PRODUCT MONOGRAPH

PrTOMUDEX®

(Raltitrexed disodium for Injection)

(2 mg raltitrexed per vial For Intravenous Injection)

(ANTINEOPLASTIC)

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PRODUCT MONOGRAPH

NAME OF DRUG

PrTOMUDEX ®

(Raltitrexed disodium for Injection)

(2 mg raltitrexed per vial For Intravenous Injection)

THERAPEUTIC CLASSIFICATION

(ANTINEOPLASTIC)

TOMUDEX (raltitrexed) should be administered only by or under the supervision of, a physician who is experienced in cancer chemotherapy and in the management of related toxicities. This includes myelosuppression, hepatic and renal impairment. TOMUDEX should not be administered to patients with severe hepatic impairment.

ACTIONS AND CLINICAL PHARMACOLOGY

TOMUDEX (raltitrexed) is a quinazoline folate analogue that selectively inhibits thymidylate synthase (TS). Thymidylate synthase is a key enzyme in the de novo synthesis of thymidine triphosphate (TTP), a nucleotide required exclusively for deoxyribonucleic acid (DNA) synthesis. Inhibition of thymidylate synthase leads to DNA fragmentation and cell death.

Raltitrexed is transported into cells via a reduced folate carrier (RFC) and is then extensively polyglutamated by the enzyme folyl polyglutamate synthetase (FPGS) to polyglutamate forms that are retained in cells and are even more potent inhibitors of thymidylate synthase. Raltitrexed polyglutamation enhances thymidylate synthase inhibitory potency and increases the duration of thymidylate synthase inhibition in cells which may improve antitumour activity. Polyglutamation could also contribute to increased toxicity due to drug retention in normal tissues.

Raltitrexed is 93% protein bound in humans.

Pharmacokinetics

Following intravenous administration at 3.0 mg/m^2, the concentration time profile in patients is triphasic. Peak concentrations, at the end of infusion, are followed by a rapid initial decline in concentration. This is followed by a slow elimination phase. The key pharmacokinetic parameters are presented below:

Table 1 Key Pharmacokinetic Parameters of Raltitrexed.

C_{max} (ng/mL)	AUC_0-∞ (ng.h/mL)	CL (mL/min)	CL_r (mL/min)	Vss (L)	$T_{½}\beta$ (h)	$t_{½}\gamma$ (h)
656	1856	51.6	25.1	548	1.79	198

C_{max} : peak plasma concentration
CL : clearance
CL_r : renal clearance
$t_{½}\beta$: half life of the second phase
$t_{½}\gamma$: terminal half life
AUC: area under plasma concentration-time curve
Vss: volume of distribution at steady state

The maximum concentrations of raltitrexed increased linearly with dose over the clinical dose range tested.

There is no clinically significant plasma accumulation of raltitrexed in patients with normal renal function during repeat administration at three week intervals. Apart from the expected intracellular polyglutamation, raltitrexed was mainly (approximately 50%) excreted unchanged in the urine. It is also excreted in the faeces with approximately 15% of the dose being eliminated over a 10 day period. In the study following [^{14}C] labelled raltitrexed, approximately half of the radiolabel was not recovered during the study period suggesting that a proportion (50%) of the raltitrexed dose is retained within tissues, perhaps as raltitrexed polyglutamates, beyond the end of the measurement period. Trace levels of radiolabel were detected in red blood cells on Day 29.

Raltitrexed pharmacokinetics are independent of age and gender. Pharmacokinetics have not been evaluated in children.

Mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment led to a reduction in plasma clearance of less than 25%.

Mild to moderate renal impairment (creatinine clearance of 25 to 65 mL/min) led to a significant reduction (approximately 50%) in raltitrexed plasma clearance.

Clinical Experience

In clinical trials TOMUDEX (raltitrexed), administered as a single 3mg/m^2 i.v. dose every 3 weeks, demonstrated clinical antitumour activity with an acceptable toxicity profile in patients with advanced colorectal cancer.

Four large clinical trials have been conducted with TOMUDEX in advanced colorectal cancer. Of the three comparative trials, two showed no statistical difference between TOMUDEX and the combination of 5-Fluorouracil plus leucovorin for survival, while one trial showed a statistically significant difference in favour of the combination of 5-Fluorouracil plus leucovorin. TOMUDEX as a single agent was as effective as the combination of 5-Fluorouracil and leucovorin in terms of objective response rate in all trials.

INDICATIONS AND CLINICAL USE

TOMUDEX (raltitrexed) is indicated in the treatment of advanced colorectal cancer.

CONTRAINDICATIONS

TOMUDEX (raltitrexed) is contraindicated in patients with hypersensitivity to the drug or any of its components.

TOMUDEX is contraindicated in pregnant women, in women who may become pregnant during treatment or women who are breast feeding. Teratology studies in the rat indicate that TOMUDEX caused embryolethality and fetal abnormalities in pregnant rats. Pregnancy should be excluded before treatment with TOMUDEX is commenced and should be avoided during treatment and for at least 6 months after cessation of treatment if either partner is receiving TOMUDEX.

