impairment was not associated with increased oxaliplatin toxicity. Dose reduction was not considered to be necessary in patients with mild to moderate renal impairment (as defined by creatinine clearance of 20 mL/minute or more).[1] UK licensed product information concurs that no dose adjustment is necessary in mild to moderate renal impairment, but contra-indicates the use of oxaliplatin in severe renal impairment (defined as creatinine clearance of less than 30 mL/minute), due to lack of data.

1. Takimoto CH, *et al.* Dose-escalating and pharmacological study of oxaliplatin in adult cancer patients with impaired renal function: a National Cancer Institute organ dysfunction working group study. *J Clin Oncol* 2003; **21:** 2664–72.

## Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Crisapla; Dabenzol; Dacplat; Goxyral; Kebir; Metaplatin; Mitog; O-Plat; Oxaltie; Platenk†; Platinostyl; Plusplatin; Uxalun; Xaliplat; ***Austral.:*** Eloxatin; ***Belg.:*** Eloxatin; ***Braz.:*** Eloxatin; Evoxali†; Ezulen; O-Plat; Uxalun; ***Chile:*** Eloxatin; O-Plat; ***Cz.:*** Ebeoxal; Eloxatin; Oxiplat; Platox; ***Fr.:*** Eloxatine; ***Ger.:*** Eloxatin; ***Hong Kong:*** Eloxatin; ***Hung.:*** Eloxatin; ***India:*** Dacotin; ***Indon.:*** Eloxatin; ***Ital.:*** Eloxatin; ***Malaysia:*** Eloxatin; ***Mex.:*** Eloxatin; Olipcis; Oxitan; Riptam; ***Neth.:*** Eloxatin; ***NZ:*** Eloxatin; ***Philipp.:*** Eloxatin; ***Pol.:*** Eloxatin; ***Port.:*** Eloxatin; ***Rus.:*** Eloxatine (Элоксатин); ***Singapore:*** Eloxatin; ***Spain:*** Eloxatin; ***Swed.:*** Eloxatin; ***Switz.:*** Eloxatine; ***Thai.:*** Eloxatin; Oxalip; Oxitan; ***Turk.:*** Eloxatin; ***UK:*** Eloxatin; ***USA:*** Eloxatin; ***Venez.:*** Eloxatin.

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# Paclitaxel *(BAN, USAN, rINN)*

BMS-181339-01; NSC-125973; Paclitaxelum; Paklitakseeli; Paklitaksel; Paklitaxel; Taxol; Taxol A. (2*S*,5*R*,7*S*,10*R*,13*S*)-10,20-Bis(acetoxy)-2-benzoyloxy-1,7-dihydroxy-9-oxo-5,20-epoxytax-11-en-13-yl (3*S*)-3-benzoylamino-3-phenyl-D-lactate.

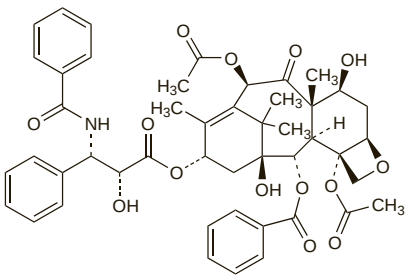
Паклитаксел

$C_{47}H_{51}NO_{14}$ = 853.9.

*CAS — 33069-62-4.*

*ATC — L01CD01.*

*ATC Vet — QL01CD01.*



NOTE. Paclitaxel was formerly referred to as taxol, but the use of this name is now limited, as Taxol is a trademark.

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

**Ph. Eur. 6.2** (Paclitaxel). Isolated from natural sources or produced by fermentation or by a semisynthetic process. A white or almost white, crystalline powder. Practically insoluble in water; freely soluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

**USP 31** (Paclitaxel). A white to off-white powder. Insoluble in water; soluble in alcohol. Store in airtight containers at a temperature between 20° and 25°. Protect from light.

**Incompatibility.** The vehicle for paclitaxel injection, which contains alcohol and polyoxl castor oil, was found to leach the plasticiser diethylhexyl phthalate from some plastic giving sets.[1,2] Consequently, licensed product information recommends the use of non-PVC containers and giving sets.

Paclitaxel was found to be compatible with doxorubicin for at least 24 hours, but microcrystalline precipitation of paclitaxel occurred after 3 to 5 days.[3] For mention of the incompatibility of paclitaxel and cisplatin see p.698.

1. Trissel LA, *et al.* Compatibility of paclitaxel injection vehicle with intravenous administration and extension sets. *Am J Hosp Pharm* 1994; **51:** 2804–10.
2. Mazzo DJ, *et al.* Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. *Am J Health-Syst Pharm* 1997; **54:** 566–9.
3. Trissel LA, *et al.* Compatibility and stability of paclitaxel combined with doxorubicin hydrochloride in infusion solutions. *Ann Pharmacother* 1998; **32:** 1013–6.

