Preparations

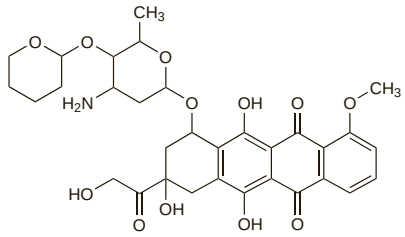
Proprietary Preparations (details are given in Part 3)
Fr.: Vercyte; ***Ital.:*** Vercite.

Pirarubicin *(rINN)*

Pirarubicina; Pirarubicine; Pirarubicinum; 1609-RB; Tepirubicin; THP-ADM; THP-doxorubicin. (8*S*,10*S*)-10-{[3-Amino-2,3,6-trideoxy-4-*O*-(2*R*-tetrahydro-2*H*-pyran-2-yl)-α-L-*lyxo*-hexopyranosyl]oxy}-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione.

Пирарубицин

$C_{32}H_{37}NO_{12}$ = 627.6.
CAS — 72496-41-4.
ATC — L01DB08.
ATC Vet — QL01DB08.



Pharmacopoeias. In *Jpn.*

Profile

Pirarubicin is an antineoplastic anthracycline antibiotic that is a structural analogue of doxorubicin (p.712), and has similar properties. It is used in the management of breast cancer and has also been tried in other solid neoplasms, acute leukaemias and lymphomas.

Pirarubicin is formulated as the hydrochloride but doses are in terms of the base. A usual dose of 25 to 50 mg/m^2 every 3 to 4 weeks has been recommended in breast cancer, but other dosage regimens have been used. Doses may be given by intravenous injection over 5 to 10 minutes into a rapidly-flowing intravenous infusion of glucose 5%. Patients should undergo regular blood counts and monitoring of cardiac function: at cumulative doses above 600 mg/m^2 ventricular ejection fraction should be checked before each course. Pirarubicin has also been given by the intra-arterial and intravesical routes.

Preparations

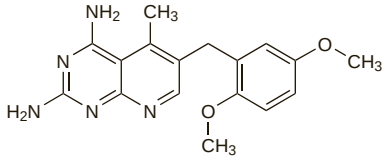
Proprietary Preparations (details are given in Part 3)
Cz.: Pinorubin†; ***Fr.:*** Theprubicine.

Piritrexim Isetionate *(rINNM)*

BW-301U (piritrexim); Isetionato de piritrexima; NSC-351521; Piritrexim Isethionate *(USAN)*; Piritreximе, Isétionate de; Piritreximi Isetionas. 2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine mono(2-hydroxyethanesulphonate).

Пиритрексима Изетионат

$C_{17}H_{19}N_5O_2,C_2H_6O_4S$ = 451.5.
CAS — 72732-56-0 (piritrexim); 79483-69-5 (piritrexim isetionate).



(piritrexim)

Profile

Piritrexim is a folate antagonist with general properties similar to those of methotrexate (p.745). It has been tried by mouth for its antineoplastic properties, and has also been used (as the isetionate) for the treatment of opportunistic infections in immunosuppressed patients. Myelosuppression, gastrointestinal disturbances, and hepatotoxicity have been reported.

Piritrexim isetionate has also been investigated for severe psoriasis.

◊ References.

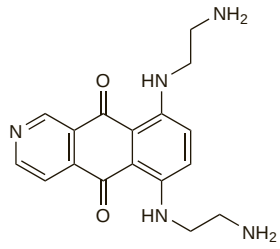
1. Khorsand M, *et al.* Phase II trial of oral piritrexim in advanced, previously treated transitional cell cancer of bladder. *Invest New Drugs* 1997; **15:** 157–63.
2. Roth BJ, *et al.* Piritrexim in advanced, refractory carcinoma of the urothelium (E3896): a phase II trial of the Eastern Cooperative Oncology Group. *Invest New Drugs* 2002; **20:** 425–9.
3. Huie M, *et al.* Phase I study of piritrexim and gemcitabine in patients with advanced solid tumors. *Am J Clin Oncol* 2005; **28:** 613–17.
4. Lassiter LK, *et al.* Phase II open-label study of oral piritrexim in patients with advanced carcinoma of the urothelium who have experienced failure with standard chemotherapy. *Clin Genitourin Cancer* 2008; **6:** 31–5.

