Adverse Effects, Treatment, and Precautions

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

Leucopenia and thrombocytopenia with dacarbazine, although usually moderate, may be severe. The nadir of the white cell count usually occurs 21 to 25 days after a dose. Anorexia, nausea, and vomiting occur in more than 90% of patients initially but tolerance may develop after repeated doses. Less frequent adverse effects include diarrhoea, skin reactions, alopecia, a flu-like syndrome, facial flushing and paraesthesia, headache, blurred vision, seizures, and rare but potentially fatal hepatotoxicity. There may be local pain at the injection site; extravasation produces pain and tissue damage. Anaphylaxis has occurred occasionally.

Dacarbazine should be used with caution in hepatic and renal impairment, and consideration given to reducing the dose. Haematological monitoring is required during therapy. Dacarbazine is potentially carcinogenic, mutagenic, and teratogenic.

Effects on the bladder. A report[1] of haemorrhagic cystitis associated with dacarbazine treatment for melanoma. The patient developed gross haematuria with inflammation and oedema of the bladder wall 2 weeks after completing 3 cycles of monotherapy with dacarbazine; the condition responded to symptomatic management with saline lavage and oral and intravenous hydration. Two subsequent transient episodes of haematuria resolved spontaneously.

1. Mohammadianpanah M, *et al.* Hemorrhagic cystitis in a patient receiving conventional doses of dacarbazine for metastatic malignant melanoma: case report and review of the literature. *Clin Ther* 2007; **29:** 1161–5.

Effects on the liver. Dacarbazine has been associated with fatal hepatic vascular toxicity, caused by thrombosis of the hepatic veins, necrosis, and extensive haemorrhage.[1] As the reaction usually occurs during the second course of dacarbazine it is thought to be immune mediated, and early corticosteroid treatment has been tried with a few reported cases of patient survival.[2] Other adverse hepatic effects have included[3] necrosis without inflammation, granulomatous hepatitis, and acute toxic hepatitis during the first course of dacarbazine. Morphological studies have suggested that dacarbazine may exert a toxic effect on the microfilamentous cytoskeleton of the hepatocytes.[3]

1. Ceci G, *et al.* Fatal hepatic vascular toxicity of DTIC: is it really a rare event? *Cancer* 1988; **61:** 1988–91.
2. Herishanu Y, *et al.* The role of glucocorticoids in the treatment of fulminant hepatitis induced by dacarbazine. *Anticancer Drugs* 2002; **13:** 177–9.
3. Dancygier H, *et al.* Dacarbazine (DTIC)-induced human liver injury. *Gut* 1982; **23:** A447.

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

Interactions

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

Levodopa. For a report of dacarbazine reducing the effects of levodopa, see Antineoplastics, p.807.

Pharmacokinetics

Dacarbazine is poorly absorbed from the gastrointestinal tract. On intravenous injection it is rapidly distributed with an initial plasma half-life of about 20 minutes; the terminal half-life is reported to be about 5 hours. The volume of distribution is larger than body water content, suggesting localisation in some body tissues, probably mainly the liver. Only about 5% is bound to plasma protein. It crosses the blood-brain barrier to a limited extent; concentrations in CSF are about 14% of those in plasma. Dacarbazine is extensively metabolised in the liver by the cytochrome P450 isoenzymes CYP1A2 and CYP2E1 (and possibly in the tissues by CYP1A1) to its active metabolite 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC), which spontaneously decomposes to the major metabolite 5-aminoimidazole-4-carboxamide (AIC). About half of a dose is excreted unchanged in the urine by tubular secretion.

Uses and Administration

Dacarbazine is a cell-cycle non-specific antineoplastic that is thought to function as an alkylating agent after it has been activated in the liver. Dacarbazine is used mainly in the treatment of metastatic malignant melanoma (p.673). It is also given to patients with Hodgkin's disease (p.655), notably with doxorubicin, bleomycin, and vinblastine (ABVD). Dacarbazine is used with other drugs in the treatment of soft-tissue sarcoma (p.676), and may be given in neuroblastoma (p.674), Kaposi's sarcoma (p.675), and other tumours.

