lactic anticonvulsants should be used during high dose therapy (see Effects on the Nervous System, above).

Busulfan should be stopped if lung toxicity develops. The use of oxygen may exacerbate possible lung toxicity; if anaesthesia is required the concentration of oxygen should be minimised.

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

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

Radiotherapy. Severe cutaneous reactions occurred in patients given radiotherapy at least 30 days after combined chemotherapy with high-dose busulfan.[1]

It is possible that radiotherapy could worsen subclinical lung injury caused by busulfan.

1. Vassal G, *et al*. Radiosensitisation after busulphan. *Lancet* 1987; **i:** 571.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Phenytoin increases the clearance of busulfan (see Effects on the Nervous System, above).

Antifungals. Giving *itraconazole* with busulfan resulted in a decrease in the clearance of busulfan; *fluconazole* had no such effect.[1] Busulfan doses may need to be decreased if itraconazole is also given.

1. Buggia I, *et al*. Itraconazole can increase systemic exposure to busulfan in patients given bone marrow transplantation. *Anticancer Res* 1996; **16:** 2083–8.

Antineoplastics. When *tioguanine* was given with busulfan for chronic myeloid leukaemia, a number of cases of hepatic nodular regenerative hyperplasia, with abnormal liver function tests, portal hypertension, and oesophageal varices were noted. There were no cases in patients treated with busulfan alone, and the mechanism of this possible interaction is unclear.[1,2]

1. Key NS, *et al*. Oesophageal varices associated with busulfan-thioguanine combination therapy for chronic myeloid leukaemia. *Lancet* 1987; **ii:** 1050–2.
2. Shepherd PCA, *et al*. Thioguanine used in maintenance therapy of chronic myeloid leukaemia causes non-cirrhotic portal hypertension. *Br J Haematol* 1991; **79:** 185–92.

Antiprotozoals. In a study[1] of patients who received high-dose busulfan as part of a myeloablative regimen before stem cell transplantation, the use of *metronidazole* significantly increased plasma concentrations of busulfan and the degree of associated toxicity, including elevation of liver function tests, veno-occlusive disease, and mucositis.

1. Nilsson C, *et al*. The effect of metronidazole on busulfan pharmacokinetics in patients undergoing hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2003; **31:** 429–35.

Pharmacokinetics

Busulfan is readily absorbed from the gastrointestinal tract and rapidly disappears from the blood with a half-life of 2 to 3 hours. It is extensively metabolised, and excreted in the urine almost entirely as sulfur-containing metabolites. It crosses the blood-brain barrier.

Metabolism. In a study of the pharmacokinetics of high-dose busulfan in 5 patients receiving 1 mg/kg orally every six hours for 4 days, the mean elimination half-life decreased from about 3.4 hours after the first dose to about 2.3 hours after the final dose, suggesting that busulfan may induce its own metabolism.[1]

1. Hassan M, *et al*. Pharmacokinetic and metabolic studies of high-dose busulphan in adults. *Eur J Clin Pharmacol* 1989; **36:** 525–30.

Therapeutic drug monitoring. A review concluded that therapeutic drug monitoring of busulfan would maximise engraftment and minimise toxicity and relapse in haematopoietic stem cell transplantation. In regimens using busulfan with cyclophosphamide, steady-state plasma concentrations of busulfan above 600 micrograms/litre appeared to favour engraftment.[1] A pharmacokinetic analysis found that in patients with graft rejections, busulfan trough concentrations were below 150 nanograms/mL; steady state concentrations also tended to be lower in this group but not significantly so.[2]

The bioavailability of oral busulfan is variable, particularly in children; intravenous conditioning regimens, adjusted on the basis of first-dose pharmacokinetics and therapeutic drug monitoring, have been used to overcome this problem.[3,4] A study found a significant correlation between busulfan concentration in plasma and saliva after oral dosing in children; busulfan saliva analysis may therefore be a useful, non-invasive alternative to plasma analysis.[5]

1. McCune JS, *et al*. Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin Pharmacokinet* 2000; **39:** 155–65.
2. Chandy M, *et al*. Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia—the role of busulfan pharmacokinetics in determining outcome. *Bone Marrow Transplant* 2005; **36:** 839–45.
3. Tran H, *et al*. Pharmacokinetics and individualized dose adjustment of intravenous busulfan in children with advanced hematologic malignancies undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2004; **10:** 805–12.
4. Kletzel M, *et al*. Pharmacokinetics of a test dose of intravenous busulfan guide dose modifications to achieve an optimal area under the curve of a single daily dose of intravenous busulfan in children undergoing a reduced-intensity conditioning regimen with hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006; **12:** 472–9.
5. Rauh M, *et al*. Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children : validation of liquid chromatography tandem mass spectrometry method. *Clin Pharmacokinet* 2006; **45:** 305–16.

