of procarbazine 100 mg/m^2 for 10 to 14 days of each 4- or 6-week cycle. If used as a single agent in adults a dose equivalent to 50 mg of procarbazine daily, increased by 50 mg daily to 250 to 300 mg daily in divided doses has been suggested in the UK, while in the USA the recommended regimen is 2 to 4 mg/kg daily for the first week, subsequently increased to 4 to 6 mg/kg daily, doses being given to the nearest 50 mg. These doses are continued until maximum response is achieved or leucopenia, thrombocytopenia, or other signs of toxicity ensue. Maintenance doses are usually 50 to 150 mg daily, or 1 to 2 mg/kg, daily, until a cumulative dose of at least 6 g has been given. In children, initial daily doses of the equivalent of 50 mg/m^2 have been suggested in the USA (UK product information simply suggests a dose of 50 mg), increased to 100 mg/m^2 and then adjusted according to response.

Blood disorders, non-malignant. Chemotherapy with regimens including procarbazine has been used in a few patients with refractory idiopathic thrombocytopenic purpura (p.1505), and has produced prolonged remission although in most cases of the disease such aggressive therapy is difficult to justify.

Preparations

USP 31: Procarbazine Hydrochloride Capsules.

Proprietary Preparations (details are given in Part 3)
Austral.: Natulan; ***Canad.:*** Matulane; Natulan†; ***Fr.:*** Natulan; ***Ger.:*** Natulan; ***Gr.:*** Natulan; ***Hung.:*** Natulan†; ***Ital.:*** Natulan; ***Neth.:*** Natulan; ***NZ:*** Natulan†; ***Rus.:*** Natulan (Натулан); ***Spain:*** Natulan; ***USA:*** Matulane.

Raltitrexed *(BAN, USAN, rINN)*

D-1694; ICI-D1694; Raltitreksed; Raltitreksedi; Raltitrexedum; ZD-1694. *N*-{5-[3,4-Dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl(methyl)amino]-2-thenoyl}-L-glutamic acid.

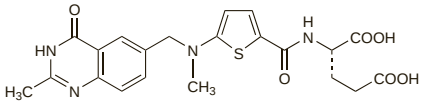
Ралтитрексед

$C_{21}H_{22}N_4O_6S$ = 458.5.

CAS — 112887-68-0.

ATC — L01BA03.

ATC Vet — QL01BA03.



Adverse Effects, Treatment, and Precautions

Raltitrexed produces bone marrow depression, usually mild to moderate, with leucopenia, anaemia, and, less frequently, thrombocytopenia. The nadir of the white cell count usually occurs 7 to 14 days after a dose, with recovery by the third week. Gastrointestinal toxicity is also common, with nausea and vomiting, diarrhoea, and anorexia: mucositis may occur. Reversible increases in liver enzyme values have occurred. Other adverse effects include weakness and malaise, fever, pain, headache, skin rashes, desquamation, arthralgia, muscle cramps, weight loss, dehydration, peripheral oedema, alopecia, increased sweating, taste disturbance, and conjunctivitis. The use of folinic acid 25 mg/m^2 every 6 hours intravenously has been suggested in licensed product information for patients who develop very severe toxicity.

Raltitrexed should be given with care to patients with hepatic impairment and should be avoided if impairment is severe. It should also be avoided in severe renal impairment and be given in reduced doses in moderate impairment. Care is also advisable in debilitated or elderly patients or in patients who have had radiotherapy.

Raltitrexed is teratogenic; pregnancy should be avoided while either partner is receiving the drug and for at least 6 months after treatment. It may impair male fertility.

Toxicity. A large multicentre study comparing raltitrexed with fluorouracil plus folinic acid was suspended in 1999 due to an excess of deaths in the raltitrexed arm.[1] This decision has led to some controversy,[1-3] as in 11 of the 17 deaths in patients taking raltitrexed there was evidence that the dose had not been correctly adjusted to take account of renal function. In addition, and further confusing the issue, the incidence of reported serious adverse effects was lower in raltitrexed-treated patients than in controls. A further study[4] reported an increased rate of raltitrexed-related deaths compared with fluorouracil-based regimens. Almost all of the 18 deaths were caused by gastrointestinal and haematological toxicity, and in 3 of these the dose of raltitrexed had not been adjusted for toxicity.

