3. Silvani A, *et al.* Intra-arterial ACNU and carboplatin versus intravenous chemotherapy with cisplatin and BCNU in newly diagnosed patients with glioblastoma. *Neurol Sci* 2002; **23:** 219–24.
4. Weller M, *et al.* Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. *J Clin Oncol* 2003; **21:** 3276–84.
5. Watanabe T, *et al.* Human interferon beta, nimustine hydrochloride, and radiation therapy in the treatment of newly diagnosed malignant astrocytomas. *J Neurooncol* 2005; **72:** 57–62.

Preparations

Proprietary Preparations (details are given in Part 3)
Ger.: ACNU; ***Jpn:*** Nidran†; ***Neth.:*** ACNU†; ***Switz.:*** ACNU†.

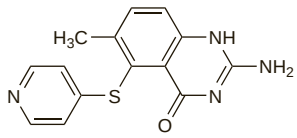
Nolatrexed *(rINN)*

AG-337 (nolatrexed dihydrochloride); Nolatrexedum. 2-Amino-6-methyl-5-(4-pyridylthio)-4(3*H*)-quinazolinone.

Нолатрексед

$C_{14}H_{12}N_4OS$ = 284.3.

CAS — 147149-76-6 (nolatrexed); 152946-68-4 (nolatrexed dihydrochloride).



Profile

Nolatrexed is, like raltitrexed (p.766), a selective inhibitor of thymidylate synthase. It has been investigated as an antimetabolite antineoplastic for the treatment of hepatocellular carcinoma, although results of single-agent studies have been disappointing. It is also under investigation in combination therapy for other solid tumours.

◊ References.

1. Mok TS, *et al.* A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999; **44:** 307–11.
2. Hughes AN, *et al.* Clinical pharmacokinetic and in vitro combination studies of nolatrexed dihydrochloride (AG337, Thymitaq) and paclitaxel. *Br J Cancer* 2000; **82:** 1519–27.
3. Estlin EJ, *et al.* A phase I study of nolatrexed dihydrochloride in children with advanced cancer. *Br J Cancer* 2001; **84:** 11–18.
4. Pivot X, *et al.* Result of two randomized trials comparing nolatrexed (Thymitaq) versus methotrexate in patients with recurrent head and neck cancer. *Ann Oncol* 2001; **12:** 1595–9.
5. Jhawer M, *et al.* Phase II trial of nolatrexed dihydrochloride [Thymitaq, AG 337] in patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2007; **25:** 85–94.
6. Gish RG, *et al.* Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007; **25:** 3069–75.

Oblimersen Sodium *(USAN, rINNM)*

G-3139; Natrii Oblimersenum; Oblimersén sódico; Oblimersen Sodique.

Натрий Облимерсен

$C_{172}H_{204}N_{62}Na_{17}O_{91}P_{17}S_{17}$ = 6058.3.

CAS — 190977-41-4.

Profile

Oblimersen sodium is an antisense oligonucleotide that blocks the production of BCL-2, a mitochondrial protein that prevents apoptosis. It is under investigation for the treatment of various malignant neoplasms, including leukaemias, lung cancer, and malignant melanoma.

◊ References.

1. Frankel SR. Oblimersen sodium (G3139 Bcl-2 antisense oligonucleotide) therapy in Waldenstrom's macroglobulinemia: a targeted approach to enhance apoptosis. *Semin Oncol* 2003; **30:** 300–304.
2. Büchele T. Proapoptotische Therapie mit Oblimersen (bcl-2-Antisense-Oligonukleotid)—Übersicht über präklinische und klinische Daten. *Onkologie* 2003; **26** (suppl 7): 60–9.
3. Herbst RS, Frankel SR. Oblimersen sodium (Genasense bcl-2 antisense oligonucleotide): a rational therapeutic to enhance apoptosis in therapy of lung cancer. *Clin Cancer Res* 2004; **10** (suppl): 4245s–4248s.
4. Chi KN. Targeting Bcl-2 with oblimersen for patients with hormone refractory prostate cancer. *World J Urol* 2005; **23:** 33–7.
5. O'Brien SM, *et al.* Phase I to II multicenter study of oblimersen sodium, a Bcl-2 antisense oligonucleotide, in patients with advanced chronic lymphocytic leukemia. *J Clin Oncol* 2005; **23:** 7697–7702.
6. Mita MM, *et al.* A phase I, pharmacokinetic and biologic correlative study of oblimersen sodium (Genasense, G3139) and irinotecan in patients with metastatic colorectal cancer. *Ann Oncol* 2006; **17:** 313–21.
7. Bedikian AY, *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24:** 4738–45.
8. O'Brien S, *et al.* Randomized phase III trial of fludarabine plus cyclophosphamide with or without oblimersen sodium (Bcl-2 antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2007; **25:** 1114–20. Correction. *ibid.* 2008; **26:** 820.