## Adverse Effects, Treatment, and Precautions

For a general outline see Antineoplastics, p.635, p.639, and p.641.

Paclitaxel produces severe dose-limiting bone marrow depression, the nadir of the white cell count usually occurring after about 11 days, with recovery usually by day 15 to 21 after a dose. Myelosuppression may be less frequent and less severe when infusions are given over 3 rather than 24 hours.

Peripheral neuropathy can also be severe, and occasionally dose-limiting. Hypersensitivity reactions, with flushing, rash, dyspnoea, hypotension, chest pain, and angioedema may occur, and all patients should be given initial premedication with corticosteroids, antihistamines, and histamine $H_2$-antagonists. Other adverse effects include alopecia, arthralgia and myalgia, gastrointestinal disturbances, mucositis, bradycardia and ECG changes, nail dystrophies, and elevation of liver enzyme values. Infections are common, as are injection site reactions; extravasation may result in tissue damage. Rare adverse events include hypertension, severe thrombotic events, myocardial infarction, heart failure, severe cardiac conduction abnormalities, seizures, neuroencephalopathy, paralytic ileus, optic nerve disturbances, severe skin reactions, hepatic necrosis, and hepatic encephalopathy. There are rare reports of interstitial pneumonia and other lung disorders.

Paclitaxel is not recommended in patients with severely impaired hepatic function. The drug is formulated in polyoxyl castor oil and should be avoided in patients hypersensitive to this substance. The formulation also contains alcohol, the CNS effects of which should be considered. Blood counts should be monitored frequently. Continuous cardiac monitoring is needed in patients who have had previous significant conduction abnormalities when given paclitaxel.

**Alcohol intoxication.** Acute alcohol intoxication resulting from high-dose paclitaxel infusion has been reported;[1] it was calculated that the dose used (348 mg/m$^2$) supplied 50 mL of alcohol, or the equivalent of about 3 drinks (half a bottle of wine).

1. Wilson DB, *et al.* Paclitaxel formulation as a cause of ethanol intoxication. *Ann Pharmacother* 1997; **31:** 873–5.

**Effects on the eyes.** Optic neuritis has occurred with paclitaxel. There is a report of glaucoma possibly related to the use of docetaxel and paclitaxel in a patient also receiving corticosteroids.[1]

1. Fabre-Guillevin E, *et al.* Taxane-induced glaucoma. *Lancet* 1999; **354:** 1181–2.

**Effects on the heart.** Infusion of paclitaxel has been associated with sinus bradycardia, atrial arrhythmias, ventricular tachycardia, heart block, myocardial infarction, and sudden death.[1,2] Symptoms of heart failure have been reported.[3] In another report sudden death 7 days after paclitaxel treatment raised the question of whether paclitaxel might have had a delayed effect.[4] There is some evidence of cellular damage to the myocardium of a patient with paclitaxel-associated cardiac symptoms.[3] Licensed product information notes that severe cardiovascular events have been seen more frequently after the use of paclitaxel in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

1. Rowinsky EK, *et al.* Cardiac disturbances during the administration of taxol. *J Clin Oncol* 1991; **9:** 1704–12.
2. Arbuck SG, *et al.* A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst Monogr* 1993; **15:** 117–30.
3. Jekunen A, *et al.* Paclitaxel-induced myocardial damage detected by electron microscopy. *Lancet* 1994; **343:** 727–8.
4. Alagaratnam TT. Sudden death 7 days after paclitaxel infusion for breast cancer. *Lancet* 1993; **342:** 1232–3.

**Effects on the musculoskeletal system.** Gabapentin has been reported to be of benefit in the management of taxane-induced arthralgia and myalgia.[1,2]

1. van Deventer H, Bernard S. Use of gabapentin to treat taxane-induced myalgias. *J Clin Oncol* 1999; **17:** 434–5.
2. Nguyen VH, Lawrence HJ. Use of gabapentin in the prevention of taxane-induced arthralgias and myalgias. *J Clin Oncol* 2004; **22:** 1767–9.

**Effects on the respiratory system.** Acute bilateral interstitial pneumonitis has been reported rarely in patients receiving paclitaxel, despite premedication with corticosteroids and histamine antagonists.[1] Symptoms resolved on treatment with parenteral corticosteroids.

