PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr TOMUDEX®

Raltitrexed for Injection

lyophilized powder, 2 mg raltitrexed per vial, intravenous injection

Antineoplastic

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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RECENT MAJOR LABEL CHANGES

NA	NA

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see section **2 CONTRAINDICATIONS**).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see section **7 WARNINGS AND PRECAUTIONS**, **7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

- TOMUDEX (raltitrexed) is contraindicated in patients with hypersensitivity to the drug or any of its components **(see section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).**

- TOMUDEX is contraindicated in pregnant women, in women who may become pregnant during treatment or women who are breast feeding (see **7 WARNINGS AND PRECAUTIONS**, **7.1.1 Pregnant Women** and **7.1.2 Breast-feeding**).

- TOMUDEX is not recommended for use in children (<18 years of age), 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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. 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/mm3, the neutrophil count greater than 2,000/mm3 and the platelet count greater than 100,000/mm3 prior to treatment (See 4.2 **Recommended Dose and Dosage Adjustment**).

Pregnancy should be excluded before treatment with TOMUDEX is commenced (see **2 CONTRAINDICATIONS**).

4.2 Recommended Dose and Dosage Adjustment

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 shot, 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.

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.

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 **7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics**).

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 1

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 **10 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.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Parenteral Products:

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 continuous 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 **12 SPECIAL HANDLING 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.

Table 2

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

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.

4.4 Administration

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

5 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Raltitrexed 2 mg sterile lyophilized powder per vial	Dibasic sodium phosphate Mannitol Nitrogen Sodium hydroxide

Composition:

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

Table 4

Ingredient	mg per vial
Raltitrexed	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.

AVAILABILITY OF DOSAGE FORMS

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

7 WARNINGS AND PRECAUTIONS

General

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 **4 DOSAGE AND ADMINISTRATION**).

TOMUDEX (raltitrexed) is a cytotoxic agent and should be handled according to normal procedures adopted for such agents (see **12 SPECIAL HANDLING INSTRUCTIONS**).

Driving and Operating Machinery

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

Hematologic

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

Hepatic/Biliary/Pancreatic

A proportion of TOMUDEX is excreted via the faecal route (see **10 CLINICAL PHARMACOLOGY)** therefore, patients with mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment should be treated with caution.

Reproductive Health: Female and Male Potential

(see **2 CONTRAINDICATIONS, 7.1.1 Pregnant Women)**

Fertility: No data available

7.1 Special Populations

7.1.1 Pregnant Women

TOMUDEX is contraindicated in pregnant women, in women who may become pregnant during treatment. 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 (see **2 CONTRAINDICATIONS**).

7.1.2 Breast-feeding

TOMUDEX is contraindicated in women who are breast-feeding (see **2 CONTRAINDICATIONS**).

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **2 CONTRAINDICATIONS**).

7.1.4 Geriatrics

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).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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 **4 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 5 Drug-related adverse events reported for at least 2% of patients treated with TOMUDEX 3 mg/m² in core colorectal cancer trials.

Body System	Number and Percentage of patients					
COSTART Term	Four colorectal cancer trials		Controlled colorectal cancer trials			
	Tomudex 3 mg/m² (N=861)		Tomudex 3 mg/m² (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%

Body System COSTART Term	Number and Percentage of patients Four colorectal cancer trials Tomudex 3 mg/m² (N=861)		Controlled colorectal cancer trials Tomudex 3 mg/m² (N=684)		5-FU-LV (N=656)	
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%
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%*

Body System COSTART Term	Number and Percentage of patients Four colorectal cancer trials Tomudex 3 mg/m² (N=861)		Controlled colorectal cancer trials Tomudex 3 mg/m² (N=684)		5-FU-LV (N=656)	
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%
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 6 Adverse Events of WHO Grade 3/4 (incidences 2% or more)

Adverse Event	Four Colorectal Trials Tomudex 3.0 mg/m² n[a]= 861		Controlled Colorectal Cancer Trials Tomudex 3.0 mg/m² 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%

