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)

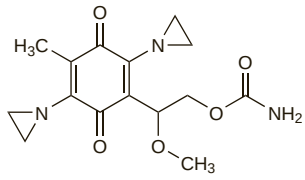
Arg.: Carbokebir; Carboplat; Carboxtie; Omilipis; Paraplatin†; ***Austria:*** Carbosol; Paraplatin; ***Belg.:*** Carbosin; Paraplatin; ***Braz.:*** B-Platin; Biocarbo; Displata†; Evocarb†; Oncocarb†; Oncoplatin; Paraplatin; Platamine; Platicarb†; Tecnocarb; Vancel; ***Canad.:*** Paraplatin; ***Chile:*** 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

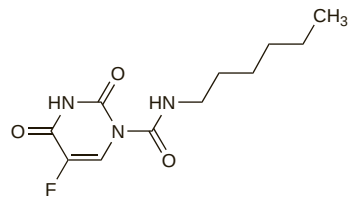
Carboquone is an alkylating agent that has been used in the treatment of a variety of malignant neoplasms including those of the lung, stomach, and ovary; it has also been used in lymphomas and in chronic myeloid leukaemia. It has been given by the intravenous or intra-arterial route, or orally.

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

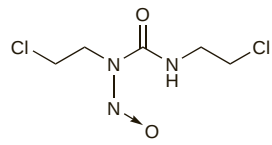
Proprietary Preparations (details are given in Part 3)
Fin.: Mirafur.

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