1. Khan A, *et al.* Paclitaxel-induced acute bilateral pneumonitis. *Ann Pharmacother* 1997; **31:** 1471–4.

**Effects on the skin and nails.** Nail changes, noted as pigmentation or discoloration of the nail-bed, may occur with paclitaxel. Onycholysis (separation of the nail from the nail-bed) has also been reported.[1] Discoloration and onycholysis can also occur after docetaxel use, and there are reports of subungual hyperkeratosis and haemorrhage.[2-4]

Localised oedema evolving into skin sclerosis, mimicking systemic sclerosis, has been reported after taxane use. In most patients, the sclerosis developed mainly on the extremities, and especially the lower extremities. Joint contracture may occur. The total cumulative dose of the taxane may contribute to the onset.[5]

1. Flory SM, *et al.* Onycholysis associated with weekly administration of paclitaxel. *Ann Pharmacother* 1999; **33:** 584–5.
2. Wasner G, *et al.* Clinical picture: nail changes secondary to docetaxel. *Lancet* 2001; **357:** 910.
3. Pavithran K, Doval DC. Nail changes due to docetaxel. *Br J Dermatol* 2002; **146:** 709–10.
4. Leonard GD, Zujewski JA. Docetaxel-related skin, nail, and vascular toxicity. *Ann Pharmacother* 2003; **37:** 148.
5. Itoh M, *et al.* Taxane-induced scleroderma. *Br J Dermatol* 2007; **156:** 363–7.

**Hypersensitivity.** Despite premedication with corticosteroids, antihistamines, and $H_2$-antagonists, hypersensitivity reactions are common in patients given paclitaxel; up to about 40% of patients may have a mild reaction and about 2% a severe reaction. Fatalities have been reported. There are rare reports of delayed hypersensitivity reactions with paclitaxel; necrotic ulceration has occurred, without evidence of extravasation.[1] Some consider the cause to be the polyoxyl castor oil diluent for paclitaxel, and docetaxel has been suggested as a suitable alternative.[2] However, hypersensitivity reactions have also occurred with docetaxel and taxane cross-reactivity has been reported.[3,4] Although the manufacturers of both drugs consider further use to be contra-indicated after a severe reaction, strategies for continuation of treatment and desensitisation have been described.[5,6]

Hypersensitivity reactions to paclitaxel-eluting stents have also been reported;[7] however, the incidence is low, and some consider the polymer coating of the stent to be the likely cause.[8]

1. Beri R, *et al.* Severe dermatologic reactions at multiple sites after paclitaxel administration. *Ann Pharmacother* 2004; **38:** 238–41.
2. Bernstein BJ. Docetaxel as an alternative to paclitaxel after acute hypersensitivity reactions. *Ann Pharmacother* 2000; **34:** 1332–5.
3. Denman JP, *et al.* Hypersensitivity reaction (HSR) to docetaxel after a previous HSR to paclitaxel. *J Clin Oncol* 2002; **20:** 2760–1.
4. Karacan Ö, *et al.* Acute interstitial pneumopathy associated with docetaxel hypersensitivity. *Onkologie* 2004; **27:** 563–5.
5. Markman M, *et al.* Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. *J Clin Oncol* 2000; **18:** 102–5.
6. Feldweg AM, *et al.* Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. *Gynecol Oncol* 2005; **96:** 824–9.
7. Nebeker JR, *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; **47:** 175–81.
8. Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents: is it the pill or the polymer? *J Am Coll Cardiol* 2006; **47:** 182–3.

**Pregnancy.** Paclitaxel has been shown to be fetotoxic in *animal* studies, but although the use of potentially teratogenic drugs would normally be avoided during pregnancy, the risk to the mother of inadequate treatment may outweigh whatever risks exist of abnormality in the fetus. Paclitaxel has been used in the treatment of a patient who presented at 27 weeks of gestation with ovarian cancer. She had cytoreductive surgery and then adjuvant chemotherapy consisting of 3 cycles of paclitaxel and cisplatin given every 3 weeks. A healthy child was delivered by caesarean section at 37 weeks, and showed normal growth and development at 30 months of age.[1]

Anhydramnios has been associated with the use of trastuzumab and paclitaxel, see Pregnancy, under Trastuzumab, p.783.

1. Sood AK, *et al.* Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy. *Gynecol Oncol* 2001; **83:** 599–600.

## Interactions

For a general outline of antineoplastic drug interactions, see p.642. Pretreatment with cisplatin may reduce the clearance of paclitaxel, resulting in increased toxicity, and when both drugs are given, paclitaxel should be given first.

**Antineoplastics.** For reference to enhanced cardiotoxicity when paclitaxel was given with *doxorubicin*, see p.714. For the pharmacokinetic changes reported when paclitaxel was given with *gemcitabine*, see p.728.

Pretreatment with *fluorouracil* has been reported to inhibit paclitaxel's cytotoxic action, possibly by preventing tumour cells from entering the $G_2$-M phases of the cell cycle.[1] The effect also occurred when the 2 drugs were given simultaneously, suggesting that combination therapy might not be appropriate.

*Valspodar* inhibits P-glycoprotein, and a pharmacokinetic study[2] found that it decreased clearance of paclitaxel and prolonged the terminal half-life, increasing exposure to paclitaxel and myelosuppressive effects. The authors suggested that the dose of paclitaxel may need to be reduced by about 60%.