Adverse Event	Four Colorectal Trials Tomudex 3.0 mg/m² na= 861		Controlled Colorectal Cancer Trials Tomudex 3.0 mg/m² na = 684		5FU + LV (LD+HD) na = 656	
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%
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 7 **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/m² na = 177		1694IL/0003 3 mg/m2 na = 222		1694IL/0010 3 mg/m2 na = 217		1694IL/0012 3 mg/m2 na = 245		Total Four Colorectal Cancer Trials na = 861	
	N	%	N	%	N	%	N	%	N	%
Total number of SAEbs	234	21	319	29	309	28	245	22	1107	-
Total number of SAEbs where hospitalisation was a criterion of seriousness	181	19	280	29	274	29	216	23	951	-
Total number of patients with an SAEb	81	46	116	52	91	42	87	35	375	44
Total number of patients with an SAEb 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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.2 Pharmacodynamics

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.

10.3 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 8 Key Pharmacokinetic Parameters of Raltitrexed.

C_{max} (ng/mL)	$AUC_{0-\infty}$ (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
AUC: area under plasma concentration-time curve
CL : clearance
Vss: volume of distribution at steady state
CL_r : renal clearance
$t_{½}\beta$: half life of the second phase
$t_{½}\gamma$: terminal half life

Absorption

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

Distribution:

Raltitrexed is 93% protein bound in humans.

Metabolism:

There is no clinically significant plasma accumulation of raltitrexed in patients with normal renal function during repeat administration at three week intervals.

In the study following [14C] 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.

Elimination

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.

Special Populations and Conditions

Raltitrexed pharmacokinetics are independent of age and gender.

- **Pediatrics:** Pharmacokinetics have not been evaluated in children.
- **Hepatic Insufficiency:** Mild (WHO grade 2) to moderate (WHO grade 3) hepatic impairment led to a reduction in plasma clearance of less than 25%.

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

11 STORAGE, STABILITY AND DISPOSAL

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 **4 DOSAGE AND ADMINISTRATION**, **4.3 Reconstitution**).

12 SPECIAL HANDLING INSTRUCTIONS

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

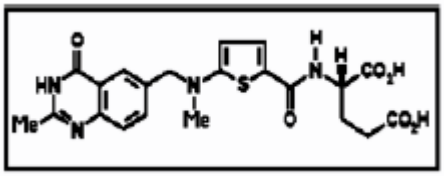
Drug Substance

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)

Molecular formula and molecular mass: C21H22N4O6S, 458.49

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

In clinical trials TOMUDEX (raltitrexed), administered as a single 3mg/m2 i.v. dose every 3 weeks, demonstrated clinical antitumour activity with an acceptable toxicity profile in patients with advanced colorectal cancer.

14.2 Study Results

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute Toxicity

The approximate LD50 values for the mouse range from 875 to 1249 mg/kg. The approximate LD value for the rat is greater than 500 mg/kg. 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 cytotoxic 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 9 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 & Developmental Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞TOMUDEX®

Raltitrexed for Injection

Read this carefully before you start taking **TOMUDEX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TOMUDEX**.

What is TOMUDEX used for?

TOMUDEX is used in adults to treat cancer which affects the colon and rectum (parts of your large intestine).

How does TOMUDEX work?

TOMUDEX contains a medicine called raltitrexed. This belongs to a group of medicines known as chemotherapy. These medicines are used to treat cancer.

TOMUDEX works by killing cells within your body which cause certain types of cancer. Your healthcare professional will explain this to you in more detail.

What are the ingredients in TOMUDEX?

