of vascular injury was unrelated to cardiac dysfunction. Trastuzumab therapy was stopped permanently and her symptoms gradually resolved over the course of a year.[1]

1. Pansegrau GK, *et al.* Trastuzumab-associated peripheral vascular toxicity. *J Clin Oncol* 2007; **25:** 1438–40.

Pregnancy. A 28-year-old woman who had been given trastuzumab 6 mg/kg every 3 weeks was found to be pregnant after 5 months of therapy. Trastuzumab was stopped at about 20 weeks of gestation. Ultrasound study of the fetus at 23 weeks indicated no amniotic fluid. On observation, the anhydramnios slowly resolved. No further complications occurred and a healthy female infant was induced at 37+ weeks; amniotic fluid was clear at delivery.[1] Similarly, 2 cycles of trastuzumab and paclitaxel were given to a 38-year-old pregnant woman between 26 and 32 weeks of gestation: fetal abdominal circumference stopped increasing and the volume of amniotic fluid decreased to almost total anhydramnios. There was also evidence of fetal renal failure. Fetal lung maturation was induced and a caesarean section done at about 32 weeks of gestation. The infant showed signs of bacterial sepsis with hypotension, transient renal failure, and respiratory failure necessitating mechanical ventilation. After antibacterial therapy, blood pressure normalised, ventilation was ended, and diuresis was deemed adequate. He was discharged at age 6 weeks in healthy condition and development at 12 weeks of age was deemed to be normal.[2] In another report, a 30-year-old patient conceived 3 days after her second cycle of trastuzumab; no further therapy was given. Her pregnancy went successfully to term and a healthy female was born with no sequelae.[3] Low amniotic fluid volume was seen in another case of trastuzumab use during pregnancy; at 5 years of age, the child was reported to have normal growth and development.[4]

1. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol* 2005; **105:** 642–3.
2. Bader AA, *et al.* Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007; **8:** 79–81.
3. Waterston AM, Graham J. Effect of adjuvant trastuzumab on pregnancy. *J Clin Oncol* 2006; **24:** 321–2.
4. Pant S, *et al.* Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 2008; **26:** 1567–9.

Interactions

For reports of trastuzumab enhancing the effect of warfarin, see p.1429.

Pharmacokinetics

The half-life of trastuzumab varies considerably: it has been reported to be 1.7 days after a 10-mg dose, 12 days after a 500-mg dose, and 5.8 days after the recommended dose (4 mg/kg followed by 2 mg/kg weekly); 28.5 days has also been reported after the recommended dose. Detectable concentrations of the cell surface protein of the HER2 receptor (shed antigen) have been found in patients' serum; those patients with higher baseline values for shed antigen had lower serum trough concentrations of trastuzumab, although target trastuzumab concentrations were still achieved after weekly dosing, and no relationship to clinical response was observed.

Uses and Administration

Trastuzumab is a humanised monoclonal antibody directed against a cell surface protein produced by the human epidermal growth factor receptor 2 (HER2) gene. HER2 protein is overexpressed in about one-third of all breast cancers. Trastuzumab is used in the treatment of breast cancer (p.661) with such characteristics.

The recommended dose in **metastatic** breast cancer, alone, with an aromatase inhibitor, or followed by a taxane, is 4 mg/kg initially, by intravenous infusion in 250 mL of sodium chloride 0.9% over 90 minutes. This may be followed by 2 mg/kg over 30 minutes at weekly intervals.

Trastuzumab is also given in **early** breast cancer after surgery, chemotherapy, and radiotherapy. There are 2 recommended schedules, with trastuzumab given either weekly or every 3 weeks.

- The recommended dose for the 3-weekly schedule is 8 mg/kg initially, by intravenous infusion in 250 mL sodium chloride 0.9% over 90 minutes. This may be followed by 6 mg/kg at 3-weekly intervals. Treatment is continued for 1 year or until disease recurrence.