TOMUDEX is not recommended for use in children, as safety and efficacy have not been established in this group of patients.

TOMUDEX is contraindicated in patients with severe renal and/or hepatic impairment.

WARNINGS

It is recommended that TOMUDEX (raltitrexed) is only given by or under the supervision of a physician who is experienced in cancer chemotherapy, and in the management of chemotherapy related toxicity. Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions (particularly diarrhoea) may be detected and treated promptly (see DOSAGE AND ADMINISTRATION).

As with other cytotoxic agents of this type, caution is necessary in patients with depressed bone marrow function, poor general condition, or prior radiotherapy.

A proportion of TOMUDEX is excreted via the faecal route (see ACTION AND CLINICAL PHARMACOLOGY) therefore, patients with mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment should be treated with caution.

PRECAUTIONS

TOMUDEX (raltitrexed) is a cytotoxic agent and should be handled according to normal procedures adopted for such agents (see DOSAGE AND ADMINISTRATION, Special Instructions).

TOMUDEX may cause malaise or asthenia following infusion and the ability to drive or use machinery could be impaired while symptoms continue.

Use in Elderly

Elderly patients are more vulnerable to the toxic effects of TOMUDEX. Extreme care should be taken to ensure adequate monitoring of adverse reactions, especially signs of gastrointestinal toxicity (diarrhoea or mucositis).

Drug Interactions

No specific clinical drug drug interaction studies have been conducted.

Leucovorin (folinic acid), folic acid or vitamin preparations containing these agents must not be given immediately prior to or during administration of TOMUDEX, since they may interfere with its action.

There is no experience to date in relation to the combined use of TOMUDEX with other cytotoxic agents.

TOMUDEX is 93% protein bound and while it has the potential to interact with other highly protein bound drugs, no interactions due to displacement between TOMUDEX and warfarin has been observed in vitro. Active tubular secretion may contribute to the renal excretion of raltitrexed, indicating a potential interaction with other actively secreted drugs such as non steroidal anti inflammatory drugs (NSAIDS). However, a review of the clinical trial safety database does not reveal evidence of clinically significant interaction in patients treated with TOMUDEX who also received concomitant NSAIDS, warfarin and other commonly prescribed drugs.

ADVERSE REACTIONS

As with other cytotoxic drugs, the administration of TOMUDEX (raltitrexed) is associated with certain adverse reactions; these mainly include reversible effects on the gastrointestinal tract, haematopoietic system and liver enzymes.

Gastrointestinal system

The most frequent effects were nausea (58%), vomiting (37%), diarrhoea (38%) and anorexia (28%). Other less frequent effects were mucositis, stomatitis (including mouth ulceration), dyspepsia and constipation. Gastrointestinal bleeding which may be associated with mucositis and/or thrombocytopenia has been reported.

Diarrhoea is usually mild or moderate (WHO grade 1 and 2) and can occur at any time following the administration of TOMUDEX. However, severe diarrhoea (WHO grade 3 and 4) can occur, and may be associated with concurrent haematological suppression, especially leucopenia (neutropenia in particular). Subsequent treatment may need to be discontinued or the dose reduced depending on the grade of toxicity (see DOSAGE AND ADMINISTRATION).

Nausea and vomiting are usually mild (WHO grade 1 and 2), occur usually for the first week following the administration of TOMUDEX, and are responsive to antiemetics.

Haematopoietic system

Leucopenia (neutropenia in particular), anemia and thrombocytopenia, alone and in combination, have been reported as possible adverse drug reactions in clinical trials (22%, 18% and 5% of patients, respectively). They are usually mild to moderate (WHO grade 1 and 2) and occur in the first or second week after treatment and recovering by the third week. Severe (WHO grade 3 and 4) leucopenia (neutropenia in particular) and thrombocytopenia of WHO grade 4 can occur and may be life threatening or fatal, especially if associated with signs of gastrointestinal toxicity.

Hepatic

Reversible increases in AST and ALT have been commonly reported as adverse drug reactions in clinical trials (16% and 14% of patients, respectively). Such changes have usually been asymptomatic and self limiting when not associated with progression of the underlying malignancy. Other less frequent effects are weight loss, dehydration, peripheral edema, hyperbilirubinaemia and increases in alkaline phosphatase.

Cardiovascular system

A number of cardiac rhythm or cardiac function abnormalities have been reported in clinical trials in advanced colorectal cancer. These ranged from sinus tachycardia and supraventricular tachycardia to atrial fibrillation and congestive heart failure. The incidence of disorders of rhythm and function in patients treated with TOMUDEX was 2.8% and 1.8% respectively compared to 1.9% and 1.4% for patients on the comparator treatment. A causal relationship could not be established since many of the abnormalities were concurrent with the underlying conditions such as sepsis and dehydration and more than one third of the patients reported cardiovascular abnormalities prior to treatment.