Dacarbazine is given by the intravenous route. Injections may be given over 1 to 2 minutes. The reconstituted solution can be further diluted with up to 300 mL of glucose 5% or sodium chloride 0.9% and given by infusion over 15 to 30 minutes.

Dacarbazine is licensed for use as a single agent for **metastatic melanoma** in doses of 2 to 4.5 mg/kg daily for 10 days, repeated at intervals of 4 weeks, or 200 to 250 mg/m^2 daily for 5 days, repeated at intervals of 3 weeks. It can also be given in a dose of 850 mg/m^2 by intravenous infusion at 3-week intervals. In the treatment of **Hodgkin's disease** doses of 150 mg/m^2 daily for 5 days repeated every 4 weeks, or 375 mg/m^2 every 15 days have been given with other agents. In the treatment of **soft-tissue sarcoma**, dacarbazine 250 mg/m^2 is given daily for 5 days repeated every 3 weeks; it is usually given with doxorubicin.

◊ References.

1. D'Incan M, Souteyrand P. Dacarbazine (Déticène). *Ann Dermatol Venereol* 2001; **128:** 517–25.
2. Eggermont AMM, Kirkwood JM. Re-evaluating the role of dacarbazine in metastatic melanoma: what have we learned in 30 years? *Eur J Cancer* 2004; **40:** 1825–36.

Preparations

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

Proprietary Preparations (details are given in Part 3)
Arg.: Deticene†; Oncocarbil; ***Austral.:*** DTIC; ***Austria:*** DTIC-Dome; ***Braz.:*** Asercit†; Dacarb; ***Canad.:*** DTIC†; ***Chile:*** Deticene; ***Fin.:*** Dacatic; ***Fr.:*** Deticene; ***Ger.:*** Detimedac; ***Gr.:*** Dacarbion; Deticene; ***India:*** Dacarin; Decarb; DTIC†; ***Israel:*** Deticene; ***Ital.:*** Deticene; ***Malaysia:*** DTI†; ***Mex.:*** Deticene†; Detilem; Ifadac; ***Neth.:*** Deticene; ***NZ:*** DTIC-Dome†; ***Philipp.:*** Duticin; ***Port.:*** Deticene; Fauldetic; ***S.Afr.:*** DTIC-Dome; ***Swed.:*** DTIC; ***Switz.:*** Dacin; DTIC; ***Turk.:*** Deticene; ***UK:*** DTIC-Dome†; ***USA:*** DTIC-Dome.

Dactinomycin *(BAN, USAN, rINN)*

Actinomycin C_1; Actinomycin D; Dactinomicina; Dactinomycine; Dactinomycinum; Daktinomisin; Daktinomycin; Daktinomysiini; Daktynomycyna; Meractinomycin; NSC-3053. $N^{2.1}$,$N^{2'.1'}$-(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyldicarbonyl)-bis[threonyl-D-valylprolyl(*N*-methylglycyl)(*N*-methylvaline) 1.5–3.1-lactone].

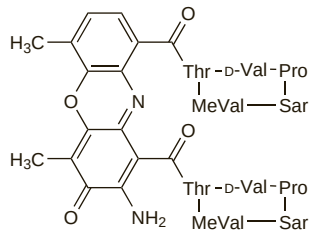
Дактиномицин

$C_{62}H_{86}N_{12}O_{16}$ = 1255.4.

CAS — 50-76-0.

ATC — L01DA01.

ATC Vet — QL01DA01.