Ofatumumab *(rINN)*

HuMax-CD20; Ofatumumabum. Immunoglobulin G1, anti-(human CD20 (antigen))(human monoclonal HuMax-CD20 heavy chain), disulfide with human monoclonal HuMax-CD20 κ-chain, dimer.

Офатумумаб

CAS — 679818-59-8.

Profile

Ofatumumab is an anti-CD20 monoclonal antibody that is under investigation for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.

◊ References.

1. Coiffier B, *et al.* Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. *Blood* 2008; **111:** 1094–1100.
2. Hagenbeek A, *et al.* First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; **111:** 5486–95.
3. Robak T. Ofatumumab, a human monoclonal antibody for lymphoid malignancies and autoimmune disorders. *Curr Opin Mol Ther* 2008; **10:** 294–309.

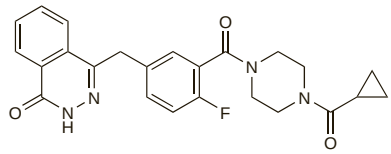
Olaparib *(rINN)*

Olaparibum. 4-[(3-{[4-(Cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one.

Олапариб

$C_{24}H_{23}FN_4O_3$ = 434.5.

CAS — 763113-22-0.



Profile

Olaparib is an antineoplastic that is under investigation for the treatment of ovarian cancer.

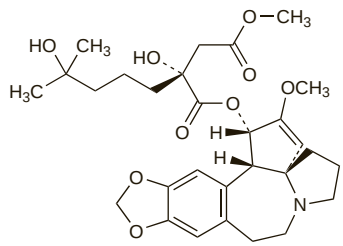
Omacetaxine Mepesuccinate *(pINN)*

CGX-635; HHT; Homoharringtonine; Mepesuccinato de omacetaxina; NSC-141633; Omacétaxine, Mépésuccinate d'; Omacetaxini mepesuccinas. 1-[(1*S*,3a*R*,14b*S*)-2-Methoxy-1,5,6,8,9,14b-hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-1-yl] 4-methyl (2*R*)-2-hydroxy-2-(4-hydroxy-4-methylpentyl)butanedioate.

Омацетаксин Мепесукцинат

$C_{29}H_{39}NO_9$ = 545.6.

CAS — 26833-87-4.



Pharmacopoeias. In *Chin.*

Profile

Omacetaxine mepesuccinate is a semisynthetic formulation of homoharringtonine, which is an alkaloid derived from the tree *Cephalotaxus harringtonia*, and related species. It is thought to induce apoptosis by inhibition of protein synthesis. It is under investigation for the treatment of chronic myeloid leukaemia (p.653). It has also been tried in the treatment of acute leukaemias and other neoplastic disorders.

The related compounds harringtonine, isoharringtonine, and deoxyharringtonine have also been investigated.

Adverse effects of omacetaxine mepesuccinate may include severe hypotension, cardiac arrhythmias, myelosuppression, gastrointestinal disturbances, chest pain, headache, fatigue, alopecia, rashes, and hyperglycaemia.

◊ References.

1. Kantarjian HM, *et al.* Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic myelogenous leukemia. *J Clin Oncol* 2000; **18:** 3513–21.
2. Kantarjian HM, *et al.* Homoharringtonine: history, current research, and future direction. *Cancer* 2001; **92:** 1591–1605.
3. O'Brien S, *et al.* Simultaneous homoharringtonine and interferon-alpha in the treatment of patients with chronic-phase chronic myelogenous leukemia. *Cancer* 2002; **94:** 2024–32.
4. Tang J, *et al.* A homoharringtonine-based regimen for childhood acute myelogenous leukemia. *Med Pediatr Oncol* 2003; **41:** 70–2.
5. O'Brien S, *et al.* Results of triple therapy with interferon-alpha, cytarabine, and homoharringtonine, and the impact of adding imatinib to the treatment sequence in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in early chronic phase. *Cancer* 2003; **98:** 888–93.
6. Luo CY, *et al.* Homoharringtonine: a new treatment option for myeloid leukemia. *Hematology* 2004; **9:** 259–70.
7. Quintás-Cardama A, Cortes J. Homoharringtonine for the treatment of chronic myelogenous leukemia. *Expert Opin Pharmacother* 2008; **9:** 1029–37.
8. Quintás-Cardama A, Cortes J. Omacetaxine mepesuccinate - a semisynthetic formulation of the natural antitumoral alkaloid homoharringtonine, for chronic myelocytic leukemia and other myeloid malignancies. *IDrugs* 2008; **11:** 356–72.