Musculoskeletal and Nervous System

Arthralgia and hypertonia (usually muscular cramps) have each been reported as possible adverse drug reactions in less than 2% of patients who received TOMUDEX in clinical trials.

Skin, Appendages and Special Senses

Rash was commonly reported in clinical trials (14% of patients), sometimes associated with pruritus. Other less frequent effects were desquamation, alopecia, sweating, taste perversion and conjunctivitis.

Whole Body

The most frequent effects in clinical trials were asthenia (49% of patients) and fever (22% of patients), which were usually mild to moderate following the first week of administration of TOMUDEX, and reversible. Severe asthenia can occur and may be associated with malaise and a flu like syndrome. Other less frequent effects were abdominal pain, pain, headache, cellulitis and sepsis.

The following effects were reported as possible adverse drug reactions occurring with an incidence of 2% or more in patients with colorectal cancer treated with TOMUDEX in clinical trials.

Table 2 Drug-related adverse events reported for at least 2% of patients treated with TOMUDEX 3 mg/m^2 in core colorectal cancer trials.

Body System and COSTART Term	**Number and Percentage of patients**					
	Four colorectal cancer trials		**Controlled colorectal cancer trials**			
	Tomudex 3 mg/m^2 (N=861)		**Tomudex 3 mg/m^2 (N=684)**		**5-FU-LV (N=656)**	
Whole Body						
Asthenia	418	48.5%	315	46.1%	243	37%
Fever	192	2.3%	158	23.1%	108	16.5%
Mucous membrane disorder	103	12.0%	85	12.4%	269	41.0%
Flu syndrome	70	8.1%	38	5.6%	17	2.6%
Abdominal pain	146	17.0%	126	18.4%	115	17.5%
Headache	51	5.9%	44	6.4%	25	3.8%
Infection	25	2.9%	21	3.1%	15	2.3%
Cellulitis	27	3.1%	18	2.6%	0	0%
Pain	36	4.2%	30	4.4%	35	5.3%
Malaise	33	3.8%	27	3.9%	15	2.3%
Chills	31	3.6%	30	4.4%	15	2.3%
Sepsis	20	2.3%	18	2.6%	12	1.8%
Digestive						
Nausea	502	58.3%	390	57.0%	327	49.8%
Diarrhoea	324	37.6%	256	37.4%	382	58.2%
Vomiting	320	37.2%	257	37.6%	197	30.0%
Anorexia	238	27.6%	180	26.3%	98	14.9%
Stomatitis	94	10.9%	77	11.2%	229	34.9%
Constipation	115	13.4%	104	15.2%	77	11.7%
Dyspepsia	55	6.4%	38	5.6%	31	4.7%
Flatulence	20	2.3%	18	2.6%	14	2.1%
Dry mouth	21	2.4%	18	2.6%	17	2.6%

Body System and COSTART Term	Number and Percentage of patients					
	Four colorectal cancer trials		Controlled colorectal cancer trials			
	Tomudex 3 mg/m^2 (N=861)		Tomudex 3 mg/m^2 (N=684)		5-FU-LV (N=656)	
Haemic and lymphatic						
Leucopenia	188	21.8%	139	20.3%	231	35.2%
Anemia	152	17.7%	103	15.1%	50	7.6%
Thrombocytopenia	45	5.2%	39	5.7%	16	2.4%
Metabolic and nutritional						
AST increased	137	15.9%	121	17.7%	14	2.1%
ALT increased	118	13.7%	104	15.2%	17	2.6%
Peripheral edema	82	9.5%	69	10.1%	31	4.7%
Weight loss	51	5.9%	39	5.7%	19	2.9%
Dehydration	49	5.7%	45	6.6%	35	5.3%
Alkaline phosphatase increased	20	2.3%	17	2.5%	4	0.6%
Creatinine increased	20	2.3%	20	2.9%	1	0.2%
Bilirubinemia	19	2.2%	18	2.6%	9	1.4%
Hypokalemia	17	2.0%	15	2.2%	12	1.8%
Musculoskeletal						
Arthralgia*	8*	2%*	4	2%*	0	0%*
Myalgia	22	2.6%	17	2.5%	11	1.7%
Nervous System						
Insomnia	29	3.4%	28	4.1%	19	2.9%
Depression	22	2.6%	21	3.1%	11	1.7%
Dizziness	35	4.1%	33	4.8%	22	3.4%
Paresthesia	21	2.4%	18	2.6%	18	2.7%
Hypertonia*	9*	2%*	5	2%*	0	0%*
Respiratory						
Cough increased	41	4.8%	36	5.3%	26	4.0%
Dyspnea	37	4.3%	34	5.0%	25	3.8%
Pharyngitis	37	4.3%	36	5.3%	41	6.3%