  If the patient misses a dose of trastuzumab by 1 week or less, then the usual dose of 6 mg/kg should be given as soon as possible, without waiting until the next planned cycle. Subsequent cycles are then given according to the previous schedule.

  If the dose is missed by more than 1 week, a re-loading dose of trastuzumab 8 mg/kg should be given, and subsequent maintenance doses of 6 mg/kg should then be given every 3 weeks thereafter.
- In the weekly schedule, trastuzumab is given with paclitaxel after 4 cycles of the AC regimen (doxorubicin and cyclophosphamide). It is given at an initial loading dose of 4 mg/kg followed by 2 mg/kg weekly thereafter for 1 year; paclitaxel is given either weekly or 3-weekly for a total of 12 weeks.

HER2 may also be overexpressed in other epithelial cancers, and trastuzumab is under investigation for use in non-small cell lung cancer, pancreatic, prostate, and ovarian malignancies.

◊ References.

1. Spigel DR, Burstein HJ. Trastuzumab regimens for HER2-over-expressing metastatic breast cancer. *Clin Breast Cancer* 2003; **4:** 329–37.
2. Ferrone M, Motl SE. Trastuzumab for the treatment of non-small-cell lung cancer. *Ann Pharmacother* 2003; **37:** 1904–8.
3. Langer CJ, *et al.* Trastuzumab in the treatment of advanced non—small-cell lung cancer: is there a role? Focus on Eastern Cooperative Oncology Group Study 2598. *J Clin Oncol* 2004; **22:** 1180–7.
4. Tripathy D, *et al.* Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. *J Clin Oncol* 2004; **22:** 1063–70.
5. Papazisis KT, *et al.* Safety and efficacy of the combination of trastuzumab with docetaxel for HER2-positive women with advanced breast cancer: a review of the existing clinical trials and results of the expanded access programme in the UK. *Int J Clin Pract* 2004; **58:** 581–6.
6. Jones RL, Smith IE. Efficacy and safety of trastuzumab. *Expert Opin Drug Saf* 2004; **3:** 317–27.
7. Piccart-Gebhart MJ, *et al.* HERA Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1659–72.
8. Romond EH, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.
9. Kabe KL, Kolesar JM. Role of trastuzumab in adjuvant therapy for locally invasive breast cancer. *Am J Health-Syst Pharm* 2006; **63:** 527–33.
10. Plosker GL, Keam SJ. Trastuzumab: a review of its use in the management of HER2-positive metastatic and early-stage breast cancer. *Drugs* 2006; **66:** 449–75.
11. Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007; **369:** 29–36.
12. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007; **357:** 39–51.
13. Orman JS, Perry CM. Trastuzumab: in HER2 and hormone receptor co-positive metastatic breast cancer. *Drugs* 2007; **67:** 2781–9.

Preparations

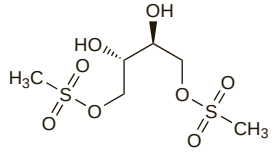
Proprietary Preparations (details are given in Part 3)
Arg.: Herceptin; ***Austral.:*** Herceptin; ***Belg.:*** Herceptin; ***Braz.:*** Herceptin; ***Canad.:*** Herceptin; ***Chile:*** Herceptin; ***Cz.:*** Herceptin; ***Denm.:*** Herceptin; ***Fin.:*** Herceptin; ***Fr.:*** Herceptin; ***Ger.:*** Herceptin; ***Gr.:*** Herceptin; ***Hong Kong:*** Herceptin; ***Hung.:*** Herceptin; ***Indon.:*** Herceptin; ***Irl.:*** Herceptin; ***Israel:*** Herceptin; ***Ital.:*** Herceptin; ***Jpn:*** Herceptin; ***Malaysia:*** Herceptin; ***Mex.:*** Herceptin; ***Neth.:*** Herceptin; ***Norw.:*** Herceptin; ***NZ:*** Herceptin; ***Philipp.:*** Herceptin; ***Pol.:*** Herceptin; ***Port.:*** Herceptin; ***Rus.:*** Herceptin (Герцептин); ***S.Afr.:*** Herceptin; ***Singapore:*** Herceptin; ***Spain:*** Herceptin; ***Swed.:*** Herceptin; ***Switz.:*** Herceptin; ***Thai.:*** Herceptin; ***Turk.:*** Herceptin; ***UK:*** Herceptin; ***USA:*** Herceptin; ***Venez.:*** Herceptin.