Pixantrone *(BAN, USAN, rINN)*

BBR-2778; Pixantrona; Pixantronum. 6,9-Bis[(2-aminoethyl)amino]benzo[*g*]isoquinoline-5,10-dione.

Пиксантрон

$C_{17}H_{19}N_5O_2$ = 325.4.
CAS — 144510-96-3 (pixantrone); 144675-97-8 (pixantrone maleate);.



Profile

Pixantrone is an anthracycline antineoplastic that is under investigation for the treatment of non-Hodgkin's lymphoma.

◊ References.

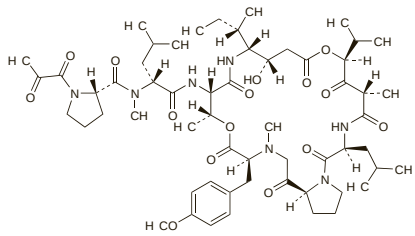
1. Borchmann P, Schnell R. The role of pixantrone in the treatment of non-Hodgkin's lymphoma. *Expert Opin Invest Drugs* 2005; **14:** 1055–61.

Plitidepsin *(BAN, rINN)*

Aplidine; Dehydrodidemnin B; Plitidepsina; Plitidepsine; Plitidepsinum. 3,6-Anhydro(*N*-{(2*S*,4*S*)-4-[(3*S*,4*R*,5*S*)-3-hydroxy-4-{[*N*-(2-oxopropanoyl)-L-prolyl-*N*-methyl-D-leucyl-L-threonyl]amino}-5-methylheptanoyloxy]-2,5-dimethyl-3-oxohexanoyl}-L-leucyl-L-prolyl-*N*,*O*-dimethyl-L-tyrosine).

Плитидепсин

$C_{57}H_{87}N_7O_{15}$ = 1110.3.
CAS — 137219-37-5.



Profile

Plitidepsin is an antineoplastic isolated from the marine tunicate *Aplidium albicans*. It is under investigation in the treatment of acute lymphoblastic leukaemia, multiple myeloma, and solid tumours.

◊ References.

1. Faivre S, *et al.* Phase I and pharmacokinetic study of aplidine, a new marine cyclodepsipeptide in patients with advanced malignancies. *J Clin Oncol* 2005; **23:** 7871–80.
2. Maroun JA, *et al.* Phase I study of Aplidine in a daily×5 one-hour infusion every 3 weeks in patients with solid tumors refractory to standard therapy. A National Cancer Institute of Canada Clinical Trials Group study: NCIC CTG IND 115. *Ann Oncol* 2006; **17:** 1371–8.
3. Izquierdo MA, *et al.* Phase I clinical and pharmacokinetic study of plitidepsin as a 1-hour weekly intravenous infusion in patients with advanced solid tumors. *Clin Cancer Res* 2008; **14:** 3105–12.
4. Peschel C, *et al.* Phase II study of plitidepsin in pretreated patients with locally advanced or metastatic non-small cell lung cancer. *Lung Cancer* 2008; **60:** 374–80.

Porfimer Sodium *(BAN, USAN, rINN)*

CL-184116; Dihaematoporphyrin Ether; Porfimeerinatrium; Porfimère Sodique; Porfimernatrium; Porfímero sódico; Porfimerum Natricum.

Порфимер Натрий
CAS — 87806-31-3.
ATC — L01XD01.
ATC Vet — QL01XD01.

Adverse Effects and Precautions

Photosensitivity occurs in all patients treated with porfimer sodium. This effect is likely to be prolonged, and patients should avoid sunlight or bright indoor light for at least 30 days. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Other reported adverse effects include local inflammation, chest pain, respiratory insufficiency or distress (including dyspnoea), abdominal pain, dysphagia, constipation, nausea and vomiting, fever, tachycardia and atrial fibrillation, pleural effusion, mucositis, and anaemia due to tumour bleeding. Pneumonia and bronchitis may occur. Anxiety and insomnia have also been reported. Photodynamic therapy with porfimer sodium is contra-indicated in patients with severe hepatic impairment, oesophageal fistulae, erosion of major blood vessels, or severe acute respiratory distress. Sufficient time should be allowed between photodynamic therapy and radiotherapy to allow inflammatory reactions from either treatment to subside.

Porphyria. The use of porfimer sodium is contra-indicated in patients with porphyria.

Interactions

Use of porfimer sodium with other drugs causing photosensitivity should be avoided as the reaction may be increased.