Oregovomab *(USAN, rINN)*

MAb-B43.13; Orégovomab; Oregovomabum. Immunoglobulin G1, anti-(human CA125 (carbohydrate antigen)) (mouse monoclonal B43.13 γ1-chain), disulfide with mouse monoclonal B43.13 κ-chain, dimer.

Ореговомаб

CAS — 213327-37-8.

Profile

Oregovomab is a murine monoclonal antibody that binds to CA-125, an antigen that is overexpressed in the majority of ovarian cancer patients, and stimulates an immune response to the tumour cells. It is under investigation for the treatment of ovarian cancer.

Oxaliplatin *(BAN, USAN, rINN)*

JM-83; NSC-266046; *l*-OHP; Oksaliplatiini; Oksaliplatin; Oksaliplatina; Oxaliplatina; Oxaliplatine; Oxaliplatino; Oxaliplatinum; RP-54780; SR-96669. [(1*R*,2*R*)-1,2-Cyclohexanediamine-*N*,*N*′]-[oxalato(2-)-*O*,*O*′]platinum.

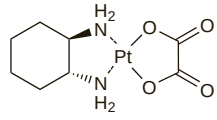
Оксалиплатин

$C_8H_{14}N_2O_4Pt$ = 397.3.

CAS — 61825-94-3.

ATC — L01XA03.

ATC Vet — QL01XA03.



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

Ph. Eur. 6.2 (Oxaliplatin). A white or almost white, crystalline powder. Slightly soluble in water; practically insoluble in dehydrated alcohol; very slightly soluble in methyl alcohol.

Incompatibility. Licensed product information states that oxaliplatin should not be mixed with chloride-containing solutions (including sodium chloride) or alkaline drugs or solutions. In particular, oxaliplatin should not be mixed with fluorouracil or any trometamol salts. While oxaliplatin may be infused through a Y-site with folinic acid (in glucose 5% solution), they may not be mixed in the same infusion bag, and folinic acid must not contain trometamol as an excipient. The infusion line should be flushed with glucose 5% before giving any other medication. Oxaliplatin may degrade on contact with aluminium, and injection equipment containing aluminium should not be used.

Stability. UK licensed product information states that oxaliplatin must be diluted in glucose 5% to give a concentration not less than 200 micrograms/mL. From a microbiological point of view, the infusion preparation should be used immediately; the infusion should not be stored for longer than 24 hours at 2° to 8° unless it has been prepared in controlled and validated aseptic conditions. Chemical and physical stability has been shown for 48 hours at 2° to 8°, and for 24 hours at 25°. US licensed product information states that, after dilution in 250 to 500 mL of glucose

5%, oxaliplatin infusion solutions have a shelf-life of 6 hours at room temperature (20° to 25°) and up to 24 hours when refrigerated (2° to 8°), and that protection from light is not required.

A study[1] found that oxaliplatin solutions at 700 micrograms/mL in polyolefin infusion bags of glucose 5% were chemically stable for at least 30 days at both 3° to 7° and 20° to 24° without regard to light.

1. André P, *et al.* Stability of oxaliplatin in infusion bags containing 5% dextrose injection. *Am J Health-Syst Pharm* 2007; **64:** 1950–4.

Adverse Effects and Precautions

The adverse affects of oxaliplatin are similar to those of cisplatin (p.698) but nausea and vomiting, nephrotoxicity, and myelosuppression, seem to be less marked. Raised liver enzyme values may occur. Neurotoxicity can be dose-limiting. Peripheral neuropathy occurs in 85 to 95% of patients given oxaliplatin; pain, functional impairment, and loss of tendon reflexes may develop. Pulmonary fibrosis, potentially fatal, has also been reported. Extravasation of oxaliplatin can cause local pain and inflammation; complications may sometimes be severe, including necrosis.