Body System and COSTART Term	Number and Percentage of patients					
	Four colorectal cancer trials		Controlled colorectal cancer trials			
	Tomudex 3 mg/m^2 (N=861)		Tomudex 3 mg/m^2 (N=684)		5-FU-LV (N=656)	
Skin and Appendages						
Rash	123	14.3%	98	14.3%	127	19.4%
Alopecia	52	6.0%	42	6.1%	127	19.4%
Pruritus	28	3.3%	23	3.4%	18	2.7%
Sweating	27	3.1%	25	3.7%	19	2.9%
Special Senses						
Taste perversion	48	5.6%	40	5.8%	31	4.7%
Conjunctivitis	21	2.4%	17	2.5%	34	5.2%
Urogenital						
Urinary tract infection	22	2.6%	21	3.1%	17	2.6%

5-FU-LV = 5-fluorouracil and leucovorin
* These values are the results of only 2 clinical trials (study IL/002 and study IL/003). The incidence of these events when calculated for all 4 trials was less than 2%.

Presented below is a table that lists the incidence of WHO Grade 3/4 adverse events reported for at least 2% of patients.

Table 3 Adverse Events of WHO Grade 3/4 (incidences 2% or more)

Adverse Event	Four Colorectal Trials 3.0 mg/m^2 n[a]= 861		Controlled Colorectal Cancer Trials			
			Tomudex 3.0 mg/m^2 n[a] = 684		5FU + LV (LD+HD) n[a] = 656	
Nausea and vomiting	100	11.6%	80	11.7%	58	8.8%
Diarrhea	96	11.1%	78	11.4%	100	15.2%
Constipation	17	2.0%	16	2.3%	11	1.7%
Oral effects	18	2.1%	16	2.3%	105	16.0%
Pain	63	7.3%	54	7.9%	54	8.2%
Asthenia	-[b]	-[b]	64	9.4%	28	4.3%
Infection	43	5.0%	33	4.8%	32	4.9%
Hemoglobin decreased	56	6.5%	53	7.7%	17	2.6%
Platelets	30	3.5%	28	4.1%	7	1.1%

Adverse Event	Four Colorectal Trials 3.0 mg/m^2 n[a]= 861		Controlled Colorectal Cancer Trials			
			Tomudex 3.0 mg/m^2 n[a] = 684		5FU + LV (LD+HD) n[a] = 656	
Leukocytes	111	12.9%	85	12.4%	176	26.8%
Transaminase increases	87	10.1%	69	10.1%	2	0.3%
Bilirubin	19	2.2%	11	1.6%	12	1.8%

[a] 'n' = total number of patients
[b] COSTART term not reported

The number of serious adverse events reported in the four colorectal trials, including those where hospitalization was the criterion for seriousness, are presented below. In total, 37% of patients participating in these trials experienced a serious adverse event that included hospitalization.

Table 4 Number of SAEs where Hospitalization was a Criterion for Seriousness in Trials 1694IL/0002C, 1694IL/0003, 1694IL/0010 and 1694IL/0012.

	1694IL/0002C 3 mg/m^2 n[a] = 177		1694IL/0003 3 mg/m^2 n[a] = 222		1694IL/0010 3 mg/m^2 n[a] = 217		1694IL/0012 3 mg/m^2 n[a] = 245		Total Four Colorectal Cancer Trials n[a] = 861	
	N	%	N	%	N	%	N	%	N	%
Total number of SAE[b]s	234	21	319	29	309	28	245	22	1107	-
Total number of SAE[b]s where hospitalisation was a criterion of seriousness	181	19	280	29	274	29	216	23	951	-
Total number of patients with an SAE[b]	81	46	116	52	91	42	87	35	375	44
Total number of patients with an SAE[b] where hospitalisation was a criterion of seriousness	66	37	99	45	75	35	76	31	316	37

a 'n' is the total number of patients in trial
b SAE = Serious Adverse Event

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The expected manifestations of overdose are likely to be an exaggerated form of the adverse drug reactions anticipated with the administration of the drug. Patients should, therefore, be monitored carefully for signs of gastrointestinal and haematological toxicity. Symptomatic

treatment and standard supportive care measures for the management of this toxicity should be applied.

There is no clinically proven antidote available. In the case of inadvertent or accidental administration of an overdose, consideration should be given to the administration of leucovorin. From clinical experience with other antifolates, leucovorin may be given at a dose of 25 mg/m^2 i.v. every 6 hours. As the time interval between TOMUDEX (raltitrexed) administration and leucovorin rescue increases, its effectiveness in counteracting toxicity may decrease. Data in animals show that delayed administration of leucovorin after TOMUDEX (raltitrexed) produced earlier recovery from weight loss and some improvement to intestinal damage and neutrophil and platelet numbers.

DOSAGE AND ADMINISTRATION

The dose of TOMUDEX (raltitrexed) is calculated on the basis of body surface area. The recommended dose is 3 mg/m^2 given intravenously, as a single short, intravenous infusion in 50 to 250 mL diluted in 0.9% sodium chloride or 5% dextrose (glucose) solution. It is recommended that the infusion be given over a 15 minute period. In the absence of toxicity, treatment may be repeated every 3 weeks.