Pharmacokinetics

Porfimer sodium is distributed and eliminated slowly after intravenous injection, with plasma elimination half-life reported to be between 11 and 28 days. *In vitro* studies indicate that plasma protein binding is about 90%. Excretion occurs primarily via the faeces.

Uses and Administration

Porfimer sodium is a haematoporphyrin derivative that reportedly accumulates in malignant tissue on injection. It is then activated by laser light to release oxygen radicals within malignant cells, producing cytotoxicity. Porfimer sodium is used as a photosensitiser in the photodynamic therapy of non-small cell lung cancer (p.668), oesophageal cancer (p.664), and superficial bladder cancer (p.659). It is also used for the treatment of dysplasia associated with Barrett's oesophagus (see Gastro-oesophageal Reflux Disease, p.1696), and has been investigated in various other neoplasms, including tumours of the gastrointestinal tract and cervix.

Porfimer sodium should be reconstituted with glucose 5% to a final concentration of 2.5 mg/mL. It is given by slow intravenous injection at a dose of 2 mg/kg. This is followed, 40 to 50 hours later, by activation using a laser tuned to a wavelength of 630 nanometres and delivered to the area of the tumour using a fibre optic guide. Residual tumour may subsequently be debrided surgically. A second laser treatment may be given 96 to 120 hours after the original injection. A maximum of 3 courses of photodynamic therapy may be used, with each injection separated by a minimum of 30 days for oesophageal and endobronchial tumours, and a minimum of 90 days for dysplasia in Barrett's oesophagus. However, in the treatment of superficial bladder cancer, only one dose of drug and light is given due to an increased risk of bladder contracture, and no surgical debridement is performed.

Photodynamic therapy. Photodynamic therapy probably has the greatest potential of the various forms of light-activated treatment.[1] Photosensitising drugs are given intravenously, orally, or topically, and are selectively retained by tumour cells. When ex-

posed to the correct wavelength of light the drug produces toxic oxygen radicals that destroy cell membranes and thereby kill the tumour cells. Vascular damage and immune-mediated injury may also occur.[2,3] Tumour cells must have an adequate supply of oxygen to be sensitive to photodynamic therapy,[2] and as light penetration is usually limited, early or superficial malignant lesions respond best to therapy.[1,2] Photodynamic therapy has been tried in skin, gastrointestinal, head and neck, bladder, gynaecological, pancreatic, pulmonary, and various intraperitoneal malignancies[2-11] It is also used for the treatment of Barrett's oesophagus[11-13] and for the treatment of age-related macular degeneration (p.785); it has been tried for other ocular disorders.[14] There is also an interesting report of cytotoxicity against leukaemic cells *in vitro* when exposure to porfimer sodium was combined with ultrasound.[5]

The main adverse effect of photosensitisers such as porfimer is photosensitivity lasting 4 to 8 weeks; patients should be advised to avoid sunlight during this period and therapy is best delayed until the darker winter months if possible.[1] Newer photosensitisers are being developed to show increased tissue penetration and less prolonged photosensitivity.[2] The natural haem precursor 5-aminolevulinic acid (p.679) has the advantage that photosensitivity lasts only a few hours.

1. Bown SG. New techniques in laser therapy. *BMJ* 1998; **316:** 754–7.
2. Hsi RA, *et al.* Photodynamic therapy in the treatment of cancer: current state of the art. *Drugs* 1999; **57:** 725–34.
3. Ost D, *et al.* Photodynamic therapy in lung cancer. *Oncology* 2000; **14:** 379–86.
4. Wilson JHP, *et al.* Photodynamic therapy for gastrointestinal tumors. *Scand J Gastroenterol* 1991; **26** (suppl 188): 20–5.
5. Tachibana K, *et al.* Eliminating adult T-cell leukaemia cells with ultrasound. *Lancet* 1997; **349:** 325.
6. Walther MM. The role of photodynamic therapy in the treatment of recurrent superficial bladder cancer. *Urol Clin North Am* 2000; **27:** 163–70.
7. Metz JM, Friedberg JS. Endobronchial photodynamic therapy for the treatment of lung cancer. *Chest Surg Clin North Am* 2001; **11:** 829–39.
8. Biel MA. Photodynamic therapy in head and neck cancer. *Curr Oncol Rep* 2002; **4:** 87–96.
9. Moghissi K. Role of bronchoscopic photodynamic therapy in lung cancer management. *Curr Opin Pulm Med* 2004; **10:** 256–60.
10. Bown SG, *et al.* Photodynamic therapy for cancer of the pancreas. *Gut* 2002; **50:** 549–57.
11. Brown SB, *et al.* The present and future role of photodynamic therapy in cancer treatment. *Lancet Oncol* 2004; **5:** 497–508.
12. Wolfsen HC, *et al.* Photodynamic therapy for dysplastic Barrett esophagus and early esophageal adenocarcinoma. *Mayo Clin Proc* 2002; **77:** 1176–81.
13. Kelty CJ, *et al.* Photodynamic therapy for Barrett's esophagus: a review. *Dis Esophagus* 2002; **15:** 137–44.
14. Sivaprasad S, Hykin P. The role of photodynamic therapy in ophthalmology. *Br J Hosp Med* 2006; **67:** 647–50.

