feeding is contra-indicated due to lack of data, and should be avoided for the duration of treatment and for 3 months after therapy is stopped.

Interactions

Trabectedin is metabolised by the cytochrome P450 isoenzyme CYP3A4, and drugs that inhibit this enzyme (such as azole antifungals, macrolide antibacterials, or ritonavir) may increase blood concentrations of trabectedin. Equally, inducers of CYP3A4 (such as rifampicin, phenobarbital, and St John's wort) may decrease systemic exposure to trabectedin. Trabectedin is a substrate of P-glycoprotein, and use with P-glycoprotein inhibitors (such as ciclosporin and verapamil) may alter trabectedin pharmacokinetics, although the clinical significance of this interaction has not been established. Alcohol and other hepatotoxic drugs should be avoided during trabectedin treatment due to possible potentiation of hepatotoxicity. Use with live attenuated vaccines is not recommended, and use with yellow fever vaccine is specifically contra-indicated. For the effect of trabectedin on phenytoin, see p.499.

Pharmacokinetics

Trabectedin is extensively distributed in the tissues. Plasma protein binding is about 94 to 98%. It is metabolised in the liver, mainly by cytochrome P450 isoenzyme CYP3A4. The terminal half-life is about 180 hours. Trabectedin is excreted mainly in the faeces, with a small amount in the urine, of which less than 1% is unchanged drug.

◊ References.

1. Beumer JH, *et al.* Metabolism of trabectedin (ET-743, Yondelis) in patients with advanced cancer. *Cancer Chemother Pharmacol* 2007; **59:** 825–37.
2. Perez-Ruixo JJ, *et al.* Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet* 2007; **46:** 867–84.

Uses and Administration

Trabectedin is a novel DNA-binding agent derived from the marine tunicate, *Ecteinascidia turbinata*. It is used for the treatment of advanced soft-tissue sarcomas, after failure of anthracyclines or ifosfamide, or in patients for whom these drugs are unsuitable. The recommended dose is 1.5 mg/m^2, given as an intravenous infusion over 24 hours. The dose can be repeated at 3-week intervals as long as clinical benefit persists, provided haematological, hepatic, and renal function parameters are met. If these baseline criteria are not met, treatment must be delayed for up to 3 weeks, until the criteria are met. If haematological toxicity or hepatotoxicity occurs at any time between cycles, the dose for subsequent cycles must be reduced to 1.2 mg/m^2. Once a dose has been reduced, dose escalation for subsequent cycles is not recommended. If any toxicities recur in subsequent cycles, a further dose reduction to 1 mg/m^2 may be made; thereafter, if further toxicity occurs, treatment should be stopped. If trabectedin is given via a central venous line, which is the preferred method, the dose should be diluted in at least 500 mL of sodium chloride 0.9% or glucose 5%. If central access is unfeasible, and it is given peripherally, the dose should be diluted in at least 1 litre of diluent. Dexamethasone 20 mg is given intravenously 30 minutes before treatment with trabectedin, to reduce nausea and hepatotoxicity.

Trabectedin is also under investigation for the treatment of ovarian cancer.

◊ References.

1. van Kesteren C, *et al.* Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. *Anticancer Drugs* 2003; **14:** 487–502.
2. D'Incalci M, Jimeno J. Preclinical and clinical results with the natural marine product ET-743. *Expert Opin Invest Drugs* 2003; **12:** 1843–53.
3. Beumer JH, *et al.* Hepatotoxicity and metabolism of trabectedin: a literature review. *Pharmacol Res* 2005; **51:** 391–8.
4. Fayette J, *et al.* ET-743: a novel agent with activity in soft tissue sarcomas. *Oncologist* 2005; **10:** 827–32.
5. Schöffski P, *et al.* Trabectedin (ET-743): evaluation of its use in advanced soft-tissue sarcoma. *Future Oncol* 2007; **3:** 381–92.
6. Carter NJ, Keam SJ. Trabectedin : a review of its use in the management of soft tissue sarcoma and ovarian cancer. *Drugs* 2007; **67:** 2257–76.
7. Schöffski P, *et al.* Clinical impact of trabectedin (ecteinascidin-743) in advanced/metastatic soft tissue sarcoma. *Expert Opin Pharmacother* 2008; **9:** 1609–18.

Administration in hepatic impairment. Licensed product information states that there are no studies of trabectedin in hepatic impairment and data are unavailable to recommend doses in these patients. However, since systemic exposure is likely to be increased in these patients, thus increasing the risk of hepatotoxicity, caution is advised and dose adjustments may be needed. Trabectedin should not be given to patients with hyperbilirubinaemia.