1. Anonymous. Drug-company decision to end cancer trial. *Lancet* 1999; **354:** 1045.
2. Ford HER, Cunningham D. Safety of raltitrexed. *Lancet* 1999; **354:** 1824–5.
3. Kerr D. Safety of raltitrexed. *Lancet* 1999; **354:** 1825.
4. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.

Interactions

Raltitrexed should not be given with folic or folinic acid, which may impair its cytotoxic action. (For the deliberate use of folinic acid to counteract the effects of raltitrexed in patients with severe toxicity, see above.)

Pharmacokinetics

After intravenous doses raltitrexed exhibits triphasic pharmacokinetics, with an initial rapid decline from peak plasma concentrations followed by a slow terminal elimination phase. Raltitrexed is actively transported into cells and metabolised to active polyglutamate forms. The remainder of a dose is excreted unchanged, about 50% of a dose appearing in the urine, and about 15% in the faeces. The terminal elimination half-life is about 8 days. Clearance is markedly reduced in renal impairment.

◊ References.

1. Clarke SJ, *et al.* Clinical and preclinical pharmacokinetics of raltitrexed. *Clin Pharmacokinet* 2000; **39:** 429–43.

Uses and Administration

Raltitrexed is a folate analogue that is a potent and specific inhibitor of the enzyme thymidylate synthase, which is involved in the synthesis of DNA. It has been used in the treatment of advanced colorectal cancer (p.665) and has also been tried in breast cancer (p.661) and other solid neoplasms.

The recommended initial dose of raltitrexed in patients with normal renal function is 3 mg/m^2 given by intravenous infusion over 15 minutes. Subsequent doses, which should be reduced by up to 50% depending on the severity of initial toxicity, may be given at intervals of 3 weeks provided toxicity has resolved.

A full blood count should be performed before each dose and treatment withheld if the white cell or platelet counts are below acceptable levels (see also Bone-marrow Depression, p.639). Hepatic and renal function should also be tested. It is essential that doses be adjusted in renal impairment (see below).

◊ References.

1. Gunasekara NS, Faulds D. Raltitrexed: a review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer. *Drugs* 1998; **55:** 423–35.
2. Cunningham D, *et al.* Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer: a review of phase II/III trials. *Eur J Cancer* 2002; **38:** 478–86.
3. Scheithauer W, *et al.* Randomized multicenter phase II trial of oxaliplatin plus irinotecan versus raltitrexed as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2002; **20:** 165–72.
4. Feliu J, *et al.* Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. *Eur J Cancer* 2002; **38:** 1204–11.
5. Comella P, *et al.* Oxaliplatin plus raltitrexed and leucovorin-modulated 5-fluorouracil i.v. bolus: a salvage regimen for colorectal cancer patients. *Br J Cancer* 2002; **86:** 1871–5.
6. Maughan TS, *et al.* Comparison of survival, palliation, and quality of life with three chemotherapy regimens in metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2002; **359:** 1555–63.
7. van Meerbeeck JP, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; **23:** 6881–9.
8. Ducreux M, *et al.* FFCD 9601 Collaborative Group. Randomised trial comparing three different schedules of infusional 5FU and raltitrexed alone as first-line therapy in metastatic colorectal cancer. Final results of the Fédération Francophone de Cancérologie Digestive (FFCD) 9601 trial. *Oncology* 2006; **70:** 222–30.
9. Wilson KS, *et al.* Adjuvant therapy with raltitrexed in patients with colorectal cancer intolerant of 5-fluorouracil: British Columbia Cancer Agency experience. *Cancer Invest* 2007; **25:** 711–14.
10. Hind D, *et al.* The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2008; **12:** 1–182.