Preparations

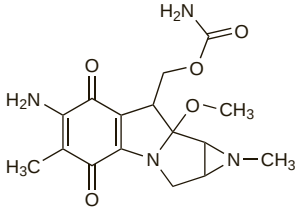
Proprietary Preparations (details are given in Part 3)
Canad.: Photofrin; ***Cz.:*** Photobarr; ***Fr.:*** Photobarr; ***Ger.:*** Photofrin; ***Gr.:*** Photofrin; ***Hung.:*** Photofrin; ***Israel:*** Photofrin; ***Neth.:*** Photobarr; Photofrin; ***Port.:*** Photobarr; Photofrin; ***USA:*** Photofrin.

Porfiromycin *(BAN, USAN, rINN)*

Methyl Mitomycin; NSC-56410; Porfiromicina; Porfiromycine; Porfiromycinum; U-14743. 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-1,5-dimethylazirino[2′,3′:3,4]-pyrrolo[1,2-*a*]-indole-4,7-dione carbamate ester.

Порфиромицин

$C_{16}H_{20}N_4O_5$ = 348.4.
CAS — 801-52-5.



Profile
Porfiromycin is an antibiotic antineoplastic structurally related to mitomycin (p.752). It is being studied as a radiosensitiser in the management of malignant neoplasms of the head and neck.

◊ References.

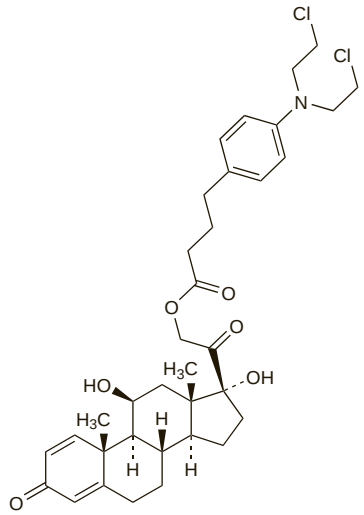
1. Haffty BG, *et al.* Bioreductive alkylating agent porfiromycin in combination with radiation therapy for the management of squamous cell carcinoma of the head and neck. *Radiat Oncol Invest* 1997; **5:** 235–45.
2. Haffty BG, *et al.* Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. *Int J Radiat Oncol Biol Phys* 2005; **61:** 119–28.

Prednimustine *(USAN, rINN)*

Leo-1031; NSC-134087; Prednimustiini; Prednimustin; Prednimustina; Prednimustinum. 11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(4-{4-[bis(2-chloroethyl)amino]phenyl}butyrate).

Преднимустин

$C_{35}H_{45}Cl_2NO_6$ = 646.6.
CAS — 29069-24-7.
ATC — L01AA08.
ATC Vet — QL01AA08.



Profile
Prednimustine is the prednisolone ester of chlorambucil, (p.696) and has been given orally in the treatment of various malignant diseases.

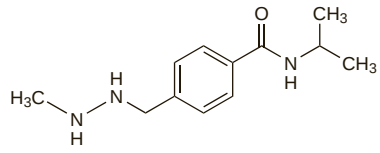
Procarbazine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de procarbazina; Ibenzmethyzin Hydrochloride; NSC-77213; Procarbazine, Chlorhydrate de; Procarbazini Hydrochloridum; Ro-4-6467/1. *N*-Isopropyl-α-(2-methylhydrazino)-*p*-toluamide hydrochloride.