Treosulfan *(BAN, rINN)*

Dihydroxybusulphan; NSC-39069; Treosulfaani; Tréosulfan; Treosulfano; Treosulfanum. L-Threitol 1,4-dimethanesulphonate.

Треосульфан

$C_6H_{14}O_8S_2$ = 278.3.
CAS — 299-75-2.
ATC — L01AB02.
ATC Vet — QL01AB02.



Profile

Treosulfan is an antineoplastic agent related to busulfan (p.690), which is reported to act by alkylation after conversion *in vivo* to epoxide compounds. It is used palliatively or as an adjunct to surgery mainly in the treatment of ovarian cancer (p.670).

Treosulfan 1 g daily is licensed for oral use in 4 divided doses for 2 or 4 weeks followed by the same period without treatment. Alternatively 1.5 g daily in 3 divided doses may be given for 1 week, followed by 3 weeks without therapy. The cycle is then repeated, the dose being adjusted if necessary according to the effect on bone marrow. Doses of 3 to 8 g/m^2 may instead be given intravenously every 1 to 3 weeks. Doses larger than 3 g/m^2 should be given by infusion at a rate of 3 g/m^2 every 5 to 10 minutes. Doses up to 1.5 g/m^2 have been given intraperitoneally. Lower doses should be used if treatment with other antineoplastic drugs or radiotherapy is being given.

Regular blood counts should be made and treatment should be interrupted if the white cell or platelet counts fall below acceptable levels (see also Bone-marrow Depression, p.639). Because bone-marrow depression may be cumulative the interval between blood counts should be reduced after the second course of treatment with treosulfan.

Preparations

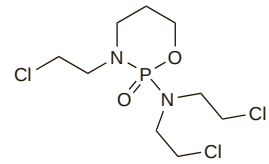
Proprietary Preparations (details are given in Part 3)
Ger.: Ovastat.

Trofosfamide *(rINN)*

A-4828; NSC-109723; Trilophosphamide; Trofosfamid; Trofosfamida; Trofosfamidi; Trofosfamidum; Trophosphamide; Z-4828. 3-(2-Chloroethyl)-2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,-2-oxazaphosphorine-2-oxide.

Трофосфамид

$C_9H_{18}Cl_3N_2O_2P$ = 323.6.
CAS — 22089-22-1.
ATC — L01AA07.
ATC Vet — QL01AA07.



Profile

Trofosfamide is a derivative of cyclophosphamide (p.702) and has the same general properties. It is used in the treatment of malignant disorders in usual initial oral doses of 300 to 400 mg daily. Doses of 50 to 150 mg daily have been given for maintenance therapy.

Uses. References[1-10] to the use of trofosfamide, including its investigational use with pioglitazone and rofecoxib as antiangiogenic therapy.[4,5,7]