Other drugs should not be mixed with TOMUDEX in the same infusion container.

Dose escalation above 3 mg/m^2 is not recommended, since higher doses have been associated with an increased incidence of life threatening or fatal toxicity.

Prior to the initiation of treatment and before each subsequent treatment a full blood count (including a differential count and platelets), liver transaminases, serum bilirubin and serum creatinine measurements should be performed. The total white cell count should be greater than 4,000/mm^3, the neutrophil count greater than 2,000/mm^3 and the platelet count greater than 100,000/mm^3 prior to treatment.

In the event of toxicity the next scheduled dose should be withheld until signs of toxic effects regress. In particular, signs of gastrointestinal toxicity (diarrhoea or mucositis) and haematological toxicity (neutropenia or thrombocytopenia) should have resolved completely before subsequent treatment is allowed. Patients who develop signs of gastrointestinal toxicity should have their full blood counts monitored at least weekly for signs of haematological toxicity. Treatment in patients with suspected drug-related rises in liver enzymes should be deferred until they show evidence of reversibility to at least WHO grade 2.

Based on the worst grade of gastrointestinal and haematological toxicity observed on the previous treatment and provided that such toxicity has resolved completely, the following dose reductions are recommended for subsequent treatment:

*** 25% dose reduction**: in patients with WHO grade 3 haematological toxicity (neutropenia or thrombocytopenia) or WHO grade 2 gastrointestinal toxicity (diarrhoea or mucositis).

*** 50% dose reduction**: in patients with WHO grade 4 haematological toxicity (neutropenia or thrombocytopenia) or WHO grade 3 gastrointestinal toxicity (diarrhoea or mucositis). Once a dose reduction has been made, all subsequent doses should be given at the reduced dose level.

Treatment should be discontinued in the event of any WHO grade 4 gastrointestinal toxicity (diarrhoea or mucositis) or in the event of a WHO grade 3 gastrointestinal toxicity associated with WHO grade 4 haematological toxicity. Patients with such toxicity should be managed promptly with standard supportive care measures including i.v. hydration and bone marrow support to help neutrophil and platelet recovery thus reducing the likelihood of fatal sepsis or haemorrhage. Based on data in animals where delayed administration of leucovorin after TOMUDEX (raltitrexed) produced earlier recovery from weight loss and some improvement to intestinal damage and recovery of neutrophil and platelet numbers, consideration should be given to the administration of leucovorin (folinic acid). From clinical experience with other antifolates leucovorin may be given at a dose of 25 mg/m^2 i.v. every 6 hours until the resolution of symptoms. Further use of TOMUDEX in such patients is not recommended.

It is essential that the dose reduction scheme be adhered to since the potential for life threatening and fatal toxicity increases if the dose is not reduced or treatment not stopped as appropriate.

Geriatric Patients:

Dosage and administration as for adults. However, as with other cytotoxics, TOMUDEX should be used with caution in elderly patients (see PRECAUTIONS).

Renal Impairment:

For patients with abnormal serum creatinine, before the first or any subsequent treatment, a creatinine clearance should be performed or calculated. For patients with a normal serum creatinine when the serum creatinine may not correlate well with the creatinine clearance due to factors such as age or weight loss, the same procedure should be followed. If creatinine clearance is < 65 mL/min, the following dose modifications are recommended:

Table 5

Creatinine clearance	Dose as % of 3.0 mg/m^2	Dosing interval
> 65 mL/min	Full dose	3-weekly
55 to 65 mL/min	75%	4-weekly
25 to 54 mL/min	% equivalent to mL/min*	4-weekly
<25 mL/min	No therapy	Not applicable

*For example, if the creatinine clearance = 30 mL/min, 30% of the full dose should be given.

Patients with renal impairment may have an increased propensity for side-effects and should be monitored appropriately.

Hepatic Impairment: No dosage adjustment is necessary for patients with mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment. However, given that a proportion of the drug is excreted via the faecal route (see ACTION AND CLINICAL PHARMACOLOGY) and that these patients usually form a poor prognosis group, patients with mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment need to be treated with caution. Treatment in patients with suspected drug-related rises in liver enzymes should be deferred until they show evidence of reversibility to at least WHO grade 2. TOMUDEX has not been studied in patients with severe hepatic impairment, clinical jaundice or decompensated liver disease and its use in such patients is not recommended.

Special Instructions:

TOMUDEX is a cytotoxic agent and should be handled according to the normal procedures adopted for such agents in each institution. At minimum the following are recommended:

Any unused injection or reconstituted solution should be discarded in a suitable manner for cytotoxics.

TOMUDEX should be reconstituted for injection by trained personnel in a designated area for the reconstitution of cytotoxic agents. Cytotoxic preparations such as TOMUDEX should not be handled by pregnant women.