Description. Dactinomycin is an antineoplastic antibiotic produced by *Streptomyces parvulus* and other species of *Streptomyces.*

Cactinomycin (actinomycin C; HBF-386; NSC-18268) is a mixture of dactinomycin (actinomycin D) (10%), actinomycin C_2 (45%), and actinomycin C_3 (45%) produced by *Streptomyces chrysomallus.*

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, *Pol.*, and *US*.

USP 31 (Dactinomycin). A bright red, somewhat hygroscopic, crystalline powder, affected by light and heat. It has a potency of not less than 950 and not more than 1030 micrograms/mg, calculated on the dried basis. Soluble in water at 10° and slightly soluble in water at 37°; freely soluble in alcohol; very slightly soluble in ether. Store at a temperature not exceeding 40° in airtight containers. Protect from light.

Adsorption. Dactinomycin binds to cellulose ester filters,[1] and such filtration should be avoided.[2] Although it has been suggested that significant amounts of drug may be adsorbed to glass or plastic,[3] dactinomycin is reportedly compatible with glass and PVC infusion containers,[4] and giving into the tubing of a fast-running intravenous infusion is recommended—see Uses and Administration, below.

1. Kanke M, *et al.* Binding of selected drugs to a "treated" inline filter. *Am J Hosp Pharm* 1983; **40:** 1323–8.
2. D'Arcy PF. Reactions and interactions in handling anticancer drugs. *Drug Intell Clin Pharm* 1983; **17:** 532–8.
3. Rapp RP, *et al.* Guidelines for the administration of commonly-used intravenous drugs—1984 update. *Drug Intell Clin Pharm* 1984; **18:** 218–32.
4. Benvenuto JA, *et al.* Stability and compatibility of antitumor agents in glass and plastic containers. *Am J Hosp Pharm* 1981; **38:** 1914–18.

Adverse Effects, Treatment, and Precautions

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

Apart from nausea and vomiting adverse effects are often delayed, beginning 2 to 4 days after the completion of a course of treatment and reaching a maximum after 1 to 2 weeks. Fatalities have occurred. Bone-marrow depression and gastrointestinal effects (particularly stomatitis and diarrhoea) may prove dose-limiting. Bone-marrow depression is apparent 1 to 7 days after therapy and may be manifest first as thrombocytopenia; the nadir of the platelet and white cell counts usually occurs within 14 to 21 days, with recovery in 21 to 25 days. Other adverse effects include oral and gastrointestinal effects such as cheilitis, oesophagitis, gastrointestinal ulceration, and proctitis; fever, malaise, hypocalcaemia, erythema, myalgia, alopecia, pneumonitis, and kidney and liver abnormalities. Anaphylactoid reactions have occurred. Dactinomycin is very irritant and extravasation results in severe tissue damage.

The effects of radiotherapy are enhanced by dactinomycin and severe reactions may follow the use of high doses. Erythema and pigmentation of the skin may occur in areas previously irradiated. An increase in incidence of second primary tumours has been seen in patients treated with radiation and dactinomycin.

Dactinomycin should not be given to patients with varicella or herpes zoster, as severe and even fatal systemic disease may occur. Its use is best avoided in infants under 1 year as they are reported to be highly susceptible to the toxicity of dactinomycin. Blood counts and renal and hepatic function should be monitored frequently.

Effects on the liver. Although doses less than about 50 micrograms/kg or 1.5 mg/m^2 do not seem to be associated with an unacceptable degree of hepatotoxicity,[1] giving dactinomycin as a single dose of 60 micrograms/kg (about 1.8 mg/m^2) every 3 weeks to children with Wilms' tumour was associated with a high incidence of severe hepatotoxicity;[2] reduction of the dose to 45 micrograms/kg every 3 weeks reduced this incidence to levels comparable with a standard regimen of 15 micrograms/kg daily for 5 successive days.[3] Others have not seen such a high incidence of hepatotoxicity with doses of 60 micrograms/kg (despite some raised liver enzyme values), but in this case the high dose was given only every 6 weeks.[4] In general, dactinomycin should be given with caution to children with a history of antecedent liver damage, including abdominal irradiation or recent halothane anaesthesia.[1]