Uses and Administration

Busulfan is an antineoplastic with a cell-cycle non-specific alkylating action unlike that of the nitrogen mustards, and having a selective depressant action on bone marrow. In small doses, it depresses granulocytopoiesis and to a lesser extent thrombocytopoiesis but has little effect on lymphocytes. With larger doses, severe bone-marrow depression eventually ensues.

Because of its selective action, busulfan has been used in the palliative treatment of chronic myeloid leukaemia (p.653). It provides symptomatic relief with a reduction in spleen size and a general feeling of well-being. The fall in leucocyte count is usually accompanied by a rise in the haemoglobin concentration. Permanent remission is not induced and resistance to its beneficial effects gradually develops.

Busulfan may be used in patients with polycythaemia vera (p.654) and in some patients with myelofibrosis and primary thrombocythaemia (p.654). It is also used at high doses as part of a conditioning regimen to prepare patients for bone marrow transplantation, a procedure discussed on p.1811 under Haematopoietic Stem Cell Transplantation.

The licensed initial oral dosage of busulfan in **chronic myeloid leukaemia** is 60 micrograms/kg daily, with a usual maximum single daily dose of 4 mg. This is continued until the white cell count has fallen to between 15 000 and 25 000 cells/mm^3 (typically 12 to 20 weeks). It should be stopped earlier if the platelet count falls below 100 000 cells/mm^3. Higher doses may be given if the response after 3 weeks is inadequate but this increases the risk of irreversible damage to the bone marrow and calls for special vigilance. Complete blood counts should be made at least every week and the trends followed closely; if haemorrhagic tendencies occur or there is a steep fall in the white cell count indicating severe bone-marrow depression, busulfan should be withdrawn until marrow function has returned.

Once an initial remission has been attained treatment is stopped and not resumed until the white cell count returns to 50 000 cells/mm^3. If this occurs within 3 months continuous maintenance treatment with a usual dose of 0.5 to 2 mg daily may be given.

In patients with **polycythaemia vera** the usual oral dose is 4 to 6 mg daily, continued for 4 to 6 weeks with careful monitoring of blood counts. Further courses are given when relapse occurs; alternatively, maintenance therapy may be given at half the dose required for induction. Doses of 2 to 4 mg daily have been given for **essential thrombocythaemia** or myelofibrosis.

In conditioning regimens for **bone marrow transplantation** busulfan has been given in usual doses of 3.5 to 4 mg/kg daily in divided doses for 4 days orally (total dose 14 to 16 mg/kg), with cyclophosphamide, for ablation of the recipient's bone marrow. When given by intravenous infusion in a regimen with phenytoin (see Effects on the Nervous System, above), a recommended dose is 3.2 mg/kg ideal body-weight daily for 4 days (total dose 12.8 mg/kg); actual body-weight is used for the calculation if it is less than the ideal weight. The daily dose is given as 4 infusions of 800 micrograms/kg at intervals of 6 hours; each dose should be diluted in sodium chloride 0.9% or glucose 5% to a final concentration of about 500 micrograms/mL, and given over 2 hours through a central venous catheter using an infusion pump. UK licensed product information states that cyclophosphamide dosing should not be started for at least 24 hours after the last dose of busulfan; US information permits use no sooner than 6 hours after the last busulfan dose.