Neurological examinations should be carried out at regular intervals during treatment and the dose should be reduced if symptoms are prolonged or severe. Regular blood counts should be performed during treatment and courses should not be repeated until blood counts have recovered (see also Bone-marrow Depression, p.639). Oxaliplatin should not be given to patients with pre-existing sensory neuropathies or myelosuppression, nor to those with severe renal impairment. Renal function and toxicity should be carefully monitored in those with more moderate degrees of renal impairment.

Patients are recommended to use appropriate contraceptive measures during treatment and for 6 months after stopping treatment for men and for 4 months for women.

Effects on the blood. Acute haemolysis, with[1-4] and without[5] anaemia, has been reported with the use of oxaliplatin. The reactions were considered to be immune-mediated. Evan's syndrome (immune-mediated thrombocytopenia and haemolytic anaemia) has also been reported.[6]

1. Desrame J, *et al.* Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; **354:** 1179–80.
2. Garufi C, *et al.* Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000; **11:** 497.
3. Hofheinz R-D, *et al.* Two potential mechanisms of oxaliplatin-induced haemolytic anaemia in a single patient. *Cancer Chemother Pharmacol* 2004; **53:** 276–7.
4. Chen VMY, *et al.* An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; **44:** 838–43.
5. Koutras AK, *et al.* Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis: a case report and review of the literature. *Oncology* 2004; **67:** 179–82.
6. Earle CC, *et al.* Oxaliplatin-induced Evan's syndrome. *Br J Cancer* 2001; **84:** 441.

Effects on the liver. The development of ascites, portal hypertension, and hepatic lesions in a patient with colorectal cancer was considered to be due to oxaliplatin; metastatic or recurrent cancer had been originally suspected.[1]

1. Tisman G, *et al.* Oxaliplatin toxicity masquerading as recurrent colon cancer. *J Clin Oncol* 2004; **22:** 3202–4.

Effects on the nervous system. Neurological toxicity is the principal dose-limiting adverse effect with oxaliplatin.[1-3] The toxicity is biphasic:

- acute paraesthesias or dysaesthesias of the extremities, triggered or exacerbated by cold, are seen in 85 to 95% of patients within hours of infusion, but are normally mild and resolve within hours or days. Some patients also have distressing laryngopharyngeal symptoms, such as difficulty in breathing or swallowing.
- with increasing cumulative dose, peripheral sensory symptoms increase in duration and intensity. Symptoms are sometimes associated with pain and cramps, and may progress to functional impairment (loss of fine sensorimotor coordination). Dosage reduction may be required, but in clinical practice the onset of functional impairment often occurs after the maximum response to therapy has been attained. Cumulative neurotoxicity is reversible in most cases, and about 80% of patients exhibit symptom regression within 4 to 6 months.

The incidence of neurotoxicity may be higher when oxaliplatin is given with fluorouracil. There is some evidence that more prolonged infusion of oxaliplatin can reduce acute toxicity, particularly laryngopharyngeal symptoms. Antiepileptics such as carbamazepine (see Neuropathic Pain, p.477) or gabapentin have been investigated in the management of oxaliplatin-induced neurotoxicity and glutathione has been tried for prevention. Intravenous calcium gluconate and magnesium chloride infusions have been used to prevent acute oxaliplatin neuropathy with good initial results; similarly, intravenous calcium gluconate and magnesium sulfate have been reported to dramatically improve oxaliplatin-associated neuropathy.[4-6] However, a study designed to evaluate potential reduction of cumulative neurotoxicity associated with oxaliplatin, using calcium and magnesium salts, was terminated after those patients receiving calcium and magnesium reported a significantly lower response to chemotherapy (which consisted of oxaliplatin, folinic acid, fluorouracil, and bevacizumab). Although these results need confirmation, the possibility that calcium and magnesium may reduce the activity of certain drugs in the treatment of colorectal cancer should be considered.[7]

1. Extra JM, *et al.* Pharmacokinetics and safety profile of oxaliplatin. *Semin Oncol* 1998; **25** (suppl 5): 13–22.
2. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
3. Cassidy J, Misset J-L. Oxaliplatin-related side effects: characteristics and management. *Semin Oncol* 2002; **29** (suppl 15): 11–20.
4. Gamelin L, *et al.* Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res* 2004; **10:** 4055–61.
5. Cersosimo RJ. Oxaliplatin-associated neuropathy: a review. *Ann Pharmacother* 2005; **39:** 128–35.
6. Gamelin L, *et al.* Neurotoxicité de l'oxaliplatine. *Bull Cancer* 2006; **93** (suppl 1): S17–S22.
7. Hochster HS, *et al.* Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. *J Clin Oncol* 2007; **25:** 4028–9.