Reconstitution should normally be carried out in a partial containment facility with extraction capabilities e.g. a laminar air flow cabinet, and work surfaces should be covered with disposable plastic backed absorbent paper.

Appropriate protective clothing, including surgical gloves and goggles, should be worn. In case of contact with skin, wash immediately with water. For splashes in the eyes irrigate with clean water, holding the eyelids apart, for at least 10 minutes. Seek medical attention.

Any spillage should be cleared up using standard procedures consistent with the handling of chemotherapeutic agents.

Waste material should be disposed of by incineration in a manner consistent with the handling of cytotoxic agents.

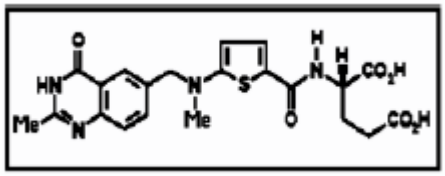
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: raltitrexed

Chemical Name: N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl)-L-glutamic acid (IUPAC)

Structural Formula:



Molecular Formula: $C_{21}H_{22}N_4O_6S$

Molecular Weight: 458.49

Description: Raltitrexed is a pale yellow-brown to brown powder. Based on the estimated pKa values of the two carboxylic acid groups (4.5 and 5.7 at 25°C) the solubility is susceptible to pH. The melting point of raltitrexed is 179-181°C.

Composition: TOMUDEX is a sterile lyophilized powder without preservative or bacteriostatic agent. The quantitative composition of TOMUDEX is shown below:

Table 6

Ingredient	mg per vial
Raltitrexed (as the disodium salt)	2.0
Mannitol	203.0
Dibasic sodium phosphate*	1.5
Sodium hydroxide	qs to pH 7.4
Nitrogen	qs (vial head space)

* Hydration state is not defined after processing. For consistency the quantity is expressed as the heptahydrate equivalent.

Stability and Storage Recommendations:

Store at 2 to 25°C protected from light. Once reconstituted, TOMUDEX is chemically stable for 24 hours at 25°C exposed to ambient light, however, it is recommended that TOMUDEX should be refrigerated to avoid bacterial contamination (for further information see Reconstituted Solutions).

Reconstituted Solutions:

Each vial, containing 2 mg of raltitrexed, should be reconstituted with 4 mL of sterile water for injections to produce a 0.5 mg/mL solution. The appropriate dose of solution, calculated on the basis of body surface area, is diluted in 50 - 250 mL of either 0.9% sodium chloride or 5% glucose (dextrose) injection and administered by a short intravenous infusion over a period of 15 minutes.

There is no preservative or bacteriostatic agent present in TOMUDEX or the materials specified for reconstitution or dilution. TOMUDEX must therefore be reconstituted and diluted under aseptic conditions (See Special Instructions) and it is recommended that solutions of TOMUDEX should be used as soon as possible. Reconstituted TOMUDEX solution may be stored refrigerated (2 - 8°C) for up to 24 hours. The admixed solution must be completely used or discarded within 24 hours of reconstitution of TOMUDEX intravenous injection.

Reconstituted and diluted solutions do not need to be protected from light.

Do not store partially used vials or admixed solutions for future patient use.

Parenteral Products:

Continuous intravenous infusion

Table 7

Vial size	Volume of diluent to be added to vial	Approximate available volume	Nominal concentration per mL
2 mg raltitrexed/vial*	4 mL sterile water for inj.	4 mL	0.5 mg/mL

* as the disodium salt

There is no information on incompatibilities at present and therefore TOMUDEX should not be mixed with any other drug.

As with all parenteral drug products, I.V. admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solutions and containers permit.

AVAILABILITY OF DOSAGE FORMS

TOMUDEX (raltitrexed) is available as a sterile, lyophilized powder containing 2 mg of raltitrexed as the disodium salt in single dose vials.

PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics: *in vitro*: Raltitrexed was found to have growth inhibitory potency against a range of wild-type tumour cell lines (L1210 murine leukaemia, W1L2 human lymphoblastoid, HeLa human cervical carcinoma, MCF-7 human breast carcinoma). The IC_{50} (drug concentration to reduce cell growth by 50%) values for raltitrexed exposed to cells for 2-5 days were as follows: L1210 8.8±3.1 nM, W1L2 4.6±1 nM, HeLa 1.7 nM, MCF-7 0.7 nM. In L1210 cells the IC_{50} of raltitrexed was only increased 10-fold when the drug exposure period was reduced to 4 hours, which is consistent with rapid drug uptake and intracellular retention as polyglutamates.

in vivo: The primary antitumour test involved L5178Y TK-/- tumour cells grown in the gastrocnemius muscle of one hind leg of DBA2 mice. Raltitrexed was administered intraperitoneally (ip) either as a single dose, or as two or three equal doses on day 3 after implant. Tumour growth was monitored by daily measurement of leg diameter. An endpoint which combined "tumour cure" (defined as no regrowth with 3 weeks) and long growth delays (greater than 5 days which is approximately 5 volume doubling of this tumour) was used. For all schedules tested, a highly significant effect was obtained with a total dose of about 10 mg/kg/day (30 mg/m^2/day, estimated from mg/kg/day by assuming a weight to surface area ratio of 3). This is about 1/50th of the maximum tolerated single dose in this mouse strain.