Reversible veno-occlusive disease has been seen particularly in children with Wilms' tumour who have received dactinomycin and vincristine. One study[5] found age of less than 1 year to be a risk factor and a study in children with rhabdomyosarcoma given dactinomycin, vincristine, and cyclophosphamide also found that young age (under 3 years) was associated with a greater risk of severe hepatic toxicity.[6] A literature review[7] noted a significant predominance of veno-occlusive disease in right-sided Wilms' tumour, possibly because the tumour mass could interfere with blood flow in the hepatic veins, which might make the liver more susceptible to the effects of dactinomycin.

1. Pritchard J, *et al.* Hepatotoxicity of actinomycin-D. *Lancet* 1989; **i:** 168.
2. D'Angio GJ. Hepatotoxicity with actinomycin D. *Lancet* 1987; **ii:** 104.
3. D'Angio GJ. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.
4. de Camargo B. Hepatotoxicity and actinomycin D. *Lancet* 1990; **335:** 1290.

5. Bisogno G, *et al.* Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997; **29:** 245–51.
6. Arndt C, *et al.* Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide. *J Clin Oncol* 2004; **22:** 1894–1901. Correction [dosage error]. *ibid.*; 3434.
7. Tornesello A, *et al.* Veno-occlusive disease of the liver in right-sided Wilms' tumours. *Eur J Cancer* 1998; **34:** 1220–3.

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

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

Pharmacokinetics
Intravenous doses of dactinomycin are rapidly distributed with high concentrations in bone marrow and nucleated cells. It undergoes only minimal metabolism and is slowly excreted in urine and bile. The terminal plasma half-life is reported to be about 36 hours. It does not cross the blood-brain barrier but is thought to cross the placenta.

In children. A study[1] involving 31 patients aged between 1 and 20 years given dactinomycin in intravenous doses of 0.7 to 1.5 mg/m^2 found that the pharmacokinetics of the drug were variable, but could be described by a 3-compartment model. Peak plasma concentrations varied from 3.2 to 99.2 nanograms/mL, and both peak plasma concentration and exposure were inversely related to body-weight. Since there was evidence that exposure was also related to more severe toxicity, younger patients might be at greater risk with a regimen based on surface area; conversely the practice of capping the dose at 2 mg in older patients might result in underdosage.

For evidence that younger patients do experience more liver toxicity with dactinomycin, see Effects on the Liver, above.

1. Veal GJ, *et al.* Pharmacokinetics of dactinomycin in a pediatric patient population: a United Kingdom Children's Cancer Study Group Study. *Clin Cancer Res* 2005; **11:** 5893–9.

Uses and Administration
Dactinomycin is a highly toxic antibiotic with antineoplastic properties. It inhibits the proliferation of cells in a cell-cycle non-specific way by forming a stable complex with DNA and interfering with DNA-dependent RNA synthesis. It may enhance the cytotoxic effects of radiotherapy (see also Adverse Effects, above). Dactinomycin also has immunosuppressant properties.

It has been used, usually with other drugs or radiotherapy, in the treatment of Wilms' tumour (p.667), gestational trophoblastic tumours (p.650), nonseminomatous testicular cancer (p.673), and sarcomas such as rhabdomyosarcoma (p.676) and Ewing's sarcoma (p.675).

In the treatment of Wilms' tumour, childhood rhabdomyosarcoma, or Ewing's sarcoma, an intravenous dose of 15 micrograms/kg daily for 5 days has been used in combination regimens. In adults, gestational trophoblastic tumours have been treated with 12 micrograms/kg daily for 5 days as a single agent, or 500 micrograms on days 1 and 2 of combination regimens. Metastatic nonseminomatous testicular cancer has been treated with 1 mg/m^2 on day 1 of combination regimens. The dose intensity for adults or children should not exceed 15 micrograms/kg or 400 to 600 micrograms/m^2 daily for 5 days per 2-week cycle, and lower doses may need to be used in some chemotherapy combinations or with radiotherapy. Using a regional perfusion technique to localise the drug has permitted the use of higher doses, 50 micrograms/kg being suggested for an isolated lower extremity or pelvis and 35 micrograms/kg for an upper extremity.