Administration in renal impairment. It is essential that doses of raltitrexed be adjusted in renal impairment (creatinine clearance less than 65 mL/minute) as fatalities have been associated with the failure to make such adjustments (see Toxicity, under Adverse Effects, above). The dosage interval should be increased from 3 to 4 weeks and the dose adjusted on the basis of creatinine clearance (CC) as follows:

- CC of 55 to 65 mL/minute, 2.25 mg/m^2
- CC of 25 to 54 mL/minute, 1.5 mg/m^2 (in some countries, adjustment of the dose to a percentage of the full dose equivalent to the value of the CC in mL/minute is suggested in this group, e.g. reduction to 30% in those with a CC of 30 mL/minute, or 40% if CC is 40 mL/minute)
- CC less than 25 mL/minute, treatment contra-indicated

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Tomudex; ***Austral.:*** Tomudex; ***Austria:*** Tomudex; ***Belg.:*** Tomudex; ***Braz.:*** Tomudex; ***Canad.:*** Tomudex; ***Cz.:*** Tomudex; ***Fin.:*** Tomudex†; ***Fr.:*** Tomudex; ***Hong Kong:*** Tomudex†; ***Hung.:*** Tomudex; ***Irl.:*** Tomudex; ***Ital.:*** Tomudex; ***Mex.:*** Tomudex; ***Neth.:*** Tomudex; ***Norw.:*** Tomudex; ***Philipp.:*** Tomudex; ***Port.:*** Tomudex; ***Rus.:*** Tomudex (Томудекс); ***S.Afr.:*** Tomudex†; ***Singapore:*** Tomudex; ***Spain:*** Tomudex; ***Switz.:*** Tomudex; ***Turk.:*** Tomudex; ***UK:*** Tomudex; ***Venez.:*** Tomudex†.

Ranimustine *(rINN)*

MCNU; NSC-0270516; Ranimustina; Ranimustinum; Ranomustine. Methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside.

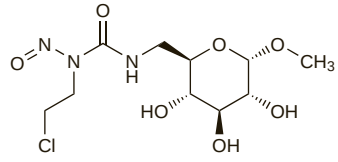
Ранимустин

$C_{10}H_{18}ClN_3O_7$ = 327.7.

CAS — 58994-96-0.

ATC — L01AD07.

ATC Vet — QL01AD07.



Profile

Ranimustine is a nitrosourea derivative with general properties similar to those of carmustine (p.694). It is used intravenously in the treatment of malignant neoplasms in usual doses of 50 to 90 mg/m^2 every 6 to 8 weeks according to haematological response.

◊ References.

1. Wada M, *et al.* Induction therapy consisting of alternating cycles of ranimustine, vincristine, melphalan, dexamethasone and interferon alpha (ROAD-IN) and a randomized comparison of interferon alpha maintenance in multiple myeloma: a co-operative study in Japan. *Br J Haematol* 2000; **109:** 805–14.
2. Hatano N, *et al.* Efficacy of post operative adjuvant therapy with human interferon beta, MCNU and radiation (IMR) for malignant glioma: comparison among three protocols. *Acta Neurochir (Wien)* 2000; **142:** 633–8.
3. Wakabayashi T, *et al.* Initial and maintenance combination treatment with interferon-beta, MCNU (ranimustine), and radiotherapy for patients with previously untreated malignant glioma. *J Neurooncol* 2000; **49:** 57–62.
4. Mizuno H, *et al.* Superior efficacy of MMCP regimen compared with VMCP and MMPP regimens in the treatment of multiple myeloma. *Intern Med* 2002; **41:** 290–4.
5. Takenaka T, *et al.* Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301. *Int J Hematol* 2004; **79:** 165–73.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Cymerin.

Ranpirnase *(USAN, rINN)*

P-30 Protein; Ranpirnasa; Ranpirnasum.

Рапирназа

CAS — 196488-72-9.

NOTE. P-30 protein has been incorrectly stated to contain ergotamine.