Hospira

(Issued to the Medical professional only)

1. NAME OF THE MEDICINAL PRODUCT

Tomudex 2 mg powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 2 mg raltitrexed.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to cream coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The palliative treatment of advanced colorectal cancer where 5-fluorouracil and folinic acid based regimens are either not tolerated or inappropriate.

4.2 Posology and method of administration

Posology

Adults

The dose of raltitrexed is calculated on the basis of the body surface area. The recommended dose is 3 mg/m² given intravenously, as a single short, intravenous infusion in 50 to 250 ml of either 0.9% sodium chloride solution or 5% dextrose (glucose) solution. It is recommended that the infusion is given over a 15 minute period. Other drugs should not be mixed with raltitrexed in the same infusion container. In the absence of toxicity, treatment may be repeated every 3 weeks.

Dose escalation above 3 mg/m² 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/mm³, the neutrophil count greater than 2,000/mm³ and the platelet count greater than 100,000/mm³ 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 completely resolved 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.

Based on the worst grade of gastrointestinal and haematological toxicity observed on the previous treatment and provided that such toxicity has completely resolved, 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.

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. In addition, preclinical data suggest that 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/m² i.v. every 6 hours until the resolution of symptoms. Further use of raltitrexed in such patients is not recommended.

It is essential that the dose reduction scheme should 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.

Elderly population

Dosage and administration as for adults. However, raltitrexed should be used with caution in elderly patients (see section 4.4).

Paediatric population

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

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:

Dose modification in the presence of renal impairment

Creatinine Clearance	Dose as % of 3.0 mg/m²	Dosing Interval
> 65 ml/min	Full dose	3-weekly
55 to 65 ml/min	75%	4-weekly
25 to 54 ml/min	50%	4-weekly
< 25 ml/min	No therapy	Not applicable

See section 4.3 for use in patients with severe renal impairment

Hepatic Impairment

No dosage adjustment is recommended for patients with mild to moderate hepatic impairment. However, given that a proportion of the drug is excreted via the faecal route, (see section 5.2) and that these patients usually form a poor prognosis group, patients with mild to moderate hepatic impairment need to be treated with caution (see section 4.4). Raltitrexed 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.

Method of administration

Each vial, containing 2mg of raltitrexed, should be reconstituted with 4ml of sterile water for injections to produce a 0.5 mg/ml solution.

The appropriate dose of solution 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Raltitrexed should not be used in pregnant women, in women who may become pregnant during treatment or women who are breast feeding. Pregnancy should be excluded before treatment with raltitrexed is commenced. (see section 4.6).

Raltitrexed is contraindicated in patients with severe renal impairment (creatinine clearance < 25ml/min). Administration of leucovorin (folinic acid), folic acid or vitamin preparations containing these agents with raltitrexed is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Raltitrexed must 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 section 4.2).

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

Patients whose disease progressed on previous treatment for advanced disease with 5-fluorouracil based regimens may also be resistant to the effects of raltitrexed.

Elderly patients are more vulnerable to the toxic effects of raltitrexed. Since renal function tends to decline with age and the plasma clearance of raltitrexed is reduced with renal function impairment, there is a potential for accumulation of raltitrexed in elderly patients. Extreme care should be taken to ensure adequate monitoring of adverse reactions especially signs of gastrointestinal toxicity (diarrhoea or mucositis) and myelosuppression (neutropenia, thrombocytopenia, infection) and dose should be reduced and /or delayed as appropriate. A proportion of the raltitrexed is excreted via the faecal route (see section 5.2), therefore patients with mild to moderate hepatic impairment should be treated with caution.

Treatment with raltitrexed in patients with severe hepatic impairment is not recommended.

It is recommended that pregnancy should be avoided during treatment and for at least 6 months after cessation of treatment if either partner is receiving raltitrexed (see section 4.6).

There is no clinical experience with extravasation. However, perivascular tolerance studies in animals did not reveal any significant irritant reaction.

Raltitrexed is a cytotoxic agent and should be handled according to normal procedures adopted for such agents (see section 6.6).

Excipients:
Each vial contains 0.26 mg sodium. This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No specific clinical drug - drug interaction studies have been conducted in man.

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

Clinical trials evaluating the use of raltitrexed in combination with other antitumour therapies are currently ongoing.

Raltitrexed is 93% protein bound and while it has the potential to interact with similarly highly protein bound drugs, no displacement interaction with warfarin has been observed *in vitro*. Data suggest that 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 did not reveal evidence of clinically significant interaction in patients treated with raltitrexed who also received concomitant NSAIDS, warfarin and other commonly prescribed drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy should be avoided if either partner is receiving raltitrexed. It is also recommended that conception should be avoided for at least 6 months after cessation of treatment.