GUILLAIN-BARRÉ SYNDROME. A patient with metastatic colon cancer developed Guillain-Barré syndrome after weekly treatment with oxaliplatin-based chemotherapy;[1] he recovered after treatment with intravenous immunoglobulin.

1. Christodoulou C, *et al.* Guillain-Barré syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. *Anticancer Drugs* 2004; **15:** 997–9.

REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME. Reversible posterior leukoencephalopathy syndrome (RPLS) was diagnosed in a woman given oxaliplatin with bevacizumab, and capecitabine. She tolerated further therapy with bevacizumab and irinotecan with no complications. The authors attributed the RPLS to oxaliplatin.[1]

1. Pinedo DM, *et al.* Reversible posterior leukoencephalopathy syndrome associated with oxaliplatin. *J Clin Oncol* 2007; **25:** 5320–1.

Extravasation. Although oxaliplatin was originally considered to be non-vesicant, there have been reports of extravasation causing inflammation, sclerosis, or, in some cases, severe necrosis.[1-4] Some consider it to be a vesicant drug,[1,2] although others state oxaliplatin extravasation to be less harmful than that of more classic vesicants.[4]

For discussion of the management of extravasation, see under Treatment of the Adverse Effects of Antineoplastics, p.640.

1. Baur M, *et al.* Extravasation of oxaliplatin (Eloxatin)–clinical course. *Onkologie* 2000; **23:** 468–71.
2. Foo KF, *et al.* A case report of oxaliplatin extravasation. *Ann Oncol* 2003; **14:** 961–2.
3. Kennedy JG, *et al.* Vesicant characteristics of oxapliplatin [sic] following antecubital extravasation. *Clin Oncol (R Coll Radiol)* 2003; **15:** 237–9.
4. Kretzschmar A, *et al.* Extravasations of oxaliplatin. *J Clin Oncol* 2003; **21:** 4068–9.

Hypersensitivity. Hypersensitivity reactions, including anaphylaxis, have been reported with oxaliplatin,[1-13] usually after several cycles of treatment. Symptoms include hypotension, tachycardia, dyspnoea, burning sensations, pruritus, erythema, sweating, and dizziness.[1,2,7,8] Rashes have also been reported[5,6,12] as have fever and chills.[9,10] While the mechanism of hypersensitivity to oxaliplatin is not clear, it has been suggested that reactions are characterised by development of symptoms during or shortly after the infusion, and are possibly due to a type I IgE-mediated reaction.[7,10] Idiosyncratic or infusional reactions, which are delayed until hours after the infusion,[6,10] are considered to be associated with cytokine release.[7,10] Cases have generally resolved on stopping oxaliplatin and giving appropriate treatment.

Prophylaxis before further oxaliplatin therapy, with corticosteroids and/or antihistamines, has shown variable efficacy.[4-7,9,10] Desensitisation protocols using dilute solutions and longer infusion times have been reported to be successful.[10,11,13]

Intradermal skin testing has been used to identify patients with suspected hypersensitivity to oxaliplatin; however, in some patients with negative skin tests, reactions have occurred upon re-challenge.[6,8]

1. Tournigand C, *et al.* Severe anaphylactic reactions to oxaliplatin. *Eur J Cancer* 1998; **34:** 1297–8.
2. Médioni J, *et al.* Anaphylaxis after oxaliplatin. *Ann Oncol* 1999; **10:** 610.
3. Larzillière I, *et al.* Anaphylactic reaction to oxaliplatin: a case report. *Am J Gastroenterol* 1999; **94:** 3387–8.
4. Stahl M, *et al.* Reaction after oxaliplatin—prevention with corticosteroids? *Ann Oncol* 2001; **12:** 874.
5. Alliot C, *et al.* Severe anaphylactic reaction to oxaliplatin. *Clin Oncol (R Coll Radiol)* 2001; **13:** 236.
6. Thomas RR, *et al.* Hypersensitivity and idiosyncratic reactions to oxaliplatin. *Cancer* 2003; **97:** 2301–7.
7. Brandi G, *et al.* Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer* 2003; **89:** 477–81.
8. Garufi C, *et al.* Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol* 2003; **14:** 497–8.
9. Lenz G, *et al.* Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. *Anticancer Drugs* 2003; **14:** 731–3.
10. Lim K-H, *et al.* Hypersensitivity reactions to oxaliplatin: a case report and the success of a continuous infusional desensitization schedule. *Anticancer Drugs* 2004; **15:** 605–7.
11. Gammon D, *et al.* Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004; **9:** 546–9.
12. Ng CVT. Hypersensitivity reactions to oxaliplatin in two Asian patients. *Ann Pharmacother* 2005; **39:** 1114–18.
13. Mis L, *et al.* Successful desensitization to oxaliplatin. *Ann Pharmacother* 2005; **39:** 966–9.

