Profile
Tumour necrosis factor is a cytokine of which 2 forms have been identified with similar biological properties: TNFα or cachectin, which is produced mainly by macrophages, and TNFβ or lymphotoxin, which is produced by lymphocytes. Various recombinant forms of TNFα, both human and mouse, are available: the names sonermin and sertenef have been used for such products.

The antitumour effects of tumour necrosis factor *in vitro* and in *animals* have prompted investigation of recombinant TNFα in the treatment of cancer either alone or with other cytokines such as interleukin-2 or the interferons. Tasonermin is a recombinant TNFα used with melphalan (p.742) for soft tissue sarcomas. It is given by mild hyperthermic isolated limb perfusion at a total dose of 3 mg for an upper limb and 4 mg for a lower limb.

Leakage of tasonermin into the systemic circulation should not exceed 10%, as severe toxicity may occur. Local adverse effects include skin reactions, oedema, and pain; less commonly, vascular thrombosis, oncycholysis, or severe tissue damage have occurred. Systemic effects include fever, chills, nausea and vomiting, arrhythmias, hepatotoxicity, and infections. Shock or hypotension, neurological disorders, thrombocytopenia, leucopenia, acute renal failure, and hypersensitivity reactions have all been reported.

◊ References.

1. van Der Veen AH, *et al.* An overview on the use of TNF-alpha: our experience with regional administration and developments towards new opportunities for systemic application. *Anticancer Res* 2000; **20:** 3467–74.
2. Libutti SK, *et al.* Technique and results of hyperthermic isolated hepatic perfusion with tumor necrosis factor and melphalan for the treatment of unresectable hepatic malignancies. *J Am Coll Surg* 2000; **191:** 519–30.
3. Lejeune FJ, *et al.* Limb salvage by neoadjuvant isolated perfusion with TNFα and melphalan for non-resectable soft tissue sarcoma of the extremities. *Eur J Surg Oncol* 2000; **26:** 669–78.
4. Eggermont AM, ten Hagen TL. Tumor necrosis factor-based isolated limb perfusion for soft tissue sarcoma and melanoma: ten years of successful antivascular therapy. *Curr Oncol Rep* 2003; **5:** 79–80.
5. ten Hagen TL, Eggermont AM. Solid tumor therapy: manipulation of the vasculature with TNF. *Technol Cancer Res Treat* 2003; **2:** 195–203.
6. Noorda EM, *et al.* Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. *Cancer* 2003; **98:** 1483–90.
7. Corti A. Strategies for improving the anti-neoplastic activity of TNF by tumor targeting. *Methods Mol Med* 2004; **98:** 247–64.

Units. The first International Standard for human tumour necrosis factor α, which contained 40 000 international units/ampoule, was considered unsuitable for the assay of recombinant *mouse* tumour necrosis factor α, for human tumour necrosis factor β, or for preparations of tumour necrosis factor α of modified structure.[1] The second International Standard for human tumour necrosis factor α has been established as having a potency of 46 500 international units/ampoule.[2]

The first Reference Reagent for tumour necrosis factor β had an assigned potency of 150 000 units/ampoule.[3]

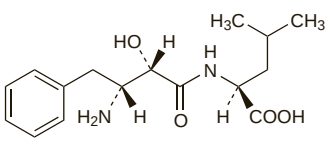
1. WHO. WHO expert committee on biological standardization: forty-second report. *WHO Tech Rep Ser 822* 1992. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf (accessed 01/08/08)
2. WHO. WHO expert committee on biological standardization: fifty-fourth report. *WHO Tech Rep Ser 927* 2005. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_927_eng.pdf (accessed 01/08/08)
3. WHO. WHO expert committee on biological standardization: forty-seventh report. *WHO Tech Rep Ser 878* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_878.pdf (accessed 01/08/08)

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Beromun†; ***Cz.:*** Beromun; ***Fr.:*** Beromun†; ***Gr.:*** Beromun; ***Ital.:*** Beromun; ***Neth.:*** Beromun; ***Port.:*** Beromun; ***Spain:*** Beromun; ***Swed.:*** Beromun.

Ubenimex *(rINN)*
NK-421; NSC-265489; Ubénimex; Ubenimexum. (–)-*N*-[(2*S*,3*R*)-3-Amino-2-hydroxy-4-phenylbutyryl]-L-leucine.

Убенимекс

$C_{16}H_{24}N_2O_4$ = 308.4.
CAS — 58970-76-6.



Pharmacopoeias. In *Chin.*

Profile
Ubenimex is a peptide derived from *Streptomyces olivoreticuli*. It is reported to have antineoplastic and immunostimulant properties. It has been used in the adjuvant treatment of acute myeloid leukaemia and is under investigation for the treatment of lung cancer. Adverse effects include gastrointestinal and hepatic function disturbances, skin rashes, headache, and paraesthesias.

◊ References.

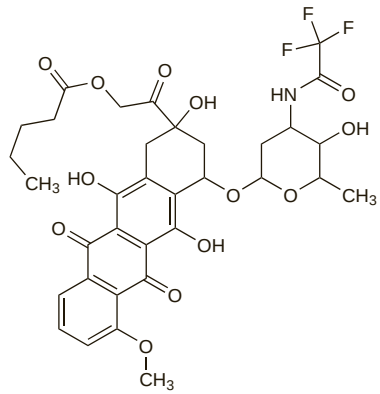
1. Ichinose Y, *et al.* Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *J Natl Cancer Inst* 2003; **95:** 605–10.