Raltitrexed should not be used during pregnancy or in women who may become pregnant during treatment (see section 5.3). Pregnancy should be excluded before treatment with raltitrexed is started.

Breast-feeding

Raltitrexed should not be given to women who are breast-feeding.

Fertility

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 embryo lethality and foetal abnormalities in pregnant rats.

4.7 Effects on ability to drive and use machines

Raltitrexed may cause malaise or asthenia following infusion and the ability to drive/use machinery could be impaired whilst such symptoms continue.

4.8 Undesirable effects

As with other cytotoxic drugs, raltitrexed may be associated with certain adverse drug reactions. These mainly include reversible effects on the haemopoietic system, liver enzymes and gastrointestinal tract. **Table 1** presents the possible adverse drug reactions occurring with Tomudex treatment.

In this section undesirable effects are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions in patients treated with Tomudex for advanced colorectal carcinoma divided by System Organ Class and frequency

System Organ Class	Frequency	Adverse drug reaction
Infections & infestations	Common	Cellulitis
		Sepsis
		Flu-like syndrome
Blood and lymphatic disorders	Very Common	Leukopenia (neutropenia in particular) [a, b]
		Anaemia [a]
	Common	Thrombocytopenia [a, b]
Metabolism and Nutrition Disorders	Very Common	Anorexia
	Common	Dehydration
Nervous system disorders	Common	Headache
		Hypertonia (usually muscular cramps)
		Taste perversion
Eye disorders	Common	Conjunctivitis
Gastrointestinal disorders	Very Common	Nausea [c]
		Diarrhoea [d,e]
		Vomiting [c,e]
		Constipation
		Abdominal Pain
	Common	Stomatitis
		Dyspepsia
		Mouth ulceration
	Frequency unknown	Gastrointestinal Bleeding [f,g]
Hepato-biliary disorder	Common	Hyperbilirubinemia
Skin & subcutaneous tissue disorders	Very Common	Rash
	Common	Alopecia
		Pruritus
		Sweating
	Uncommon	Desquamation
Musculoskeletal, Connective tissue & bone disorders	Common	Arthralgia
General disorders and administration site conditions	Very Common	Asthenia [h]
		Fever [h]
		Mucositis
	Common	Peripheral oedema
		Pain
		Malaise
Investigations	Very Common	AST increased [i]
		ALT increased [i]
	Common	Weight loss
		Alkaline phosphatase increased

[a] Leukopenia (neutropenia in particular), anaemia and thrombocytopenia, alone or in combination, are usually mild to moderate and occur in the first or second week after treatment and recover by the third week.

[b] Severe (WHO grade 3 and 4) leukopenia (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.

[c] Nausea and Vomiting are usually mild (WHO grade 1 and 2), occur usually in the first week following the administration of Tomudex, and are responsive to antiemetics.

[d] 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 leukopenia (neutropenia in particular). Subsequent treatment may need to be discontinued or dose reduced according to the grade of toxicity (see Section 4.2).

[e] Diarrhoea and vomiting may be severe and if untreated may proceed to dehydration, hypovolaemia and renal impairment

[f] from spontaneous reporting

[g] Gastrointestinal bleeding may be associated with mucositis and/or thrombocytopenia.

[h] Asthenia and fever 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.

[i] Increases in AST and ALT have usually been asymptomatic and self-limiting when not associated with progression of the underlying malignancy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinically proven antidote available. In the case of inadvertent or accidental administration of an overdose, preclinical data suggest that consideration should be given to the administration of leucovorin. From clinical experience with other antifolates leucovorin may be given at a dose of 25mg/m² i.v. every 6 hours. As the time interval between raltitrexed administration and leucovorin rescue increases, its effectiveness in counteracting toxicity may diminish.

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 carefully monitored for signs of gastrointestinal and haematological toxicity. Symptomatic treatment and standard supportive care measures for the management of this toxicity should be applied.

Pharmacode read direction
5171

Package leaflet: Information for the user
Tomudex® 2mg powder for solution for infusion
raltitrexed

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tomudex is and what it is used for

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

What it is used for?

Tomudex is used to treat cancer which affects the colon and rectum (parts of your 'bowel' or gut).

It works by killing cells within your body which cause certain types of cancer. Your doctor will probably explain this to you in more detail.