Прокарбазина Гидрохлорид

$C_{12}H_{19}N_3O$,HCl = 257.8.
CAS — 671-16-9 (procarbazine); 366-70-1 (procarbazine hydrochloride).
ATC — L01XB01.
ATC Vet — QL01XB01.



(procarbazine)

Pharmacopoeias. In *Chin.*, *Int.*, *Jpn*, and *US*.
USP 31 (Procarbazine Hydrochloride). Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

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

The most common adverse effects associated with procarbazine are gastrointestinal disturbances such as anorexia, nausea and vomiting (although patients may soon become tolerant), and bone-marrow depression. Leucopenia and thrombocytopenia may be delayed with a nadir at about 4 weeks after a dose, and recovery usually within 6 weeks. Anaemia, haemolysis, and bleeding tendencies have been reported.

Neurotoxicity is also common, with central effects such as somnolence, depression, nervousness or confusion, headache, hallucinations, and dizziness, and peripheral neuropathies including paraesthesias and decreased reflexes. Lethargy, ataxia, and sleep disorders have also occurred, and tremors, convulsions, and coma have been reported.

Other adverse effects reported include fever and myalgia, pulmonary fibrosis or pneumonitis, haematuria, urinary frequency, skin reactions including dermatitis, pruritus, and hyperpigmentation, tachycardia, orthostatic hypotension, ocular defects, infertility, and hepatic impairment.

Procarbazine is a carcinogen, mutagen, and teratogen.

Procarbazine should be used with caution in patients with hepatic or renal impairment, and is contra-indicated if impairment is severe. The haematological status of the patient should be determined at least every 3 or 4 days and hepatic and renal function determined weekly. Care is also advisable in patients with phaeochromocytoma, epilepsy, or cardiovascular or cerebrovascular disease. Treatment should be interrupted if allergic skin reactions occur.

Handling and disposal. *Urine* produced for up to 48 hours after a dose of procarbazine should be handled wearing protective clothing.[1]

1. Harris J, Dodds LJ. Handling waste from patients receiving cytotoxic drugs. *Pharm J* 1985; **235:** 289–91.

Interactions

For a general outline of antineoplastic drug interactions, see p.642. Procarbazine is a weak MAOI and the possibility of reactions with other drugs and food, although very rare, must be borne in mind—for details of MAOI reactions see p.417. Procarbazine may enhance the sedative effects of other CNS depressants. A disulfiram-like reaction has been reported with alcohol and the effects of antihypertensive agents may be enhanced.

Antiepileptics. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine, possibly through a reactive intermediate generated by induction of the cytochrome P450 isoenzyme CYP3A subfamily.[1] Non-enzyme-inducing antiepileptics might be more appropriate in patients with brain tumours in whom procarbazine therapy is anticipated.

1. Lehmann DF, *et al.* Anticonvulsant usage is associated with an increased risk of procarbazine hypersensitivity reactions in patients with brain tumors. *Clin Pharmacol Ther* 1997; **62:** 225–9.

Pharmacokinetics

Procarbazine is readily absorbed from the gastrointestinal tract. It crosses the blood-brain barrier and diffuses into the CSF. A plasma half-life of about 10 minutes has been reported. Procarbazine is rapidly metabolised (mainly in liver and kidneys) and only about 5% is excreted unchanged in the urine. The remainder is oxidised to *N*-isopropylterephthalamic acid and excreted in the urine, up to about 70% of a dose being excreted in 24 hours. Some of the drug is excreted as carbon dioxide and methane via the lungs. During oxidative breakdown in the body hydrogen peroxide is formed which may account for some of the drug's actions.

Uses and Administration

Procarbazine hydrochloride is a methylhydrazine derivative whose antineoplastic effect, although not fully understood, may resemble that of the alkylating agents; it appears to inhibit protein and nucleic acid synthesis and suppress mitosis. It does not exhibit cross-resistance with other cytotoxic drugs.

Its main use is the treatment of Hodgkin's disease (p.655) when it is usually given with other drugs, as in the MOPP regimen (with chlormethine, vincristine, and prednisone) and its variants. Procarbazine has also been used in the treatment of other lymphomas (p.656) and in some other malignant neoplasms including tumours of the brain (p.660).

Doses of procarbazine hydrochloride are calculated in terms of procarbazine; procarbazine hydrochloride 116 mg is equivalent to about 100 mg of procarbazine. In many of the combination regimens it has been given orally to adults and children in doses of the equivalent