Similar experiments were conducted with L5178Y TK+/- cells (thymidine salvage competent), except that treatment was administered for five days using single, or multiple, daily i.p. doses. In this model cures were more difficult to achieve and using an endpoint of 5 days growth delay, and a twice daily schedule, the effective dose of raltitrexed was 6.6 mg/kg/day (19.8 mg/m^2/day) which is well below the MTD (>120mg/kg/day).

It is concluded that raltitrexed is more efficacious in the L5178Y TK-/- cell line than the TK+/-, which is probably related to the high levels of circulating thymidine (TdR) in rodents. Longer treatment periods were required to produce antitumour effects in the latter model and this may be related at least in part to the need to reduce and maintain circulating TdR below a protective level.

Further antitumour studies were performed using the tetraploid L1210:ICR tumour. L1210:ICR cells were inoculated ip and treatment with raltitrexed commenced 3 days later, using a five day dose schedule. At a daily i.p. dose of 0.4 mg/kg (1.2 mg/m^2) or an intravenous (i.v.) dose of 1 mg/kg (3 mg/m^2) raltitrexed was curative in this model. The antitumour activity of raltitrexed could be prevented by co-administration of either TdR (500 mg/kg three times daily for 8 days) or LV (20 mg/kg daily for 5 days). These agents had similar protective effects against cultured cells when co-administered with raltitrexed in vitro.

Antitumour efficacy studies of raltitrexed were also performed against 15 human tumour xenografts (ovarian - HX62, SK0V3; colon - HT29, LoVo, Colo 205, GC3/C1, LS174T, CR10; SCLC - N417A, N592; bronchus - P246; gastric MKN45; bladder - HT1376, RT112; breast - MDAMB231) growing subcutaneously (s.c.) in nude mice. Treatment commenced

when the tumours reached a diameter of 5-6 mm. All compounds were administered as 15 daily i.p. bolus doses (an extended dose schedule was used in order to overcome TdR salvage problems) and activity was compared by determining the daily dose required to produce 15 days of growth delay.

Raltitrexed produced significant growth delays in all 15 tumours at doses below its MTD (MTD=333 mg/kg/day=1,000 mg/m^2/day). Raltitrexed was particularly active against HX62 (cis-platin-resistant ovarian), LoVo, Colo 205, CR10 and P246, where the effective doses were 1,6, 10, 10 and 10 mg/kg/day (3, 18, 30, 30 and 30 mg/m^2/day) respectively.

Raltitrexed was also administered orally to mice bearing the HX62 ovarian carcinoma xenograft and exhibited similar potency to that seen with the i.p. dose route.

Pharmacokinetics

Following intravenous administration, the single dose pharmacokinetics of raltitrexed were very similar in rat and dog. Plasma clearance was relatively rapid, 6-10 and 5-7 mL/min/kg respectively. The disposition was triphasic with short initial phases and a relatively slow gamma phase in both species ($t_{½}$g 22-56 h in rat: $t_{½}$g 14-29 h in dog). The long terminal phase is probably due to a slow return of raltitrexed to the plasma from a deep tissue compartment or binding site.

The pharmacokinetics appeared to be linear in both species.

The pharmacokinetics were also triphasic in patients. The half-life in man (198 hours) was significantly longer than those measured in animals and the plasma clearance of raltitrexed (approx. 1 mL/min/kg) lower than those in animals (see above).

On multiple daily dosing there was moderate accumulation in the animals, comparable with the terminal elimination half-lives observed. Due to the three weekly dose schedule adopted for man, accumulation should not be relevant in the clinic and no significant accumulation has been observed in cancer patients.

TOXICOLOGY

Acute Toxicity

The approximate LD50 values for the mouse and rat are 875 1249 mg/kg and greater than 500 mg/kg respectively. In the mouse, levels of 750 mg/kg and above caused death by general toxicity.

Long-Term Toxicity

In one month continuous and six month intermittent dosing studies in the rat, toxicity was related entirely to the cyotoxic nature of the drug. Principal target organs were the gastrointestinal tract, bone marrow and testis. In similar studies in the dog, cumulative dose levels similar to those used clinically elicited pharmacologically-mediated changes in proliferating tissue. Target organs in the dog were similar to the rat. The only finding of

questionable aetiology was a reduction in heart rate with concomitant increase in R-R interval in dogs of the high dose group given raltitrexed for more than 18 consecutive days. This phenomenon was reversible, was not associated with cardiac pathology, and occurred only after repeated daily dosing without a recovery period. The effect did not occur in studies of 6 months duration in which a recovery period similar to that used in the clinic was included between each cycle of dosing. Details of each study are provided in the following table.