2. What you need to know before you use Tomudex

Do not use Tomudex:
- if you are allergic to raltitrexed or any of the other ingredients of this medicine (listed in section 6).
- if you have severe kidney disease.
- if you are pregnant, think you might be pregnant, are trying for a baby or you are breast-feeding (see the section on 'Pregnancy and breast-feeding').
- if you are taking leucovorin or folic acid or any vitamins containing these.

Tell your doctor if any of the above applies to you before this medicine is used.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Tomudex:
- if you have any problems with your blood, kidneys or liver.
- if you have had radiotherapy (treatment with high dose X-rays).

Please tell your doctor or nurse if there is a change in your stomach or bowel (gut) problems whilst taking Tomudex.

If you are elderly, your doctor or nurse will monitor you more closely for side effects. Elderly people can be more affected by the side effects of this kind of medicine.

If you have any other treatment for other problems or illnesses, tell your doctor, nurse or pharmacist that you are having Tomudex.
If you are not sure if any of the above apply to you, talk to your doctor, nurse or pharmacist before having Tomudex.

Children

This medicine should not be used in children.

Other medicines and Tomudex

Talk to your doctor, pharmacist or nurse if you are using, have recently used, or might use any other medicines. This includes medicines that you buy without a prescription and herbal medicines. This is because Tomudex can affect the way some medicines work and some medicines can have an effect on Tomudex.

In particular, tell your doctor, pharmacist or nurse if you are using any of the following:
- vitamins or vitamin supplements.
- medicines to thin your blood and stop it clotting (anti-coagulants).

Tomudex with food and drink

There are no special recommendations concerning the use of this medicine with food and drink.

Pregnancy and breast-feeding

Pregnancy
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, you should not use Tomudex. Ask your doctor or pharmacist for advice before using Tomudex.

You should not try for a baby when either partner is using Tomudex, during the treatment or for at least six months after stopping treatment. This is because it may affect your baby.

Breast-feeding
Do not use this medicine if you are breast-feeding.

Driving and using machines
You may feel generally unwell or have flu-like symptoms for a short time after having Tomudex. If this happens, do not drive or use any tools or machines.

Information about the ingredients of Tomudex
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How to use Tomudex

Dosage and method of administration

You will be given this medicine by a doctor or nurse who is a specialist in the use of this type of medicine.

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 doctor. It will depend on your size and how you react to your treatment.

The usual dose is 3 milligrams for each square metre of your body surface area. Your doctor will calculate this from your height and weight.

Your doctor will need to take regular samples of your blood while you are having Tomudex. The results of your blood tests will also help the doctor 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.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine.

Tell your doctor or the hospital straight away if you notice any of the following side effects – you may need urgent medical treatment:
Very common: may affect more than 1 in 10 people
- **Diarrhoea.**
- **Being sick (vomiting).**
- **High temperature (fever) or chills.**
- **Mucositis (inflammation of the mouth and gut lining).**

Common: may affect up to 1 in 10 people
- **Sore throat.**
- **Any infections.**
- **Soreness or ulcers inside your mouth.**

Not known: frequency cannot be estimated from available data
- **Bleeding from the gut.**

Other possible side effects are:

Very common: may affect more than 1 in 10 people:
- Loss of appetite.
- Indigestion.
- Feeling sick (nausea).
- Stomach pain.
- Constipation.
- Weight loss.
- Itchy rash.
- Tomudex may cause changes to your blood. These occur because of effects on your bone marrow and your liver. Your doctor will take regular blood samples to check your blood.

Common: may affect up to 1 in 10 people:
- Painful joints.
- Muscle cramps.
- Swollen hands, ankles or feet.
- Yellow skin and eyes (jaundice).
- 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).

Uncommon: may affect up to 1 in 100 people:
- Red or peeling skin.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tomudex

Keep this medicine out of the sight and reach of children.

Expiry date
Do not use Tomudex after the expiry date which is stated on the vial label and carton. The expiry date refers to the last day of that month.

Storage
This medicine will normally be stored for you by the hospital. The doctor and hospital pharmacist are

2102919

Package leaflet: Information for the user
Tomudex® 2mg powder for solution for infusion
raltitrexed

responsible for storing, using and disposing of Tomudex correctly.

Do not store above 25°C. Keep unopened vials in the outer carton to protect them from light.

6. Contents of the pack and other information

What Tomudex contains
The active substance is raltitrexed. Each vial contains 2mg of raltitrexed.
The other ingredients are mannitol, dibasic sodium phosphate heptahydrate or dodecahydrate and sodium hydroxide.

What Tomudex looks like and the contents of the pack
Tomudex comes in containers of single glass vials containing white to cream coloured powder.

