocarb†; Oncocarb†; Oncoplatin; Paraplatin; Platamine; Platicarb†; Tecnocarb; Vancel; ***Canad.:*** Paraplatin; ***Chile:*** Blastocarb†; Oncocarb; Paraplatin; ***Cz.:*** Cycloplatin; Paraplatin†; ***Denm.:*** Paraplatin; ***Fin.:*** Carbosin†; Paraplatin; ***Fr.:*** Paraplatine; ***Ger.:*** Carbo-cell; Carbomedac; Carboplat; Neocarbo; Ribocarbo; ***Gr.:*** Carboplamin; Carbosin; Emorzim; Megaplatin; Paraplatin; ***Hong Kong:*** Paraplatin; ***Hung.:*** Cycloplatin; Paraplatin; ***India:*** Biocarb; Cytocarb; Kemocarb; ***Indon.:*** Carbosin; Paraplatin; ***Irl.:*** Paraplatin; ***Israel:*** Paraplatin†; ***Ital.:*** Paraplatin; ***Malaysia:*** Carbosin; Paraplatin†; ***Mex.:*** Blastocarb; Boplatex; Carboplat; Carbotec; Ifacap; Kemocarb; Novoplat†; Paraplatin; ***Neth.:*** Carbosin; Paraplatin†; ***Norw.:*** Carbosin; Paraplatin; ***NZ:*** Carbosin†; Paraplatin; ***Philipp.:*** Biovinate; Bonaplatin; Carbotinol; Crobextin; Kemocarb; Paraplatin; ***Pol.:*** Cycloplatin; Paraplatin; ***Port.:*** Nealorin; Novoplatinum; Paraplatin; ***Rus.:*** Blastocarb (Бластокарб); Cycloplatin (Циклоплатин); Paraplatin (Параплатин); ***S.Afr.:*** Carbosin; Paraplatin; ***Singapore:*** Paraplatin; ***Spain:*** Ercar†; Nealorin; Paraplatin; Platinwas; ***Swed.:*** Paraplatin; ***Switz.:*** Paraplatin; ***Thai.:*** Blastocarb; Carbosin; Kemocarb; Paraplatin; ***Turk.:*** Carbosin; Paraplatin; Platinwas; ***UK:*** Paraplatin; ***USA:*** Paraplatin†; ***Venez.:*** Bioplatinex; Oplat.

Carboquone *(rINN)*

Carbazilquinone; Carbocuona; Carboquonum; Karbokvon; Karbokvoni. 2,5-Bis(aziridin-1-yl)-3-(2-hydroxy-1-methoxyethyl)-6-methyl-*p*-benzoquinone carbamate.

Карбохон

$C_{15}H_{19}N_3O_5$ = 321.3.
CAS — 24279-91-2.
ATC — L01AC03.
ATC Vet — QL01AC03.



Profile

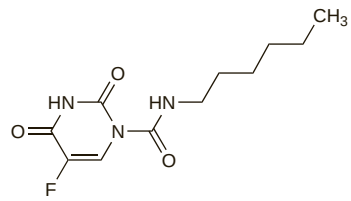
Carboquone is an alkylating agent that has been used in the treatment of a variety of malignant neoplasms including those of the lung, stomach, and ovary; it has also been used in lymphomas and in chronic myeloid leukaemia. It has been given by the intravenous or intra-arterial route, or orally.

Carmofur *(rINN)*

Carmofurum; HCFU; Karmofuuri. 5-Fluoro-*N*-hexyl-3,4-dihydro-2,4-dioxo-1-(2*H*)-pyrimidinecarboxamide; 1-Hexylcarbamoyl-5-fluorouracil.

Кармофур

$C_{11}H_{16}FN_3O_3$ = 257.3.
CAS — 61422-45-5.
ATC — L01BC04.
ATC Vet — QL01BC04.



Pharmacopoeias. In *Chin.* and *Jpn.*

Profile

Carmofur is an orally active derivative of fluorouracil (p.722) and has similar actions. It is used in the adjuvant treatment of colorectal cancer, and has been used in breast and ovarian cancers. Carmofur has been associated with the development of neurological disorders including leukoencephalopathy.

◊ References.