1. Johnson KR, *et al.* 5-Fluorouracil interferes with paclitaxel cytotoxicity against human solid tumor cells. *Clin Cancer Res* 1997; **3:** 1739–45.
2. Advani R, *et al.* A phase I trial of doxorubicin, paclitaxel, and valspodar (PSC 833), a modulator of multidrug resistance. *Clin Cancer Res* 2001; **7:** 1221–9.

**Antivirals.** ***HIV-PROTEASE INHIBITORS.*** In a patient given various antiretrovirals during paclitaxel treatment for Kaposi's sarcoma, pharmacokinetic parameters of paclitaxel were not significantly different when compared with historical controls.[1] The first course of therapy combined paclitaxel with lamivudine, stavudine, and the HIV-protease inhibitors *ritonavir* and *saquinavir*. In subsequent courses, paclitaxel was

given with nevirapine, and the final course consisted of paclitaxel given with ritonavir and *indinavir*. However, licensed product information for paclitaxel states that studies suggest that systemic clearance of paclitaxel was significantly lower in the presence of *nelfinavir* and ritonavir, but not indinavir, and that paclitaxel should be given with caution to patients taking HIV-protease inhibitors. HIV-protease inhibitors are metabolised by the cytochrome P450 isoenzyme CYP3A4, but are also reported to inhibit CYP3A activity. This may lead to increased adverse effects when given with taxanes; the combination of delavirdine and saquinavir has been reported to cause serious mucositis, severe myalgia, alopecia, and leucopenia when given with paclitaxel.[2]


1. Nannan Panday VR, *et al.* Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma—drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study. *Cancer Chemother Pharmacol* 1999; **43:** 516–19.
2. Schwartz JD, *et al.* Potential interaction of antiretroviral therapy with paclitaxel in patients with AIDS-related Kaposi's sarcoma. *AIDS* 1999; **13:** 283–4.


**Immunosuppressants.** *Ciclosporin* increased the oral absorption of paclitaxel, possibly by inhibiting the multidrug transporter P-glycoprotein in the gastrointestinal tract.[1]

For the effects of *valspodar* (an analogue of ciclosporin) on paclitaxel, see Antineoplastics, above.


1. Meerum Terwogt JM, *et al.* Co-administration of cyclosporin enables oral therapy with paclitaxel. *Lancet* 1998; **352:** 285. Correction. *ibid.*; 824.


## Pharmacokinetics

Intravenous paclitaxel exhibits a biphasic decline in plasma concentrations, with a mean terminal half-life of anywhere between about 3 and 50 hours. The pharmacokinetics are non-linear. The steady-state volume of distribution is reported to range from 200 to 700 litres/m$^2$, indicating extensive extravascular distribution, tissue binding, or both. Paclitaxel is 89% or more bound to plasma protein *in vitro*. The elimination of paclitaxel has not been fully elucidated; only about 1 to 12% of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non-renal clearance. Paclitaxel is metabolised in the liver, with the major metabolic pathway apparently mediated by the cytochrome P450 isoenzyme CYP2C8, although CYP3A4 may play a minor role. Metabolites are excreted in the faeces via the bile, the primary metabolite being 6α-hydroxypaclitaxel.

◊ References.


1. Sonnichsen DS, Relling MV. Clinical pharmacokinetics of paclitaxel. *Clin Pharmacokinet* 1994; **27:** 256–69.
2. Walle T, *et al.* Taxol metabolism and disposition in cancer patients. *Drug Metab Dispos* 1995; **23:** 506–12.
3. Sonnichsen DS, *et al.* Variability in human cytochrome P450 paclitaxel metabolism. *J Pharmacol Exp Ther* 1995; **275:** 566–75.
4. Henningsson A, *et al.* Mechanism-based pharmacokinetic model for paclitaxel. *J Clin Oncol* 2001; **19:** 4065–73.


## Uses and Administration

Paclitaxel is a taxane originally derived from the bark of the Pacific yew tree *Taxus brevifolia* (Taxaceae), and now obtained semisynthetically from a taxane precursor derived from the needles of the European yew, *Taxus baccata*. Paclitaxel's antineoplastic action arises from induction of microtubule formation and stabilisation of microtubules, thereby disrupting normal cell division in the $G_2$ and M phases of the cell cycle.

Paclitaxel is used for the primary treatment of advanced ovarian cancer (p.670) with cisplatin or carboplatin, and for secondary treatment. In the treatment of node-positive breast cancer (p.661), paclitaxel is used for primary adjuvant therapy after anthracycline-containing chemotherapy. In locally advanced or metastatic breast cancer, it is used first-line with an anthracycline, or as a second-line single-agent, usually after failure of anthracycline-based therapy. In patients with metastatic disease who overexpress HER2 (human epidermal growth receptor 2) it may be used with trastuzumab as initial therapy. Paclitaxel is used with cisplatin or carboplatin, for the primary treatment of advanced non-small cell lung cancer (p.668). It may be used for the second-line treatment of AIDS-related Kaposi's sarcoma (p.675), and has been tried in other neoplasms including cancers of the head and neck, and relapsed germ-cell tumours.