Great care must be taken to avoid extravasation and it should be given, for preference, into the tubing of a fast-running intravenous infusion. Platelet and white cell counts should be performed frequently to detect bone-marrow depression; if either count shows a marked decrease the drug should be withheld until recovery occurs, which may take up to 3 weeks (see also Bone-marrow Depression, p.639).

Preparations
USP 31: Dactinomycin for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Cosmegen; ***Austral.:*** Cosmegen; ***Austria:*** Cosmegen; ***Belg.:*** Lyovac Cosmegen; ***Braz.:*** Cosmegen; ***Canad.:*** Cosmegen; ***Fin.:*** Cosmegen; ***Fr.:*** Cosmegen; ***Ger.:*** Lyovac Cosmegen; ***Gr.:*** Cosmegen; ***Hong Kong:*** Cosmegen; ***India:*** Dacmozen; ***Irl.:*** Cosmegen; ***Ital.:*** Cosmegen; ***Malaysia:*** Cosmegen†; ***Mex.:*** Ac-De; ***Neth.:*** Lyovac Cosmegen; ***Norw.:*** Cosmegen; ***NZ:*** Cosmegen; ***Philipp.:*** Cosmegen; Trepar; ***Singapore:*** Cosmegen; ***Swed.:*** Cosmegen; ***Switz.:*** Cosmegen; ***Thai.:*** Cosmegen†; Lyovac Cosmegen; ***Turk.:*** Cosmegen; ***UK:*** Cosmegen; ***USA:*** Cosmegen.

Dasatinib *(USAN, rINN)*

BMS-354825; Dasatinibum. *N*-(2-Chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl}amino)-5-thiazolecarboxamide.

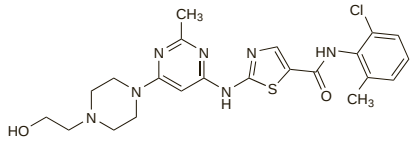
Дазатиниб

$C_{22}H_{26}ClN_7O_2S$ = 488.0.

CAS — 302962-49-8.

ATC — L01XE06.

ATC Vet — QL01XE06.



Adverse Effects, Treatment, and Precautions
The most common adverse effects of dasatinib include fluid retention, gastrointestinal disturbances, and bleeding. Fluid retention may be severe, and can result in pleural and pericardial effusion, pulmonary oedema, and ascites. Severe CNS haemorrhages, sometimes fatal, have been reported. Gastrointestinal haemorrhage may require interruption of therapy, and transfusions. Myelosuppression, manifest as neutropenia, thrombocytopenia, or anaemia, occurs more frequently in patients with advanced chronic myeloid leukaemia (CML) or acute lymphoblastic leukaemia than in patients in chronic phase. Recovery generally occurs after dose interruption and/or reduction, although treatment may need to be stopped. Febrile neutropenia has been reported. In patients with chronic phase CML, myelosuppression and fluid retention occur more often with twice daily dosing than once daily dosage. Other adverse effects include headache, pyrexia, musculoskeletal pain, fatigue, skin rashes, dyspnoea, cough, dizziness, chest pain, neuropathy, chills, and pruritus. Infections, including pneumonia, have been reported. Cardiac failure and arrhythmias can occur. Dasatinib has the potential to prolong the QT interval, and should be given with caution to patients at risk of this, such as those with hypokalaemia, hypomagnesaemia, or those on antiarrhythmic therapy, or receiving cumulative high doses of anthracyclines.