In the UK, busulfan is licensed for use with cyclophosphamide or melphalan as a conditioning regimen prior to haematopoietic stem cell transplantation in children. The recommended dose for children up to 17 years of age is weight-based as follows:

- less than 9 kg: busulfan 1 mg/kg
- 9 to 16 kg: busulfan 1.2 mg/kg
- 16 to 23 kg: busulfan 1.1 mg/kg
- 23 to 34 kg: busulfan 950 micrograms/kg
- greater than 34 kg: busulfan 800 micrograms/kg

This dose is given every 6 hours over 4 days to a total of 16 doses, diluted and infused as for adults. Cyclophosphamide or melphalan should not be started for at least 24 hours after the last dose of busulfan.

◊ References.

1. Buggia I, *et al*. Busulfan. *Ann Pharmacother* 1994; **28:** 1055–62.
2. Socié G, *et al*. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow-up of 4 randomized studies. *Blood* 2001; **98:** 3569–74.
3. Ferry C, Socié G. Busulfan-cyclophosphamide versus total body irradiation-cyclophosphamide as preparative regimen before allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia: what have we learned? *Exp Hematol* 2003; **31:** 1182–6.

Preparations

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

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

Capecitabine *(BAN, USAN, rINN)*

Capecitabina; Capécitabine; Capecitabinum; Kapecitabin; Kapesitabiini; Kapesitabin; Ro-09-1978/000. Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate.

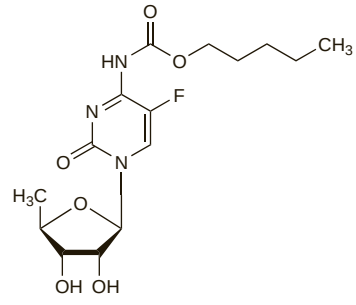
Капецитабин

$C_{15}H_{22}FN_3O_6$ = 359.4.

CAS — 154361-50-9; 158798-73-3.

ATC — L01BC06.

ATC Vet — QL01BC06.



Pharmacopoeias. In *US.*

USP 31 (Capecitabine). A white to off-white crystalline powder. Sparingly soluble in water; soluble in alcohol and in acetonitrile; freely soluble in methyl alcohol. Store in airtight containers at a temperature of 20° to 25°, excursions permitted between 15° and 30°.

Adverse Effects and Precautions

As for Fluorouracil, p.722. Diarrhoea (which may be severe), nausea and vomiting, abdominal pain, stomatitis, and palmar-plantar erythrodysesthesia syndrome (erythema and desquamation of hands and feet) occur commonly with capecitabine, and may be dose-limiting. Other common adverse effects include fatigue,

asthenia, and anorexia. Rashes, alopecia, erythema, dryness of the skin, pruritus, skin pigmentation disorders, and nail disorders can occur. Other adverse effects are fever, pain, arthralgia, constipation, dyspepsia, paraesthesia, headache, dizziness, insomnia, hypo- or hypercalcaemia, and dehydration. Dermatitis, cardiotoxicity, and bone-marrow depression have all been reported. Hyperbilirubinaemia has occurred. Doses should be reduced in patients with moderate renal impairment and the drug is contra-indicated in those with severe renal or hepatic impairment.

Effects on blood lipids. Severe hypertriglyceridaemia has been reported with oral capecitabine;[1] patients had high baseline triglyceride concentrations at the start of capecitabine. Despite the introduction of lipid-lowering therapy, triglyceride concentrations remained above baseline, and only decreased several weeks after stopping capecitabine.

1. Kurt M, *et al.* Capecitabine-induced severe hypertriglyceridemia: report of two cases. *Ann Pharmacother* 2006; **40:** 328–31.

Effects on the eyes. A report of severe ocular irritation with corneal deposits and impaired visual acuity in 2 patients given capecitabine.[1] Symptoms resolved within several weeks of stopping the drug.

1. Walkhom B, *et al.* Severe ocular irritation and corneal deposits associated with capecitabine use. *N Engl J Med* 2000; **343:** 740–1.

Effects on the heart. Acute ischaemic chest pain has been reported, usually within a few days of starting capecitabine.[1-3] Symptoms from case reports[1] and incidence in Phase III studies[4] were similar to those in patients given fluorouracil. While symptoms have generally been reported to be reversible, fatal myocardial infarction has occurred.[2] One patient had also had cardiotoxicity with fluorouracil treatment,[1] but others had no apparent risk factors.[2]

1. Frickhofen N, *et al.* Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. *Ann Oncol* 2002; **13:** 797–801.
2. Kuppens IELM, *et al.* Capecitabine induces severe angina-like chest pain. *Ann Intern Med* 2004; **140:** 494–5.
3. Bertolini A, *et al.* Acute cardiotoxicity during capecitabine treatment: a case report. *Tumori* 2001; **87:** 200–6.
4. van Cutsem E, *et al.* Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol* 2002; **13:** 484–5.