The recommended dose for the primary treatment of **ovarian cancer** is 135 mg/m$^2$ infused over 24 hours, followed by cisplatin, and repeated at 3-week intervals. Alternatively 175 mg/m$^2$ may be infused over 3 hours, followed by cisplatin, every 3 weeks. For the secondary treatment of ovarian cancer, the suggested dose as a single agent is 135 or 175 mg/m$^2$ infused over 3 hours once every 3 weeks.

For **breast cancer**, a dose of paclitaxel 175 mg/m$^2$ infused over 3 hours once every 3 weeks is recommended for adjuvant treatment (for 4 courses), for second-line monotherapy, and for first-line treatment with trastuzumab; paclitaxel is given the day after the first dose of trastuzumab, or immediately after subsequent doses if well-tolerated. When used first-line with doxorubicin, paclitaxel 220 mg/m$^2$ is infused over 3 hours once every 3 weeks; the dose is given 24 hours after doxorubicin.

In **non-small cell lung cancer**, the recommended dose is 135 mg/m$^2$ over 24 hours or 175 mg/m$^2$ over 3 hours, followed by cisplatin, and repeated at 3-week intervals.

A dose of 135 mg/m$^2$ over 3 hours once every 3 weeks has been suggested for AIDS-related **Kaposi's sarcoma**. Alternatively, 100 mg/m$^2$ over 3 hours every 2 weeks may be given, especially in patients with poor performance status.

Regular blood counts should be performed, and dosage should not be repeated until the neutrophil and platelet counts are at acceptable levels; the neutrophil count should be above 1000 cells/mm$^3$ in patients with AIDS (see also Bone-marrow Depression, p.639). The dose should be reduced by 20% in subsequent courses in patients who have severe neutropenia or peripheral neuropathy. Patients should be pretreated with corticosteroids, antihistamines, and histamine $H_2$-antagonists. The dose of paclitaxel may need to be reduced in patients with hepatic impairment (see below).

Various formulations have been developed to avoid the use of polyoxyl castor oil and improve the efficacy and safety of paclitaxel. An injectable suspension of albumin-bound paclitaxel nanoparticles (*Abraxane; Abraxis, USA*; ABI-007) is available for the treatment of refractory or relapsed breast cancer. The dose is 260 mg/m$^2$ given intravenously over 30 minutes every 3 weeks. Other formulations in development include paclitaxel linked to docosahexaenoic acid or biodegradable polymers (such as paclitaxel poliglumex), micellar and liposomal formulations, and an oral dosage form. An injectable vitamin E-based emulsion of paclitaxel has been investigated for the treatment of urothelial cancer and metastatic breast cancer.

Paclitaxel-releasing stents may be used to reduce restenosis after coronary artery stent placement.

◊ References to paclitaxel, and to taxanes as a class.


1. Gelmon K. The taxoids: paclitaxel and docetaxel. *Lancet* 1994; **344:** 1267–72.
2. Long HJ. Paclitaxel (Taxol): a novel anticancer chemotherapeutic drug. *Mayo Clin Proc* 1994: **69:** 341–5.
3. Spencer CM, Faulds D. Paclitaxel: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. *Drugs* 1994; **48:** 794–847.
4. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; **332:** 1004–14. Correction. *ibid.*; **333:** 75.
5. Anonymous. Paclitaxel and docetaxel in breast and ovarian cancer. *Drug Ther Bull* 1997; **35:** 43–6.
6. Eisenhauer EA, Vermorken JB. The taxoids: comparative clinical pharmacology and therapeutic potential. *Drugs* 1998; **55:** 5–30.
7. Crown J, O'Leary M. The taxanes: an update. *Lancet* 2000; **355:** 1176–8.
8. Michaud LB, *et al.* Risks and benefits of taxanes in breast and ovarian cancer. *Drug Safety* 2000; **23:** 401–28.
9. Simpson D, Plosker GL. Paclitaxel: as adjuvant or neoadjuvant therapy in early breast cancer. *Drugs* 2004; **64:** 1839–47.
10. Anonymous. Albumin-bound paclitaxel (Abraxane) for advanced breast cancer. *Med Lett Drugs Ther* 2005; **47:** 39–40.
11. Harries M, *et al.* Nanoparticle albumin-bound paclitaxel for metastatic breast cancer. *J Clin Oncol* 2005; **23:** 7768–71.
12. Robinson DM, Keating GM. Albumin-bound paclitaxel: in metastatic breast cancer. *Drugs* 2006; **66:** 941–8.
13. Hayes DF, *et al.* Cancer and Leukemia Group B (CALGB) Investigators. HER2 and response to paclitaxel in node-positive breast cancer. *N Engl J Med* 2007; **357:** 1496–1506.
14. Seidman AD, *et al.* Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008; **26:** 1642–9.