Table 8 Long -Term Toxicity

SPECIES	DURATION	NO. OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
Rat Wistar	5 days	24 M + 24 F*	Intravenous	0, 2,10, 50	No changes observed in the clinical findings or necropsy/histological findings.
Rat Crl:(WI)BR	30 days	15 M + 15 F	Intravenous	0, 1, 5, 15	One 5 mg/kg/day treated and 9,15 mg/kg/day - treated males died or were killed in extremis during the dosing period. 2, 15 mg/kg/day - treated males died or were killed during the withdrawal period. 5, 15 mg/kg/day - treated females died prematurely and a further 2 died during the withdrawal period. All deaths were considered due to the cytotoxic properties of the drug. Principle target organs were the gastrointestinal tract, bone marrow, testis/epididymis and thymus.
Rat Wistar	6 months dosed 5 days each month followed by a 23 day recovery period	35 M+ 35 F (0, 25 & 50 mg/kg/day) 25 M + 35 F (5 mg/kg/day)	Intravenous	0, 5, 25, 50	There were no deaths, no ophthalmological or urine changes There were no deaths, no ophthalmological or urine changes attributed to ZD1694. Decreases in both food consumption and body weight gain were recorded in all dosed groups. Abnormal incisors were observed in animals receiving 25 or 50 mg/kg/day but there were no histological changes.
Dog Beagle	5 days (pilot study)	1 animal/group	Intravenous	0.01, 0.05	The animal dosed intravenously at 0.01 mg/kg exhibited no adverse clinical findings. Five daily doses of 0.05 mg/kg/day resulted in loose faeces on days 1 and 4, and emesis occurring on days 5-7. Dehydration and low body temperature were recorded on day 7. Between days 5 and 8 the animal became subdued and ate no food. Weight loss occurred between days 1 and 8 but by day 9 recovery was evident and no further atypical signs were observed until the end of the 62 day study period.

SPECIES	DURATION	NO. OF ANIMALS/GROUP	ROUTE	DOSE MG/KG/DAY	EFFECTS
Dog Beagle	5 days	6 M+ 6 F (0 & 0.02 mg/kg/day) 3 M +3 F (0.01 & 0.04 mg/kg/day)	Intravenous	0, 0.01, 0.02, 0.04	All the dogs survived until necropsy. Inappetance, reduction in body weight and subdued behaviour were seen in the 0.02 and 0.04 mg/kg groups, emesis was recorded for 4 dogs in the latter group. No changes were seen in ophthalmology, physiology, coagulation or urine analysis.
Dog Beagle	30 days	6 M + 6 F (0 & 0.015 mg/kg/day) 3 M + 3 F (0.005 & 0.01 mg/kg/day)	Intravenous	0, 0.005, 0.01, 0.015	One male and one female receiving 0.015 mg/kg/day were killed (days 24 and 19 respectively) because of inappetance and deteriorating condition. The remaining animals scheduled for killing at 30 days in this dose group were terminated on day 24 and others were left undosed until the end of the withdrawal period. All animals given 0.01 or 0.005 mg/kg/day survived the one month dosing period. Body weight, food consumption, white blood cell count, neutrophil count, lymphocyte count and platelet count were all decreased in the 0.015 mg/kg/day groups. There was a reduction in heart rate with a concomitant increase in the R-R interval at the end of the 0.015 mg/kg/day dosing period (24 days).
Dog Beagle	6 months dosed 5 days each month followed by a 23 day recovery period	7 M + 7 F (0 & 0.02 mg/kg/day) 4 M+ 4 F (0.005 & 0.01 mg/kg/day)	Intravenous	0, 0.005, 0.01, 0.02	There were no deaths during the study and no ophthalmological or physiological changes attributed to ZD1694. There were cyclic decreases in body weight and food consumption in the 0.02 mg/kg groups.

*Reflects group related extra animals (e.g. for pharmacokinetics etc.)

Carcinogenicity

The carcinogenic potential of raltitrexed has not been evaluated.

Mutagenicity

Raltitrexed was not mutagenic in the Ames test or in supplementary tests using E. coli or chinese hamster ovary cells. Raltitrexed caused increased levels of chromosome damage in an in vitro assay of human lymphocytes. This effect was ameliorated by the addition of thymidine, thus confirming it to be due to the anti metabolic nature of the drug. An in vivo micronucleus study in the rat indicated that at cytotoxic dose levels, raltitrexed is capable of causing chromosome damage in the bone marrow.

Reproduction & Teratology

Fertility studies in the rat indicate that raltitrexed can cause impairment of male fertility. Fertility returned to normal three months after dosing ceased. Raltitrexed caused embryolethality and foetal abnormalities in pregnant rats.

Tolerance Studies

Perivascular tolerance studies in animals did not reveal any significant irritant reaction.

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