Marketing Authorisation Holder
Hospira UK Limited, Walton Oaks,
Walton-On-The-Hill, Dorking Road, Tadworth,
Surrey, KT20 7NS, UK
Manufacturer
Pfizer Service Company BV
Hermeslaan 11
1932 Zaventem
Belgium

This leaflet was last revised in 11/2025.

Ref gxTM 7_0

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, ATC code: L01BA03.

Raltitrexed is a folate analogue belonging to the family of anti-metabolites and has potent inhibitory activity against the enzyme thymidylate synthase (TS). Compared to other antimetabolites such as 5-fluorouracil or methotrexate, raltitrexed acts as a direct and specific TS inhibitor. TS is a key enzyme in the de novo synthesis of thymidine triphosphate (TTP), a nucleotide required exclusively for deoxyribonucleic acid (DNA) synthesis. Inhibition of TS 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 TS. Raltitrexed polyglutamation enhances TS inhibitory potency and increases the duration of TS inhibition in cells which may improve antitumour activity. Polyglutamation could also contribute to increased toxicity due to drug retention in normal tissues.

In clinical trials, raltitrexed at the dose of 3mg/m^2 i.v. every 3 weeks has demonstrated clinical antitumour activity with an acceptable toxicity profile in patients with advanced colorectal cancer.

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

5.2 Pharmacokinetic properties

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

Summary of mean pharmacokinetic parameters in patients administered 3.0 mg/m^2 Raltitrexed by intravenous infusion

C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	CL (ml/min)	CL_r (ml/min)	V_{ss} (l)	$t_{1/2}\beta$ (h)	$t_{1/2}\gamma$ (h)
656	1856	51.6	25.1	548	1.79	198

Key: **C_{max}:** Peak plasma concentration.
CL: Clearance.
Vss: Volume of distribution at steady state.
t½γ: Terminal half life.
AUC: Area under plasma-concentration time curve.
CLr: Renal clearance
t½β: Half life of the second (β) phase.

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

During repeated administration at three week intervals, there was no clinically significant plasma accumulation of raltitrexed in patients with normal renal function.

Apart from the expected intracellular polyglutamation, raltitrexed was not metabolised and was excreted unchanged, mainly in the urine, 40 - 50%. Raltitrexed was also excreted in the faeces with approximately 15% of the radioactive dose being eliminated over a 10 day period. In the [14C] - raltitrexed trial approximately half of the radiolabel was not recovered during the study period. This suggests that a proportion of the raltitrexed dose is retained within tissues, perhaps as raltitrexed polyglutamates, beyond the end of the measurement period (29 days). 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 to moderate hepatic impairment led to a small 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.

5.3 Preclinical safety data

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

Acute toxicity

The approximate LD_{50} values for the mouse and rat are 875-1249 mg/kg and >500 mg/kg respectively. In the mouse, levels of 750 mg/kg and above caused death by general intoxication.

Chronic 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 the testes. In similar studies in the dog, cumulative dose levels similar to that used clinically, elicited only pharmacologically-related changes to proliferating tissue. Target organs in the dog were therefore similar to the rat.

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.

Reproductive 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 embryo lethality and foetal abnormalities in pregnant rats.

Carcinogenicity

The carcinogenic potential of raltitrexed has not been evaluated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Dibasic sodium phosphate (heptahydrate or dodecahydrate)
Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf-life

Unopened Vial - 3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/ dilution (etc) has taken place in controlled and validated aseptic conditions.

Once reconstituted, Tomudex is chemically stable for 24 hours at 25°C exposed to ambient light. For storage recommendation, see sections 6.4 and 6.6.

6.4 Special precautions for storage

Unopened vial - Do not store above 25°C. Keep container in the outer carton to protect from light.

For storage conditions after reconstitution of the medical product, see section 6.3.

6.5 Nature and contents of container

Clear neutral type I glass vials, with a bromobutyl rubber closure and aluminium crimp seal with a plastic flip-off cover.

The vials are packed in individual cartons to protect the product from light.

6.6 Special precautions for disposal and other handling

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 and it is recommended that solutions of Tomudex should be used as soon as possible. Reconstituted Tomudex solution is for single use only.

In accordance with established guidelines, when diluted in 0.9% sodium chloride or 5% glucose (dextrose) solution, it is recommended that administration of the admixed solution should commence as soon as possible after admixing. 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.

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 e.g. a laminar air flow cabinet, and work surfaces should be covered with disposable plastic-backed absorbent paper.

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

Any spillages should be cleared up using standard procedures.

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

7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Walton Oaks
Walton-On-The-Hill
Dorking Road
Tadworth
Surrey
KT20 7NS
UK

02/2024

GUJ-DRUGS/G/28/1267