**Administration.** Although many of the original studies of paclitaxel employed a 24-hour infusion regimen, the use of *3-hour infusions* has subsequently become widespread. A systematic review[1] noted that although it was difficult to compare efficacy in studies of unlike malignancies there was no conclusive evidence of a difference in effectiveness with differing length of infusion; however, there were differences in the adverse effect profile, neutropenia being much less marked with the shorter infusion, although neurotoxic effects were reduced with 24-hour administration.

There has also been considerable interest in evaluating the use of paclitaxel in reduced-dose *weekly* schedules.[2-12] Various dosage regimens have been tried: most have found that doses of between 50 and about 100 mg/m$^2$ weekly, usually by infusion over 1 hour rather than a conventional 3-hour infusion, can be given with relatively modest toxicity. Although higher doses have been tried, neurotoxicity and myelosuppression become problematic and tend to limit dose intensity. A number of studies have addressed the combination of weekly paclitaxel with other antineoplastics, for example with trastuzumab in breast cancer, estramustine in prostate cancer, and with platinum compounds or gemcitabine in other solid tumours such as those of the ovary or lung. Weekly paclitaxel is also under investigation in combination with radiotherapy in the management of lung cancer and glioblastoma multiforme.


1. Williams C, *et al.* Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 12/05/05).
2. Seidman AD, *et al.* Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol* 1998; **16:** 3353–61.
3. Fountzilas G, *et al.* Radiation and concomitant weekly administration of paclitaxel in patients with glioblastoma multiforme: a phase II study. *J Neurooncol* 1999; **45:** 159–65.
4. Markman M. Weekly paclitaxel in the management of ovarian cancer. *Semin Oncol* 2000; **27** (suppl 7): 37–40.
5. De Pas T, *et al.* Phase I and pharmacologic study of weekly gemcitabine and paclitaxel in chemo-naive patients with advanced non-small-cell lung cancer. *Ann Oncol* 2000; **11:** 821–7.
6. Langer CJ, *et al.* Paclitaxel by 1-h infusion in combination with carboplatin in advanced non-small cell lung carcinoma (NSCLC). *Eur J Cancer* 2000; **36:** 183–93.
7. Akerley W. Recent developments in weekly paclitaxel therapy in lung cancer. *Curr Oncol Rep* 2001; **3:** 165–9.
8. Haas N, *et al.* Phase I trial of weekly paclitaxel plus oral estramustine phosphate in patients with hormone-refractory prostate cancer. *Urology* 2001; **58:** 59–64.
9. Seidman AD, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001; **19:** 2587–95.
10. Kouroussis C, *et al.* A dose-finding study of the weekly administration of paclitaxel in patients with advanced solid tumors. *Am J Clin Oncol* 2001; **24:** 404–7.
11. Brambilla L, *et al.* Weekly paclitaxel for advanced aggressive classic Kaposi sarcoma: experience in 17 cases. *Br J Dermatol* 2008; **158:** 1339–44.
12. Sparano JA, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 2008; **358:** 1663–71. Correction. *ibid.*; **359:** 106.


**Administration in hepatic impairment.** The US licensed product information makes recommendations for initial dosage adjustment of some paclitaxel regimens in patients with hepatic impairment, according to transaminase and bilirubin concentrations. They suggest paclitaxel should not be given if transaminase values are more than 10 times normal upper limits, or if bilirubin is more than 75 micrograms/mL or 5 times the normal upper limit.

**Reperfusion and revascularisation procedures.** Restenosis is a particular problem after percutaneous coronary revascularisation procedures (p.1181) and various drugs have been tried for its prevention. Coronary stents that elute paclitaxel effectively reduce restenosis and have been widely used, although there is some suggestion that sirolimus-eluting stents may be superior to paclitaxel-eluting stents in terms of clinical outcome and rates of restenosis.[1-3] In a study compared with bare metal stents, paclitaxel-releasing stents reduced the risk of restenosis and the need for repeat revascularisation procedures, although the follow-up rates of death from cardiac causes or myocardial infarction were not significantly reduced at 9 months[4] and 1 year.[5] However, between 9 months and 1 year, major cardiac adverse events were significantly reduced in the paclitaxel-releasing stent group compared to controls.[5] A review[6] of various stent designs concluded that safety of paclitaxel-releasing stents was independent of design, dose-density, or presence or absence of a polymer carrier system; however, those without a polymer carrier were unable to show a positive effect on clinical outcome in patients with de novo coronary lesions. However, in a paclitaxel-releasing stent system, failure of the stent-delivery balloon to deflate has been associated with serious injuries and 1 fatality.[7] The risk of late stent thrombosis may also be increased with drug eluting stents,[8]

although the evidence is controversial,[9] and their role in complex interventions is not yet established.[10,11]

Positive effects on restenosis have also been reported[12] with use of a paclitaxel-coated angioplasty balloon.