Effects on the nervous system. Peripheral neuropathy[1] and encephalopathy[2,3] have been reported in association with capecitabine use.

1. Saif MW, *et al.* Peripheral neuropathy associated with capecitabine. *Anticancer Drugs* 2004; **15:** 767–71.
2. Niemann B, *et al.* Toxic encephalopathy induced by capecitabine. *Oncology* 2004; **66:** 331–5.
3. Videnovic A, *et al.* Capecitabine-induced multifocal leukoencephalopathy: a report of five cases. *Neurology* 2005; **65:** 1792–4.

Effects on the skin and nails. While hand-foot syndrome appears to be common in patients treated with capecitabine (see Palmar-plantar Erythrodysesthesia Syndrome, below), other skin eruptions have been rarely reported.[1] Onychomadesis (total separation of the nail-bed) and onycholysis have occurred.[2,3] Pyogenic granuloma has been seen with the use of capecitabine,[1] as has re-pigmentation of chemotherapy-induced vitiligo.[4]

1. Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; **147:** 1270–2.
2. Chen G-Y, *et al.* Onychomadesis and onycholysis associated with capecitabine. *Br J Dermatol* 2001; **145:** 521–2.
3. Chen G-Y, *et al.* Exudative hyponychial dermatitis associated with capecitabine and docetaxel combination chemotherapy for metastatic breast carcinoma: report of three cases. *Br J Dermatol* 2003; **148:** 1071–3.
4. Schmid-Wendtner M-H, *et al.* Leopard-like vitiligo with capecitabine. *Lancet* 2001; **358:** 1575.

Hypersensitivity. A patient was successfully given fluorouracil by continuous infusion despite previous hypersensitivity to capecitabine. The authors supposed that the hypersensitivity was likely to have been caused by capecitabine or intermediate metabolites, and suggested a lack of cross-sensitivity between capecitabine and fluorouracil.[1]

1. Liu CY. Fluorouracil for allergic reactions to capecitabine. *Ann Pharmacother* 2002; **36:** 1897–9.

Palmar-plantar erythrodysesthesia syndrome. Hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome, p.639) has been reported to be common with use of capecitabine given either as monotherapy[1] or as part of combination chemotherapy regimens.[2,3] The syndrome developed within the first 2 cycles of monotherapy,[1] but within the first 3 cycles in combination therapy,[3] which was attributed to dose modifications of capecitabine in the latter case. Use with docetaxel, and previous chemotherapy-induced stomatitis were found to be significant risk factors for its occurrence.[3] The only effective management is treatment interruption and dose modification.[4] Supportive measures to reduce pain and discomfort and prevent secondary infection are important.[5] General recommended strategies include submersion of hands and feet in cold water, wound care, and avoidance of extreme temperature changes, tight-fitting clothing, or skin friction. Emollient creams may be of benefit for both prophylaxis and treatment. Other strategies that have been proposed include the use of amifostine, topical or systemic corticosteroids, and nicotine patches; however, use of these drugs for capecitabine-induced hand-foot syndrome remains unproven. While pyridoxine cannot be recommended for prophylaxis, some consider it a reasonable choice for treatment, since benefit has been reported with its use with topical emollients.[4] Concurrent treatment with celecoxib has been reported to reduce the incidence of hand-foot syndrome induced by capecitabine.[6,7] For reference to the use of vitamin E to alleviate hand-foot syndrome caused by capecitabine and docetaxel, see Chemotherapy-induced Toxicity, under Uses of Vitamin E, p.1994.