Administration in renal impairment. Licensed product information for trabectedin states that no dose adjustments are needed in patients with mild or moderate renal impairment, but that trabectedin should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) as no data are available for this population.

Preparations

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

Trastuzumab *(BAN, rINN)*

HER-2 Monoclonal Antibody; rhuMAb HER2; Trastutsumabi; Trastuzumabum. Immunoglobulin G1 (human-mouse monoclonal rhuMab HER2 γ_1-chain anti-human p185$^{c\text{-}erbB2}$ receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer.

Трастузумаб
CAS — 180288-69-1.
ATC — L01XC03.
ATC Vet — QL01XC03.

Adverse Effects, Treatment, and Precautions

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

Trastuzumab has been associated with fatal hypersensitivity reactions, infusion reactions characteristic of a cytokine release syndrome, and pulmonary events including acute respiratory distress syndrome. These usually occur after the first dose of trastuzumab and are more common in patients with reduced lung function. Use of trastuzumab is contra-indicated in patients with severe dyspnoea at rest. Cardiac dysfunction and congestive heart failure may also occur and left ventricular function should be monitored before and during therapy. The risk of cardiotoxicity is increased if trastuzumab is given with anthracyclines or cyclophosphamide (see below).

There is an increase in the incidence of leucopenia, thrombocytopenia, anaemia, and febrile neutropenia when trastuzumab is given with chemotherapy, but it infrequently causes myelosuppression when used alone. Diarrhoea occurs in about 25% of patients given trastuzumab as monotherapy; the incidence increases with combination therapy. Other gastrointestinal disturbances are common, as are chills, fever, headache, arthralgia, myalgia, and rashes. Asthenia, chest pain, and renal or liver disorders have also been reported.

Effects on the heart. Cardiac events related to the use of trastuzumab include asymptomatic decreases in left ventricular ejection fraction, tachycardia, palpitations, dyspnoea, and chest pain. Congestive heart failure may develop.[1]

In a pivotal comparative trial,[2] an increased incidence of cardiac adverse events prompted a retrospective analysis. This independent review identified cardiac dysfunction in 27% of patients receiving trastuzumab, an anthracycline, and cyclophosphamide, compared with only 8% receiving an anthracycline and cyclophosphamide. In patients given trastuzumab and paclitaxel, 13% developed cardiac dysfunction compared with 1% of patients given paclitaxel alone, although all these patients had previously received an anthracycline. The incidence of severe dysfunction was highest in those patients receiving trastuzumab, an anthracycline, and cyclophosphamide.

Further analysis[3] of this and 6 other studies found that, in a total of 1219 patients, 10 heart-related deaths had been reported, and that 9 of these were patients who had received trastuzumab. However, the risk of developing cardiotoxicity was less when trastuzumab was given alone than when given with anthracyclines. Advanced age was found to be a significant risk factor, whereas giving trastuzumab and the anthracycline at different times appeared to decrease the rate of cardiotoxicity.

Licensed product information for trastuzumab warns that patients who have previously received anthracyclines may also be at increased risk of cardiotoxicity with trastuzumab treatment. Furthermore, because the half-life of trastuzumab is about 28.5 days, trastuzumab may persist in the circulation for up to 24 weeks, and patients given anthracyclines after stopping trastuzumab may still be at increased risk of cardiotoxicity. If anthracyclines are used, the patient's cardiac function should be carefully monitored. Patients with pre-existing cardiovascular disease should also be treated with caution.

However, the majority of patients who develop congestive heart failure improve with standard treatment, including the use of ACE inhibitors, beta blockers, cardiac glycosides and diuretics.[1,4,5] Cardiotoxicity may improve even in those patients who continue with trastuzumab therapy.[4,5] A small retrospective study found that cardiotoxicity appeared to be largely reversible once trastuzumab was stopped, and that therapy might even be restarted. Findings from myocardial biopsy suggested that, while the mechanism of cardiotoxicity with trastuzumab remained uncertain, it differed from that with anthracyclines.[6] A retrospective review[7] of 173 patients with metastatic breast cancer who were treated with trastuzumab-based therapy for at least 1 year found that 28% of patients experienced a cardiac event; 10.9% had grade 3 cardiotoxicity, including 1 cardiac-related death. However, cardiotoxicity, whether symptomatic or not, was generally reversible, with or without specific therapy, suggesting that maintenance or re-treatment with trastuzumab may be feasible in those patients for whom no alternative therapeutic options are available.

