

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tomudex 2mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tomudex contains 2 mg raltitrexed in each vial. The reconstituted solution contains 0.5mg/ml raltitrexed, when reconstituted as directed in section 6.6.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion (Powder for Infusion).
A white to cream-coloured solid cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Palliative treatment of advanced colorectal cancer.

Tomudex in combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with inoperable malignant pleural mesothelioma.

4.2 Posology and method of administration

Tomudex must only be administered under the supervision of a physician qualified in the use of anti-cancer therapy.

For instructions on reconstitution and dilution of the product before administration, see section 6.6.

Adults

The dose of Tomudex 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 Tomudex 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.

Tomudex in combination with cisplatin

When used in combination with Tomudex, cisplatin should be administered after each Tomudex infusion. The recommended dose of cisplatin is 80 mg/m² as an intravenous infusion over 1-2 hours. In the event of toxicity, the next scheduled dose should be withheld until signs of toxic effects regress, as with Tomudex. Patients should receive appropriate hydration prior to and after receiving cisplatin and may require anti-emetic therapy. For these and other recommendations about the posology and method of administration of cisplatin, refer to the Summary of Product Characteristics for this medicinal product.

Monitoring

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 $4,000/\text{mm}^3$, the neutrophil count greater than $2,000/\text{mm}^3$ and the platelet count greater than $100,000/\text{mm}^3$ 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 completely resolved before subsequent treatment is allowed. Patients who develop signs of toxicity should have their full blood counts monitored at least weekly for signs of haematological toxicity.

Dose Adjustment

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 for Tomudex 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 with Tomudex 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, antidiarrhoeal agents 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 $25 \text{ mg}/\text{m}^2$ 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 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 patients

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

Paediatric patients

There is no relevant indication for use of Tomudex in children.

The class waiver for medicinal products intended to treat adenocarcinoma of the colon and rectum applies to Tomudex.

Tomudex has been granted a product-specific waiver for the treatment of mesothelioma of the pleura for all subsets of the paediatric population.

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 Dose adjustment in renal impairment

| Dose modification in the presence of renal impairment | | |
|---|----------------------------------|-----------------|
| Creatinine Clearance | Dose as % of 3 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 | 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). 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.

4.3 Contraindications

- Tomudex 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 Tomudex is commenced (see section 4.6).
- Tomudex is contraindicated in patients with severe renal impairment creatinine clearance < 25ml/min) (see section 4.2).
- Administration of leucovorin (folinic acid), folic acid or vitamin preparations containing these agents with Tomudex is contraindicated (see section 4.5).
- Concomitant Yellow Fever vaccine (see section 4.5).

4.4 Special warnings and precautions for use

- Tomudex must only be 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).
- Caution is necessary in patients with depressed bone marrow function, poor general condition, or prior radiotherapy.
- Elderly patients are more vulnerable to the toxic effects of Tomudex. 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 Tomudex 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 Tomudex in patients with severe hepatic impairment is not recommended (see section 4.2).

Pregnancy should be avoided during treatment and for at least 6 months after cessation of treatment if either partner is receiving Tomudex (see also section 4.6).

Immunosuppressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines is not recommended (see section 4.3 and 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.3).

Raltitrexed is mainly eliminated unchanged by the kidneys. Therefore, concomitant administration of nephrotoxic drugs, such as cisplatin, could potentially result in delayed clearance of raltitrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored (see section 4.2).

Data from previous studies suggest that active tubular secretion may contribute to the renal excretion of raltitrexed, suggesting a potential interaction with other drugs secreted actively, such as non-steroidal anti-inflammatory drugs (NSAIDs).

Interactions Common to all Cytotoxics

Due to the increased thrombotic risk in patients with cancer, the use of anticoagulation treatment is frequent. The high intra-individual variability of the coagulation status during diseases and the possibility of interaction between oral anticoagulants and anti-cancer chemotherapy require increased frequency of INR (International Normalised Ratio) monitoring, if it is decided to treat the patient with oral anticoagulants.