As a result of capecitabine-induced hand-foot syndrome, fingerprint misidentification has been reported.[8]

1. Abushullaih S, *et al.* Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest* 2002; **20:** 3–10.
2. Park YH, *et al.* High incidence of severe hand-foot syndrome during capecitabine-docetaxel combination chemotherapy. *Ann Oncol* 2003; **14:** 1691–2.
3. Heo YS, *et al.* Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol* 2004; **44:** 1166–72.
4. Gressett SM, *et al.* Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract* 2006; **12:** 131–41.
5. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome: insights from clinical trials evaluating capecitabine. *Oncology (Huntingt)* 2004; **18:** 1161–8, 1173.
6. Lin E, *et al.* Effect of celecoxib on capecitabine-induced hand-foot syndrome and antitumor activity. *Oncology (Huntingt)* 2002; **16** (12 suppl 14): 31–7.
7. Lin EH, *et al.* Retrospective study of capecitabine and celecoxib in metastatic colorectal cancer: potential benefits and COX-2 as the common mediator in pain, toxicities and survival? *Am J Clin Oncol* 2006; **29:** 232–9.
8. García-Saénz JA, *et al.* Elementary, my dear Watson. *J Clin Oncol* 2007; **25:** 1815–6.

Tumour lysis syndrome. A fatal case of tumour lysis syndrome (p.639) has been reported after the use of capecitabine.[1]

1. Kurt M, *et al.* Tumor lysis syndrome following a single dose of capecitabine. *Ann Pharmacother* 2004; **38:** 902.

Interactions

As for Fluorouracil, p.723. Altered coagulation parameters and bleeding have occurred in patients on warfarin or phenprocoumon given capecitabine. Increased phenytoin plasma concentrations and symptoms of toxicity during use with capecitabine have been reported. Capecitabine must not be given with sorivudine or its analogues as fatal fluoropyrimidine toxicity may occur (see also Antivirals, under Interactions of Fluorouracil, p.723). Antacids containing aluminium or magnesium hydroxides cause a small increase in capecitabine plasma concentration. The maximum tolerated dose of capecitabine is reduced when it is given with either folinic acid or interferon alfa.

Pharmacokinetics

Capecitabine is readily absorbed from the gastrointestinal tract, with peak plasma concentrations occurring at about 1.5 hours. Food reduces the rate and extent of absorption. Plasma protein binding of capecitabine is less than 60%. Capecitabine is hydrolysed in the liver to 5′-deoxy-5-fluorocytidine (5′-DFCR), which is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR; doxifluridine—p.712) and subsequently to 5-fluorouracil in body tissues. 5-Fluorouracil is further metabolised, as discussed on p.723. About 3% of a dose of capecitabine is excreted in the urine unchanged.

◊ References.

1. Reigner B, *et al.* Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin Cancer Res* 1998; **4:** 941–8.
2. Reigner B, *et al.* Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet* 2001; **40:** 85–104.

Uses and Administration

Capecitabine is a prodrug that is converted to fluorouracil (p.723) in body tissues. It is given orally for the treatment of metastatic colorectal cancer (p.665) and is also used for the adjuvant treatment of patients after surgery for Dukes C colon cancer. Capecitabine is given with docetaxel for the treatment of locally advanced or metastatic breast cancer (p.661) after failure of anthracycline-containing chemotherapy. It may be given as monotherapy after failure of taxanes and anthracycline-containing regimens for patients with breast cancer and for whom further anthracycline-containing therapy is not indicated. Capecitabine with lapatinib (p.739) is used for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress human epidermal receptor type 2 (HER2). Capecitabine is also used with a platinum-based regimen for the first-line treatment of gastric cancer (p.664).

For *monotherapy* in **colon**, **colorectal**, or in **breast** cancer, the recommended initial oral dose is 1.25 g/m^2 given twice daily; doses are given for 14 days, followed by a 7-day rest period. Adjuvant treatment for colon cancer is recommended for a total of 6 months. For *combination* therapy in **breast** cancer, when given with docetaxel, capecitabine is given in the same dose as listed above; docetaxel is given at 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. However, when used with lapatinib tosilate, a different regimen is used, see Uses and Administration, under Lapatinib Tosilate, p.739.

In *combination* therapy in **colorectal** or **gastric** cancer, the recommended initial oral dose of capecitabine is 0.8 to 1 g/m^2 twice daily for 14 days, followed by a 7-day rest period. Alternatively, capecitabine 625 mg/m^2 twice daily is given continuously.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Doses should be modified in subsequent cycles according to toxicity. Capecitabine doses should be reduced in patients with renal impairment (see below).