1. Yamada T, *et al.* Leukoencephalopathy following treatment with carmofur: a case report and review of the Japanese literature. *Asia Oceania J Obstet Gynaecol* 1989; **15:** 161–8.
2. Sakamoto J, *et al.* An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer. *Oncol Rep* 2001; **8:** 697–703.
3. Nakamura T, *et al.* Optimal duration of oral adjuvant chemotherapy with Carmofur in the colorectal cancer patients: the Kansai Carmofur Study Group trial III. *Int J Oncol* 2001; **19:** 291–8.
4. Tominaga T, *et al.* Postoperative chemoendocrine therapy for women with node-positive stage II breast cancer with combined cyclophosphamide, tamoxifen, and 1-hexylcarbamoyl-5-fluorouracil. *Eur J Surg* 2001; **167:** 598–604.
5. Iwagaki H, *et al.* Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection. *Anticancer Res* 2001; **21:** 4163–8.
6. Morimoto K, Koh M. Postoperative adjuvant use of carmofur for early breast cancer. *Osaka City Med J* 2003; **49:** 77–83.
7. Tominaga T, *et al.* 1-Hexylcarbamoyl-5-fluorouracil + cyclophosphamide + tamoxifen versus CMF + tamoxifen in women with lymph node-positive breast cancer after primary surgery: a randomized controlled trial. *Oncol Rep* 2004; **12:** 797–803.
8. Sakamoto J, *et al.* An individual patient data meta-analysis of adjuvant therapy with carmofur in patients with curatively resected colon cancer. *Jpn J Clin Oncol* 2005; **35:** 536–44.

Preparations

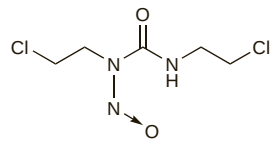
Proprietary Preparations (details are given in Part 3)
Fin.: Mirafur.

Carmustine *(BAN, USAN, rINN)*

BCNU; BiCNU; Carmustina; Carmustinum; Karmustiini; Karmustin; Karmustinas; Karmusztin; NSC-409962; WR-139021. 1,3-Bis(2-chloroethyl)-1-nitrosourea.

Кармустин

$C_5H_9Cl_2N_3O_2$ = 214.0.
CAS — 154-93-8.
ATC — L01AD01.
ATC Vet — QL01AD01.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Carmustine). A yellowish, granular powder. Very slightly soluble in water; freely soluble in dehydrated alcohol; very soluble in dichloromethane. It melts at about 31° with decomposition. Store at a temperature of 2° to 8° in airtight containers. Protect from light.

Stability. The manufacturers state that, when reconstituted, resulting carmustine solutions (undiluted or further diluted in sodium chloride 0.9% or glucose 5%) are stable for 8 hours at room temperature, or 24 hours at 2° to 8°, when protected from light. There is some evidence that carmustine interacts with plastic giving sets and containers, and licensed product information recommends the use of polyethylene or glass.

A study has indicated that diluted solutions of carmustine undergo increased degradation in the presence of sodium bicarbonate, with only 73% of the original concentration of carmustine remaining after 90 minutes, much of the loss being in the first 15 minutes.[1]

1. Colvin M, *et al.* Stability of carmustine in the presence of sodium bicarbonate. *Am J Hosp Pharm* 1980; **37:** 677–8.

Adverse Effects and Treatment

For a general outline see Antineoplastics, p.635 and p.639. Delayed and cumulative bone-marrow depression is the most frequent and serious adverse effect of intravenous carmustine. Platelets and leucocytes are mainly affected, with platelet nadirs occurring at 4 to 5 weeks after a dose and leucocyte nadirs at 5 to 6 weeks; although thrombocytopenia is usually more severe, leucopenia may also be dose-limiting. Other adverse effects include pulmonary fibrosis (mainly but not exclusively at high cumulative doses—see also Effects on the Lungs, p.638), renal and hepatic damage, and neuroretinitis. Nausea and vomiting, beginning up to 2 hours after a dose, is common but can be reduced by prophylactic antiemetic therapy. Venous irritation may follow intravenous injection and transient hyperpigmentation has been noted after contact of a solution with the skin. Flushing of the skin and suffusion of the conjunctiva may occur on rapid intravenous infusion. Hypotension, tachycardia, chest pain, headache, and hypersensitivity reactions have been reported.

Convulsions, cerebral oedema, and various neurological symptoms have been reported in patients given carmustine-containing polymer implants; abnormalities of wound healing at the site of implantation, and an increased incidence of intracranial infection have also been reported.

As with other alkylating agents, carmustine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the eyes. Ocular toxicity has been reported in patients given carmustine,[1,2] and seems to be more likely when given into the carotid artery,[1,2] although it was also seen with high-dose intravenous therapy. There is some evidence that the alcohol diluent used to prepare carmustine solutions may contribute to the retinopathy.[2]

1. Shingleton BJ, *et al.* Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 1982; **100:** 1766–72.
2. Greenberg HS, *et al.* Intra-arterial BCNU chemotherapy for treatment of malignant gliomas of the central nervous system. *J Neurosurg* 1984; **61:** 423–9.

Effects on the lungs. Studies have found a high incidence of fatal pulmonary fibrosis (see also Effects on the Lungs, p.638) in patients treated with carmustine for gliomas during childhood; patients who were treated before 5 or 6 years of age were more likely to die of pulmonary fibrosis than those treated at a later age.[1,2] However, there are reports of pulmonary toxicity and