Tomudex is 93% protein bound and while it has the potential to interact with similarly high protein bound drugs, no displacement interaction with warfarin has been observed in vitro.

Concomitant Use Contraindicated

Yellow fever vaccine: Risk of fatal generalised vaccinale disease (see section 4.3).

Concomitant Use Not Recommended

Live attenuated vaccines (except yellow fever, for which concomitant use is contraindicated): Risk of systemic, possibly fatal, disease. The risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where it exists (poliomyelitis) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Contraception in Males and Females

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

Pregnancy

Tomudex 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 Tomudex is started.

Breastfeeding

Tomudex should not be given to women who are breastfeeding.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, it has been reported that Tomudex may cause malaise or asthenia following infusion and the ability to drive/use machinery could be impaired whilst such symptoms continue. Therefore patients should be cautioned against driving or operating machines if these events occur.

4.8 Undesirable effects

As with other cytotoxic drugs, Tomudex may be associated with certain adverse drug reactions. These mainly consist of reversible effects on the haemopoietic system, liver enzymes and gastrointestinal tract.

Adverse reactions

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

Tomudex as a single agent in Advanced Colorectal Cancer

Table 2 shows the possible adverse reactions which occur with treatment with Tomudex in advanced colorectal cancer.

Table 2 Tomudex adverse drug reactions by System Organ Class and frequency for advanced colorectal carcinoma

| <u>System Organ Class</u> | <u>Frequency</u> | <u>Adverse drug reaction</u> |
|------------------------------------|------------------|--|
| Infections & infestations | Common | Cellulitis |
| | | Sepsis |
| | | Flu-like syndrome |
| Blood and lymphatic disorders | Very Common | Leucopenia (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} |
| Hepatobiliary 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 Leucopenia (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) 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.

^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 leucopenia (neutropenia in particular). Subsequent treatment may need to be discontinued or dose reduced according to the grade of toxicity (see Section 4.2 Posology and method of administration).

^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.

The treatment emergent adverse events (TEAEs) experienced in patients with malignant pleural mesothelioma treated with Tomudex and cisplatin in a Phase III clinical trial are shown in Table 3¹

Table 3: Treatment emergent adverse events that affected more than 5% patients (and >1 patient) during treatment

| Adverse event, n (%) | Treatment group | |
|--|-------------------------|---------------------------------|
| | Cisplatin alone (n=125) | Tomudex. plus cisplatin (n=125) |
| Nausea | 95 (76.0) | 106 (84.8) |
| Vomiting | 75 (60.0) | 99 (79.2) |
| Fatigue | 74 (59.2) | 85 (68.0) |
| Anorexia | 55 (44.0) | 65 (52.0) |
| Constipation | 52 (41.6) | 64 (51.2) |
| Chest pain (non-cardiac and non-pleuritic) | 29 (23.2) | 25 (20.0) |
| Neuropathy (sensory) | 26 (20.8) | 42 (33.6) |
| Cough | 26 (20.8) | 32 (25.6) |
| Dyspnoea | 25 (20.0) | 27 (21.6) |
| Alopecia | 24 (19.2) | 30 (24.0) |
| Pleuritic pain | 23 (18.4) | 23 (18.4) |
| Fever in absence of neutropenia | 19 (15.2) | 19 (15.2) |
| Tinnitus | 19 (15.2) | 21 (16.8) |
| Headache | 15 (12.0) | 22 (17.6) |
| Sweating | 15 (12.0) | 12 (9.6) |
| Diarrhoea | 13 (10.4) | 22 (17.6) |
| Stomatitis/pharyngitis | 13 (10.4) | 21 (16.8) |
| Infection (without neutropenia) | 13 (10.4) | 15 (12.0) |
| Dizziness/light headedness | 12 (9.6) | 14 (11.2) |
| Arthralgia | 7 (5.6) | 7 (5.6) |
| Weight loss | 7 (5.6) | 7 (5.6) |
| Oedema | 5 (4.0) | 15 (12.0) |
| Rash/desquamation | 5 (4.0) | 7 (5.6) |
| Gastritis | 2 (1.6) | 7 (5.6) |
| Abdominal pain (excluding tumour related) | 2 (1.6) | 7 (5.6) |
| Hearing loss | 1 (0.8) | 7 (5.6) |

¹ A TEAE was defined as either (1) an AE that was not present at baseline and occurred during treatment or (2) an AE that was present at baseline but increased in NCI-CTC Toxicity Grade during treatment. Only those events that affected >5% patients in a single treatment group are shown.