Capecitabine is also under investigation in the treatment of other malignancies.

◊ References.

1. Walko CM, Lindley C. Capecitabine: a review. *Clin Ther* 2005; **27:** 23–44.
2. Saif MW. Capecitabine versus continuous-infusion 5-fluorouracil for colorectal cancer: a retrospective efficacy and safety comparison. *Clin Colorectal Cancer* 2005; **5:** 89–100.
3. Glynne-Jones R, *et al.* The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? *Ann Oncol* 2006; **17:** 361–71.
4. Ershler WB. Capecitabine use in geriatric oncology: an analysis of current safety, efficacy, and quality of life data. *Crit Rev Oncol Hematol* 2006; **58:** 68–78.
5. Mandelblat J, *et al.* Capecitabine-docetaxel combination treatment. *Expert Rev Anticancer Ther* 2006; **6:** 1169–78.
6. Ershler WB. Capecitabine monotherapy: safe and effective treatment for metastatic breast cancer. *Oncologist* 2006; **11:** 325–35.
7. Schmoll HJ, Arnold D. Update on capecitabine in colorectal cancer. *Oncologist* 2006; **11:** 1003–9.
8. Pandor A, *et al.* The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation. *Health Technol Assess* 2006; **10:** 1–185.
9. Schellens JHM. Capecitabine. *Oncologist* 2007; **12:** 152–5.
10. Tripathy D. Capecitabine in combination with novel targeted agents in the management of metastatic breast cancer: underlying rationale and results of clinical trials. *Oncologist* 2007; **12:** 375–89.
11. Dhillon S, Scott LJ. Capecitabine: in advanced gastric or oesophagogastric cancer. *Drugs* 2007; **67:** 601–10.
12. Glen H, Cassidy J. Redefining adjuvant chemotherapy in patients with stage III colon cancer: X-ACT trial. *Expert Rev Anticancer Ther* 2008; **8:** 547–51.
13. Comella P, *et al.* Capecitabine, alone and in combination, in the management of patients with colorectal cancer: a review of the evidence. *Drugs* 2008; **68:** 949–61.

Administration in renal impairment. Renal impairment increases systemic exposure to 5′-deoxy-5-fluorouridine, a metabolite of capecitabine. An increase in the severity of adverse effects appears to correlate with decreased renal function and increased exposure to this metabolite.[1]

Licensed product information suggests the following dosage adjustments based on creatinine clearance (CC):

- mild renal impairment, CC 51 to 80 mL/minute: no dosage adjustment necessary
- moderate renal impairment, CC 30 to 50 mL/minute: when the starting dose is 1.25 g/m^2 twice daily, a dose reduction of 25%, to about 950 mg/m^2 twice daily is recommended; however, when the starting dose is 1 g/m^2 twice daily, no dose reduction is required
- severe renal impairment, CC below 30 mL/minute: capecitabine is contra-indicated

1. Poole C, *et al.* Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (Xeloda) in cancer patients. *Cancer Chemother Pharmacol* 2002; **49:** 225–34.

Preparations

USP 31: Capecitabine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Apecitab†; Categor; Xeloda; ***Austral.:*** Xeloda; ***Austria:*** Xeloda; ***Belg.:*** Xeloda; ***Braz.:*** Xeloda; ***Canad.:*** Xeloda; ***Chile:*** Xeloda; ***Cz.:*** Xeloda; ***Denm.:*** Xeloda; ***Fin.:*** Xeloda; ***Fr.:*** Xeloda; ***Ger.:*** Xeloda; ***Gr.:*** Xeloda; ***Hong Kong:*** Xeloda; ***Hung.:*** Xeloda; ***Indon.:*** Xeloda; ***Irl.:*** Xeloda; ***Israel:*** Xeloda; ***Ital.:*** Xeloda; ***Jpn:*** Xeloda; ***Malaysia:*** Xeloda; ***Mex.:*** Xeloda;

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.

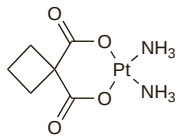
Карбоплатин

$C_6H_{12}N_2O_4Pt$ = 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