1. Windecker S, *et al.* Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med* 2005; **353:** 653–62.
2. Dibra A, *et al.* Paclitaxel-eluting or sirolimus-eluting stents to prevent restenosis in diabetic patients. *N Engl J Med* 2005; **353:** 663–70.
3. Hofma SH, *et al.* One year clinical follow up of paclitaxel eluting stents for acute myocardial infarction compared with sirolimus eluting stents. *Heart* 2005; **91:** 1176–80.
4. Stone GW, *et al.* A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350:** 221–31.
5. Stone GW, *et al.* One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation* 2004; **109:** 1942–7.
6. Silber S. Paclitaxel-eluting stents: are they all equal? An analysis of six randomized controlled trials in de novo lesions of 3,319 patients. *J Interv Cardiol* 2003; **16:** 485–90.
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### Preparations

***USP 31:*** Paclitaxel Injection.

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Asotax; Clitaxel; Dalys; Drifen; Erioxal; Paclikebir; Pacliteva; Paklitaxfil; Panataxel; Tarvexol; Taxocris; Taxol; Taycovit; ***Austral.:*** Anzatax; Taxol; ***Austria:*** Ebetaxel; Taxol; ***Belg.:*** Paclitaxin; Paxene; Taxol; ***Braz.:*** Biopaxel; Onxel; Paclitax; Parexel; Paxel†; Taclipaxol†; Taclix†; Tarvexol; Taxilan; Taxol; ***Canad.:*** Taxol; ***Chile:*** Britaxol; Oncoplaxel; Praxel; Taxodiol; ***Cz.:*** Anzatax; OncoTax; Onxol; Paclimedac; Pacline; Paxene; Taxol; ***Denm.:*** Taxol; ***Fin.:*** Taxol; ***Fr.:*** Paxene; Taxol; ***Ger.:*** NeoTaxan; Ribotax; Taxol; ***Gr.:*** Biotaxel; Ovapac; Paclit; Paclitaxin; Paclitol; Paclixel; Pataxel; Paxene; Ribotal; Taxogen; Taxol; Taxoprol; ***Hong Kong:*** Anzatax; Taxol; ***Hung.:*** Genexol; Intaxel; Magytax; Paxene; Taxol; ***India:*** Intaxel; Paclitax; Petaxel; ***Indon.:*** Anzatax; Paxus; Taxol; ***Irl.:*** Paxene; Taxol; ***Israel:*** Biotax; Ebetaxel; Medixel; Taxol†; ***Ital.:*** Anzatax; Paxene; Taxol; ***Jpn:*** Taxol; ***Malaysia:*** Anzatax; Formoxol; Mitotax; Taxol; ***Mex.:*** Asotax; BrisTaxol; Cryoxet; Daburex; Ifaxol; Paclisan; Praxel; ***Neth.:*** Paclitaxin; Paxene; Taxol; ***Norw.:*** Taxol; ***NZ:*** Taxol; ***Philipp.:*** Intaxel; Taxol; Unitaxel; ***Pol.:*** Poltaxel; Sindaxel; Taxol; ***Port.:*** Paxene; Taxobine; Taxol; ***Rus.:*** Abitaxel (Абитаксел)†; Mitotax (Митотакс); Paxene (Паксен); Taxol (Таксол); ***S.Afr.:*** Anzatax; Biolyse; Taxol; ***Singapore:*** Anzatax; Genexol; Taxol; ***Spain:*** Paxene; Taxol; ***Swed.:*** Paxene; Taxol; ***Switz.:*** Taxol; ***Thai.:*** Anzatax; Intaxel; Oncotaxel; Praxel; Taxol; ***Turk.:*** Anzatax; Taxol; ***UK:*** Paxene; Taxol; ***USA:*** Abraxane; Onxol; Taxol; ***Venez.:*** Clitaxel; Intaxel; Paclitax.

## Panitumumab *(USAN, rINN)*

ABX-EGF; E7.6.3; Panitumumabum. Immunoglobulin, anti-(human epidermal growth factor receptor) (human monoclonal ABX-EGF heavy chain), disulfide with human monoclonal ABX-EGF light chain, dimer.

Панитумумаб

*CAS — 339177-26-3.*

*ATC — L01XC08.*

*ATC Vet — QL01XC08.*

### Adverse Effects, Treatment, and Precautions

As for Cetuximab, p.695, although the use of premedication for prevention of infusion reactions with panitumumab has not been standardised. The infusion rate should be reduced by 50% in patients who have mild to moderate infusion reactions; if a severe reaction occurs, immediate and permanent discontinuation is recommended. In patients who developed skin reactions, infectious complications including abscesses and sepsis, in some cases fatal, have been reported.

### Interactions

Use of panitumumab with combination chemotherapy is not recommended. A high incidence of severe diarrhoea occurred in patients given panitumumab with fluorouracil, folinic acid, and irinotecan. Increased risk of death occurred when panitumumab was given with bevacizumab.