Preparations
Proprietary Preparations (details are given in Part 3)
Cz.: Bestatin†; ***Jpn:*** Bestatin.

Valrubicin *(USAN, rINN)*
AD-32; NSC-246131; *N*-Trifluoroacetyladriamycin-14-valerate; *N*-Trifluoroacetyldoxorubicin-14-valerate; Valrubicina; Valrubicine; Valrubicinum. (8*S*,10*S*)-8-Glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-{[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy}-5,12-naphthacenedione 8^2-valerate.

Вальрубицин

$C_{34}H_{36}F_3NO_{13}$ = 723.6.
CAS — 56124-62-0.
ATC — L01DB09.
ATC Vet — QL01DB09.



Pharmacopoeias. In *US.*
USP 31 (Valrubicin). An orange to orange-red crystalline powder. Very slightly soluble in water, in hexane, and in petroleum spirit; soluble in dehydrated alcohol, in acetone, in dichloromethane, and in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions
Increased urinary frequency and urgency, dysuria, bladder spasm and pain may follow intravesical use of valrubicin due to local irritation of the bladder, and usually resolve within 1 to 7 days of treatment. Gross haematuria has occurred rarely but should be distinguished from drug-induced red coloration of the urine. Abdominal pain and nausea may occur.

Myelosuppression similar to that seen with other anthracyclines (see Adverse Effects of Doxorubicin, p.712) is possible if significant systemic exposure occurs. Therefore valrubicin should not be given to patients with a perforated bladder or compromised bladder mucosa.

Because of the risk of metastasis, cystectomy should be reconsidered for patients with carcinoma *in situ* who do not respond completely to valrubicin treatment after 3 months.

Pharmacokinetics
On intravesical use valrubicin penetrates the bladder wall but systemic absorption is low in patients who have an intact bladder mucosa. The drug is almost entirely excreted by voiding after the installation period.

Uses and Administration
Valrubicin is a semisynthetic analogue of the anthracycline doxorubicin (p.712). It is used for carcinoma *in situ* of the bladder (p.659) refractory to BCG vaccine, when surgery is contra-indicated, although only about 20% of such patients exhibit a complete response. A dose of 800 mg has been given intravesically once a week for 6 weeks, as 75 mL of a solution diluted with sodium chloride 0.9%. The solution should be retained for 2 hours if possible before voiding.

◊ References.

1. Steinberg G, *et al.* Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol (Baltimore)* 2000; **163:** 761–7.
2. Kuznetsov DD, *et al.* Intravesical valrubicin in the treatment of carcinoma in situ of the bladder. *Expert Opin Pharmacother* 2001; **2:** 1009–13.

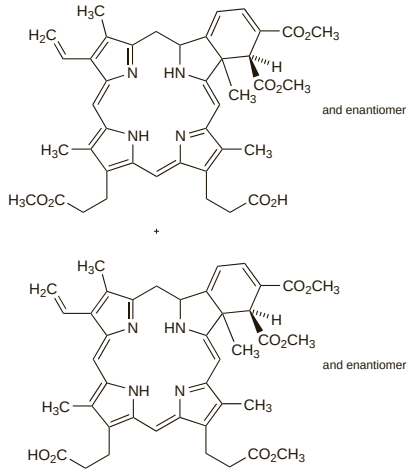
Preparations
USP 31: Valrubicin Intravesical Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Valtaxin; ***Israel:*** Valstar; ***USA:*** Valstar†.

Verteporfin *(BAN, USAN, rINN)*
Benzoporphyrin Derivative; BPD; CL-318952; Verteporfiini; Verteporfina; Vertéporfine; Verteporfinum. *trans*-18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoic acid monomethyl ester.

Вертепорфин

$C_{41}H_{42}N_4O_8$ = 718.8.
CAS — 129497-78-5.
ATC — S01LA01.
ATC Vet — QS01LA01.



Pharmacopoeias. In *US.*
USP 31 (Verteporfin). Store at a temperature between –25° and –10° in airtight containers.

Adverse Effects and Precautions
Photosensitivity will occur in all patients treated with verteporfin and patients should not be exposed to direct sunlight for 2 to 5 days after treatment. However, exposure to ambient indoor light is encouraged, as it allows gradual inactivation of any remaining drug. Headaches, injection site reactions, and visual disturbances occur frequently. Extravasation at the injection site may produce severe pain and inflammation and requires interruption of therapy. Patients who experience a severe decrease in vision should not be re-treated until their vision recovers. Other reported adverse effects include hypersensitivity, infusion-related pain (primarily presenting as back pain), chest pain, gastrointestinal disturbances, atrial fibrillation, hypertension, decreased hearing, and anaemia. Verteporfin should be used with care in patients with hepatic impairment and may be contra-indicated if impairment is severe.

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

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

Pharmacokinetics
After intravenous doses, elimination of verteporfin is bi-exponential, with a terminal plasma elimination half-life of about 5 to 6 hours. Protein binding is about 90%. It is metabolised in the liver. It is excreted in faeces via the bile, mostly as unchanged drug, with less than 1% of a dose recovered in the urine.

◊ References.

1. Houle J-M, Strong A. Clinical pharmacokinetics of verteporfin. *J Clin Pharmacol* 2002; **42:** 547–57.