Medicinal ingredients: raltitrexed

Non-medicinal ingredients: dibasic sodium phosphate, mannitol, nitrogen and sodium hydroxide

TOMUDEX comes in the following dosage forms:

Powder for solution: 2 mg per vial

Do not use TOMUDEX if:

- you are allergic to raltitrexed or any of the other ingredients of this medicine (see **What are the ingredients in TOMUDEX?**).
- you are pregnant, think you might be pregnant, or are trying to have a baby
- you are breast-feeding
- you have severe kidney and/or liver problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TOMUDEX. Talk about any health conditions or problems you may have, including if you:

- have any problems with your blood, kidneys or liver.
- have had radiotherapy (treatment with high dose X-rays).
- are elderly, your healthcare professional will monitor you more closely for side effects. Elderly people can be more affected by the side effects of TOMUDEX.

Other warnings you should know about:

TOMUDEX will be given to you by a healthcare professional who is experienced in giving chemotherapy medicines.

Male and Female Fertility:

- You must **not** get pregnant, or father a child, while you are receiving TOMUDEX and for at least 6 months after your last dose.
- Men and women must use effective birth control while they are receiving TOMUDEX. Talk to your healthcare professional about the birth control options that are right for you.
- If you are a woman who is able to get pregnant you will be given a pregnancy test before starting treatment with TOMUDEX to make sure you are not pregnant.

Driving and Using Machines: TOMUDEX may cause you to feel unwell or weak after you receive it. Your ability to drive or use machinery could be impaired while you have these symptoms. Do not drive or operate machinery until these symptoms have passed.

Blood Tests: TOMUDEX may cause changes to your blood. These occur because of effects on your bone marrow and your liver. Your healthcare professional will take regular blood samples to check your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with TOMUDEX:

- vitamins or vitamin supplements
- medicines to thin your blood and stop it from clotting (anti-coagulants).
- Non-steroidal anti-inflammatory drugs (NSAIDs), used to treat pain and inflammation

How to take TOMUDEX:

- TOMUDEX will be injected slowly into one of your veins. The injection will usually take 15 minutes.
- The exact dose you are given will be decided by your healthcare professional. It will depend on your size and how you react to your treatment.

Usual Dose

- Your healthcare professional will calculate your dose from your height and weight.
- Your healthcare professional will need to take regular samples of your blood while you are receiving TOMUDEX. The results of your blood tests will also help the healthcare professional to decide what dose you will receive. The dose you are given may be different each time.
- TOMUDEX is usually given every three weeks, but it could be less often, depending on the results of your blood tests.

Overdose:

If you think you, or a person you are caring for, have been given too much TOMUDEX, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using TOMUDEX?

These are not all the possible side effects you may have when taking TOMUDEX. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Loss of appetite
- Indigestion
- Feeling sick (nausea)
- Stomach pain
- Constipation
- Weight loss
- Itchy rash
- Painful joints
- Muscle cramps
- Swollen hands, ankles or feet
- Tenderness and swelling under the skin (cellulitis)
- Sweating
- Hair loss or thinning
- Feeling thirsty or dry skin (signs of dehydration)
- Headache
- Altered taste
- Red or itchy eyes (conjunctivitis)
- Weakness (sometimes flu-like symptoms)
- Red or peeling skin
- Trouble sleeping (insomnia)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low red blood cells): being short of breath, feeling very tired, having pale skin, fast heartbeat, loss of energy, weakness		✓	
Diarrhea		✓	
Mucositis: swelling to the mouth, soreness or ulcers inside your mouth, difficulty swallowing, eating or talking, a dry mouth and lips, bleeding from your bottom, or pain when passing stool		✓	
Neutropenia or Leukopenia (low white blood cells): fever, chills or		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
infection, fatigue, aches and pains, flu-like symptoms			
Vomiting		✓	
COMMON			
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Sore throat		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, weakness		✓	
UNKNOWN			
Bleeding from the stomach: black or tarry stools, bright red blood in vomit or stools, stomach cramps, dizziness or faintness, feeling tired, paleness, shortness of breath			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

TOMUDEX will be stored by your healthcare professional.

Keep out of reach and sight of children.

If you want more information about TOMUDEX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

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