### Pharmacokinetics

The pharmacokinetics of panitumumab are reported to be non-linear. Steady-state concentrations were reached by the third infusion with the recommended dose regimen. The elimination half-life was about 7.5 days.

### Uses and Administration

Panitumumab is a recombinant human monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is used in the treatment of EGFR-expressing metastatic colorectal cancer (p.665) in patients with disease progression after fluoropyrimidine-, oxaliplatin-, or irinotecan-containing regimens. In some countries it is licensed only in patients whose tumour contains a non-mutated *KRAS* gene (Kirsten rat sarcoma 2 viral oncogene homologue), which plays a role in cell growth regulation and angiogenesis; mutations in the *KRAS* gene occur frequently in various human tumours and are implicated in oncogenesis and tumour progression.

The recommended dose is 6 mg/kg given as an intravenous infusion every 14 days. Doses up to and including 1 g are given in 100 mL sodium chloride 0.9% over 60 minutes whereas doses above 1 g are diluted in 150 mL and given over 90 minutes; the final concentration of the infusion should not exceed 10 mg/mL. The infusion should be given via an infusion pump using a low-protein-binding 0.2 or 0.22 micrometre inline filter. It may be given through a peripheral line or indwelling catheter; the line should be flushed with sodium chloride 0.9% before and after giving panitumumab. The infusion rate should be reduced by 50% in patients who have a mild to moderate infusion reaction, and stopped immediately and permanently if a severe reaction occurs.

Panitumumab should be withheld if severe dermatological toxicity develops, and permanently stopped if toxicity does not improve within 1 month. If toxicity improves after withholding no more than 2 doses of panitumumab, treatment may be restarted at half the original dose. If toxicity recurs, therapy should be permanently stopped. If toxicity does not recur, subsequent doses may be increased in increments of 25% until the recommended dose of 6 mg/kg is reached.

◊ References.


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### Preparations

**Proprietary Preparations** (details are given in Part 3)

***Cz.:*** Vectibix; ***Port.:*** Vectibix; ***UK:*** Vectibix; ***USA:*** Vectibix.

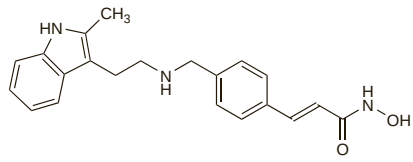
## Panobinostat *(rINN)*

Panobinostatum. (2*E*)-*N*-Hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]prop-2-enamide.

Панобиностат

$C_{21}H_{23}N_3O_2$ = 349.4.

*CAS — 404950-80-7.*



### Profile

Panobinostat is a histone deacetylase inhibitor that is under investigation as an antineoplastic for the treatment of cutaneous T-cell lymphoma.

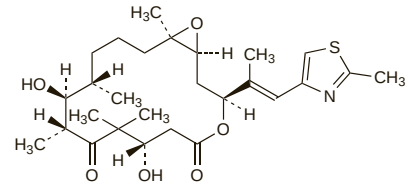
## Patupilone *(rINN)*

EPO-906; Epothilone B; Patupilona; Patupilonum. (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-(2-methyl-1,3-thiazol-4-yl)prop-1-en-2-yl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

Патупильон

$C_{27}H_{41}NO_6S$ = 507.7.

*CAS — 152044-54-7.*



### Profile

Patupilone is a metabolite isolated from the bacterium *Sorangium cellulosum*, with microtubule stabilising activity similar to that of the taxanes. It is under investigation as an antineoplastic for the treatment of ovarian cancer.

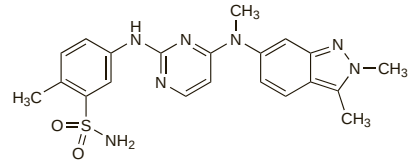
## Pazopanib Hydrochloride *(USAN, rINNM)*

GW-786034B; Hidrocloruro de pazopanib; Pazopanib, Chlorhydrate de; Pazopanibi Hydrochloridum. 5-({4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]pyrimidin-2-yl}amino)-2-methylbenzenesulfonamide hydrochloride.

Пазопаниба Гидрохлорид

$C_{21}H_{23}N_7O_2S,HCl$ = 474.0.

*CAS — 444731-52-6 (pazopanib); 635702-64-6 (pazopanib hydrochloride).*



*(pazopanib)*

### Profile

Pazopanib hydrochloride is an inhibitor of tyrosine kinase associated with the epidermal growth factor receptor. It is under investigation for the treatment of renal cell carcinoma.

## Peldesine *(USAN, pINN)*

BCX-34; Peldesina; Peldésine; Peldesinum. 2-Amino-3,5-dihydro-7-(3-pyridylmethyl)-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one.

Пельдезин

$C_{12}H_{11}N_5O$ = 241.2.

*CAS — 133432-71-0.*