Interactions

For reference to the effect of oxaliplatin on fluorouracil, see Antineoplastics, p.723.

Pharmacokinetics

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours.

Oxaliplatin is extensively metabolised to both inactive and active compounds and is predominantly excreted in the urine.

◊ References.

1. Lévi F, *et al.* Oxaliplatin: pharmacokinetics and chronopharmacological aspects. *Clin Pharmacokinet* 2000; **38:** 1–21.
2. Graham MA, *et al.* Clinical pharmacokinetics of oxaliplatin: a critical review. *Clin Cancer Res* 2000; **6:** 1205–18.

Uses and Administration

Oxaliplatin is a platinum-containing complex similar to cisplatin (see p.698). It is given with fluorouracil and folinic acid in the treatment of metastatic colorectal cancer and in the adjuvant treatment of stage III (Dukes C) colon cancer (p.665). The recommended dose is 85 mg/m^2 by intravenous infusion over 2 to 6 hours, dissolved in 250 to 500 mL of glucose 5%. The dose may be repeated at intervals of 2 weeks if toxicity permits, reduced according to tolerance. In the adjuvant setting, oxaliplatin is given for 12 cycles. After persistent neurotoxicity or recovery from severe adverse effects licensed product information recommends an initial reduction to 65 mg/m^2 in metastatic colorectal cancer, and to 75 mg/m^2 when given as adjuvant treatment. Oxaliplatin should always be given before fluoropyrimidines.

Oxaliplatin is under investigation for the treatment of ovarian and lung cancer. A liposomal formulation of oxaliplatin is in development.

◊ References.

1. Culy CR, *et al.* Oxaliplatin: a review of its pharmacological properties and clinical efficacy in metastatic colorectal cancer and its potential in other malignancies. *Drugs* 2000; **60:** 895–924.
2. Monnet I, *et al.* Oxaliplatin plus vinorelbine in advanced non-small-cell lung cancer: final results of a multicenter phase II study. *Ann Oncol* 2002; **13:** 103–7.
3. Louvet C, *et al.* Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002; **20:** 4543–8.
4. Simpson D, *et al.* Oxaliplatin: a review of its use in combination therapy for advanced metastatic colorectal cancer. *Drugs* 2003; **63:** 2127–56.
5. Winegarden JD, *et al.* A phase II study of oxaliplatin and paclitaxel in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2004; **15:** 915–20.
6. André T, *et al.* Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350:** 2343–51.
7. Chao Y, *et al.* Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. *Br J Cancer* 2004; **91:** 453–8.
8. Pectasides D, *et al.* Oxaliplatin plus high-dose leucovorin and 5-fluorouracil (FOLFOX 4) in platinum-resistant and taxane-pretreated ovarian cancer: a phase II study. *Gynecol Oncol* 2004; **95:** 165–72.
9. Keam SJ, *et al.* Oxaliplatin: in operable colorectal cancer. *Drugs* 2005; **65:** 89–96.
10. Fu S, *et al.* Clinical application of oxaliplatin in epithelial ovarian cancer. *Int J Gynecol Cancer* 2006; **16:** 1717–32.
11. Kim GP, Erlichman C. Oxaliplatin in the treatment of colorectal cancer. *Expert Opin Drug Metab Toxicol* 2007; **3:** 281–94.
12. Stordal B, *et al.* Oxaliplatin for the treatment of cisplatin-resistant cancer: a systematic review. *Cancer Treat Rev* 2007; **33:** 347–57.

Administration in renal impairment. The primary route of platinum elimination is renal, and clearance of platinum is decreased in patients with renal impairment. However, a study determined that increased platinum exposure in patients with renal

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.

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.

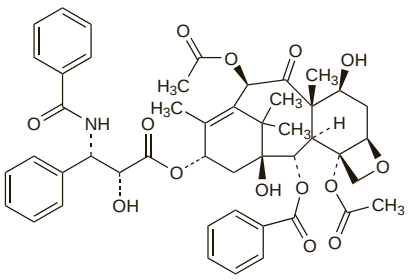
Паклитаксел

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