1. Gunsilius E, *et al.* Palliative chemotherapy in pretreated patients with advanced cancer: oral trofosfamide is effective in ovarian carcinoma. *Cancer Invest* 2001; **19:** 808–11.
2. Reichardt P, *et al.* Oral trofosfamide: an active and well-tolerated maintenance therapy for adult patients with advanced bone and soft tissue sarcomas: results of a retrospective analysis. *Onkologie* 2002; **25:** 541–6.
3. Andersson PO, *et al.* Trofosfamide as salvage therapy for anaplastic large cell lymphoma relapsing after high-dose chemotherapy. *Leuk Lymphoma* 2002; **43:** 2351–3.
4. Vogt T, *et al.* Antiangiogenetic therapy with pioglitazone, rofecoxib, and metronomic trofosfamide in patients with advanced malignant vascular tumors. *Cancer* 2003; **98:** 2251–6.
5. Reichle A, *et al.* Pioglitazone and rofecoxib combined with angiostatically scheduled trofosfamide in the treatment of far-advanced melanoma and soft tissue sarcoma. *Cancer* 2004; **101:** 2247–56.
6. Latz D, *et al.* Trofosfamide in the palliative treatment of cancer: a review of the literature. *Onkologie* 2004; **27:** 572–6.
7. Coras B, *et al.* Antiangiogenic therapy with pioglitazone, rofecoxib, and trofosfamide in a patient with endemic kaposi sarcoma. *Arch Dermatol* 2004; **140:** 1504–7.
8. Jahnke K, *et al.* Pharmacokinetics and efficacy of ifosfamide or trofosfamide in patients with intraocular lymphoma. *Ann Oncol* 2005; **16:** 1974–8.
9. Salminen EK, *et al.* Palliative chemotherapy with trofosfamide in advanced prostate cancer. *Anticancer Res* 2006; **26:** 539–42.
10. Görn M, *et al.* A pilot study of docetaxel and trofosfamide as second-line 'metronomic' chemotherapy in the treatment of metastatic non-small cell lung cancer (NSCLC). *Onkologie* 2008; **31:** 185–9.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Ixoten; ***Ger.:*** Ixoten; ***Spain:*** Genoxal Trofosfamida.

Tumour Necrosis Factor

Factor de necrosis tumoral; TNF.

Tasonermin *(BAN, rINN)*

Tasonermiini; Tasonermina; Tasonermine; Tasonerminum; TNFα-1a.

Тазонермин

$C_{778}H_{1225}N_{215}O_{231}S_2$ = 17350.5.
CAS — 94948-59-1.
ATC — L03AX11.
ATC Vet — QL03AX11.

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]

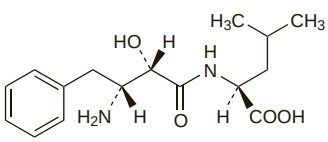
1. WHO. WHO expert committee on biological standardization: forty-second report. *WHO Tech Rep Ser 822* 1992. Available at: http://whqlibdoc.who.int/trs/WHO_TRS_822.pdf (accessed 01/08/08)
2. WHO. WHO expert committee on biological standardization: fifty-fourth report. *WHO Tech Rep Ser 927* 2005. Available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

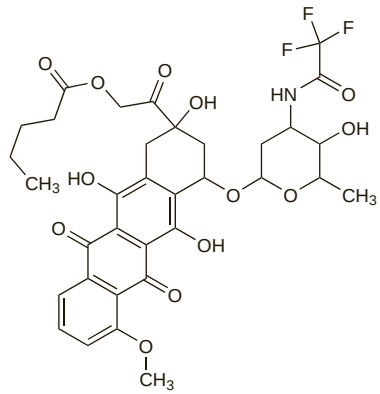
1. Ichinose Y, *et al.* Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *J Natl Cancer Inst* 2003; **95:** 605–10.

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.

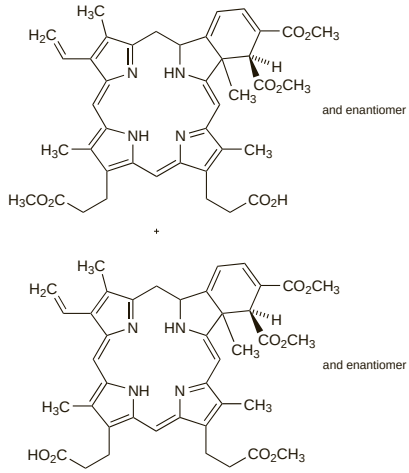
Preparations
USP 31: Valrubicin Intravesical Solution.

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.