The pathogenesis of the cardiotoxicity associated with trastuzumab is under investigation. A small study[8] showed specific uptake of a pretreatment tracer dose of radiolabelled trastuzumab into the myocardium of patients who subsequently developed cardiac adverse events. The human epidermal growth factor receptor 2 (HER2) gene appears essential for normal cardiac development; studies in *animals* suggest that trastuzumab may interfere with HER2 signalling and function in cardiomyocytes, and that loss of HER2 increases sensitivity to anthracycline toxicity.[4,5]

Analysis of symptomatic heart failure with trastuzumab suggests a lower incidence than that previously reported with retrospective data; however, this may be due to over-reported events in pivotal trials and the more recent exclusion of patients at risk of cardiotoxicity.[4] More recent analysis from a large study of patients given adjuvant chemotherapy with or without trastuzumab found a cumulative incidence of cardiac events (defined as confirmed New York Heart Association class III or IV cardiac dysfunction, or cardiac death) with trastuzumab of 4.1% at 3 years. The difference in cumulative incidence was 3.3% when compared with the control group.[9] Some have commented[10] that follow-up was relatively short and that long-term data on cardiac risks with trastuzumab are lacking. Reviews[11,12] have concluded that trastuzumab-induced cardiotoxicity is not dose-related and is generally reversible once the drug is stopped. However, others[13] have challenged the concept that cardiotoxicity is reversible, and the need for longer-term follow-up data, especially with respect to asymptomatic left ventricular dysfunction, has been emphasised.[11,13]

1. Keefe DL. Trastuzumab-associated cardiotoxicity. *Cancer* 2002; **95:** 1592–1600.
2. Slamon DJ, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; **344:** 783–92.
3. Seidman A, *et al.* Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20:** 1215–21.
4. Suter TM, *et al.* Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004; **13:** 173–83.
5. Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004; **22:** 322–9.
6. Ewer MS, *et al.* Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005; **23:** 7820–6.
7. Guarneri V, *et al.* Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the M.D. Anderson Cancer Center experience. *J Clin Oncol* 2006; **24:** 4107–15.
8. Behr TM, *et al.* Trastuzumab and breast cancer. *N Engl J Med* 2001; **345:** 995–6.
9. Tan-Chiu E, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; **23:** 7811–19.
10. Levine MN. Trastuzumab cardiac side effects: only time will tell. *J Clin Oncol* 2005; **23:** 7775–6.
11. Sengupta PP, *et al.* Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc* 2008; **83:** 197–203.
12. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. *Drug Safety* 2008; **31:** 459–67.
13. Telli ML, *et al.* Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007; **25:** 3525–33.

Metastatic disease. There is some suggestion that patients treated with trastuzumab for metastatic breast cancer have a higher incidence of cerebral metastases. This may reflect increased survival of patients given trastuzumab, and the lack of CNS penetration by the drug,[1,2] or tumours overexpressing human epidermal growth receptor 2 (HER2) may be more likely to metastasise to the CNS.[2] A comparison[1] of trastuzumab-treated patients with a control group found that, although trastuzumab reduced the incidence of bone metastases, the development of brain metastases was similar in both groups. However, trastuzumab improved overall survival in all patients developing metastases, including those with brain metastases. A retrospective review[2] found an association between the development of cerebral metastases and both hormone-receptor negative status and the presence of visceral disease.

1. Lower EE, *et al.* Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival. *Clin Breast Cancer* 2003; **4:** 114–19.
2. Clayton AJ, *et al.* Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer* 2004; **91:** 639–43.

Peripheral vascular toxicity. A woman developed a painless prominence of the veins in her left arm and hand 3 days after receiving trastuzumab via a left hand vein. The veins were thickened and rope-like on palpation but there was no tenderness, oedema, or skin changes; there was no evidence of thrombus. She had previously received intravenous chemotherapy into left hand veins without sequelae. Biopsy suggested venous wall injury. Cardiac function was preserved, suggesting the mechanism

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

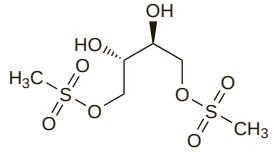
Proprietary Preparations (details are given in Part 3)
Arg.: Herceptin; ***Austral.:*** Herceptin; ***Belg.:*** Herceptin; ***Braz.:*** Herceptin; ***Canad.:*** Herceptin; ***Chile:*** Herceptin; ***Cz.:*** Herceptin; ***Denm.:*** Herceptin; ***Fin.:*** Herceptin; ***Fr.:*** Herceptin; ***Ger.:*** Herceptin; ***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

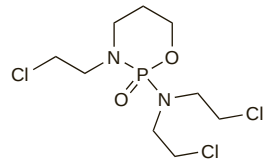
Proprietary Preparations (details are given in Part 3)
Ger.: Ovastat.

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.