Effects on the skin. Panniculitis has been reported with the use of dasatinib, which resolved upon stopping therapy. In one case, dasatinib was restarted with prednisone, and no recurrence of panniculitis was noted. In another patient, however, a rash recurred on restarting therapy that was not sensitive to corticosteroid treatment.[1]

1. Assouline S, *et al.* Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. *N Engl J Med* 2006; **354:** 2623–4.

Interactions
Dasatinib is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme, such as azole antifungals, macrolide antibacterials, HIV-protease inhibitors, and nefazodone may increase blood concentrations of dasatinib. Equally, inducers of CYP3A4 (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin) may reduce blood concentrations of dasatinib. When use with such drugs cannot be avoided, dose adjustment of dasatinib may be necessary (see Uses and Administration, below). Since St John's wort may decrease dasatinib concentrations unpredictably, these drugs should not be given together.

Dasatinib is a substrate of the cytochrome P450 isoenzyme CYP3A4, and may alter blood concentrations of other drugs that are substrates of this enzyme.

Since the solubility of dasatinib is dependent on pH, use with antacids should be avoided. If antacid therapy is needed, it should be given at least 2 hours before or 2 hours after the dose of dasatinib. Similarly, histamine H_2-receptor antagonists or proton pump inhibitors such as famotidine or omeprazole should not be given with dasatinib as long-term suppression of gastric acid secretion is likely to reduce dasatinib exposure.

Pharmacokinetics
Maximum plasma concentrations of dasatinib are achieved between 0.5 and 6 hours after an oral dose. The mean terminal half-life is about 5 hours. Consumption of a high-fat meal may increase exposure to dasatinib, but this effect is not considered to be of clinical significance. Dasatinib is extensively distributed and metabolised. Metabolism occurs primarily by the cytochrome P450 isoenzyme CYP3A4, forming an active metabolite. Plasma protein binding of dasatinib and its active metabolite is about 96% and 93%, respectively. Elimination is mainly via the faeces; about 4% is recovered in the urine.

Uses and Administration
Dasatinib is a tyrosine kinase inhibitor that is used for the treatment of adults with all phases of chronic myeloid leukaemia (CML; p.653) who have resistance or intolerance to previous therapy, including imatinib. It is also used for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL; p.651) who are resistant to or intolerant of prior therapy.

A recommended oral starting dose of dasatinib in chronic phase CML is 100 mg once daily: tablets, which should be swallowed whole, not crushed or chewed, should be taken consistently either in the morning or the evening. The recommended starting dose for accelerated, myeloid, or lymphoid blast phase CML or Philadelphia chromosome-positive ALL is 70 mg twice daily. Dosage may be adjusted according to response and tolerability; doses of up to 140 mg once daily have been used in patients with chronic phase CML, and up to 100 mg twice daily in those with advanced phase, or with ALL. Treatment is continued until disease progression or unacceptable toxicity occurs.

If concurrent use of potent inhibitors or inducers of cytochrome P450 isoenzyme CYP3A4 cannot be avoided, dose adjustments are considered necessary. A dose increase should be considered in those patients given strong CYP3A4 inducers, and the patient should be monitored for toxicity. For those given a strong CYP3A4 inhibitor, the dose of dasatinib should be reduced to 20 mg daily. If this is not tolerated, then either drug should be stopped; if the inhibitor is stopped, a washout period of about 1 week should be allowed before the dose of dasatinib is increased.

◊ References.

1. Talpaz M, *et al.* Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med* 2006; **354:** 2531–41.
2. Hochhaus A, *et al.* Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; **109:** 2303–9. Correction. *ibid.*; **110:** 1438.
3. Cortes J, *et al.* Dasatinib induces complete hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood* 2007; **109:** 3207–13.
4. Guilhot F, *et al.* Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007; **109:** 4143–50.
5. Ottmann O, *et al.* Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. *Blood* 2007; **110:** 2309–15.