The most common TEAEs across both treatment groups were nausea, vomiting, and fatigue. Anorexia and constipation also affected more than 50% of patients in the Tomudex plus cisplatin group. The proportion of patients affected between treatment groups was similar (within 10% of each other) for most TEAEs. There was a 10% or greater difference between the proportions of patients that experienced vomiting and neuropathy (sensory) between treatment groups. These both affected more patients in the Tomudex. plus cisplatin group.

The majority of TEAEs were Grade 1 or 2 events in all treatment groups across both studies. TEAEs classed as CTC Grade 3 or 4 are presented in Table 4.

Table 4: Treatment emergent adverse events classed as CTC Grade 3 or 4 that affected >1 patient

| Adverse event, n (%) | Treatment group | |
|--|-------------------------|---------------------------------|
| | Cisplatin alone (n=125) | Tomudex. plus cisplatin (n=125) |
| Nausea | 12 (9.6) | 18 (14.4) |
| Dyspnoea | 10 (8.0) | 11 (8.8) |
| Vomiting | 9 (7.2) | 16 (12.8) |
| Fatigue | 7 (5.6) | 15 (12.0) |
| Pleuritic pain | 7 (5.6) | 5 (4.0) |
| Chest pain (non-cardiac and non-pleuritic) | 4 (3.2) | 4 (3.2) |
| Anorexia | 3 (2.4) | 2 (1.6) |
| Thrombosis/embolism | 3 (2.4) | 2 (1.6) |
| Diarrhoea | 0 | 3 (2.4) |
| Infection (without neutropenia) | 2 (1.6) | 1 (0.8) |
| Hypertension | 2 (1.6) | 0 |

The types of Grade 3 or 4 TEAEs reported in both treatment groups were similar, and all had an incidence of <15% in any treatment group. The most frequently occurring TEAEs that were classed at CTC Grade 3 or 4 were nausea, fatigue, vomiting and dyspnoea.

Grade 3 or 4 laboratory anomalies occurred in 5% or more of the patients with neutropenia (16%) and leucopenia (7%).

Table 5: Adverse drug reactions occurring in patients treated with Tomudex in combination with cisplatin for advanced malignant pleural mesothelioma divided by System Organ Class and Frequency

| System Organ Class | Frequency | Adverse Drug Reaction |
|---|-------------|---|
| Infections and infestations | Very common | Infection without neutropenia |
| Blood and lymphatic disorders | Very common | Neutropenia |
| | Common | Leucopenia |
| Metabolism and Nutrition Disorders | Very Common | Anorexia |
| | Common | Dehydration |
| Respiratory, thoracic and mediastinal disorders | Very common | Cough, Dyspnoea, Chest pain (non-cardiac and non-pleuritic), Pleuritic pain |
| Nervous system disorders | Very common | Headache |
| | | Dizziness |
| | | Sensory neuropathy |
| Ear and labyrinth disorders | Very common | Tinnitus |
| | Common | Hearing loss |

| | | |
|---|--------------------|--|
| | | |
| <i>Gastrointestinal disorders</i> | <i>Very Common</i> | <i>Nausea</i> <i>Vomiting</i> <i>Constipation</i> <i>Diarrhoea</i> <i>Stomatitis/pharyngitis</i> |
| | <i>Common</i> | <i>Abdominal pain</i> <i>Gastritis</i> |
| <i>Skin and subcutaneous tissue disorders</i> | <i>Very common</i> | <i>Alopecia</i> |
| | <i>Common</i> | <i>Sweating, rash/desquamation</i> |
| <i>Musculoskeletal and connective tissue disorders</i> | <i>Common</i> | <i>Arthralgia</i> |
| <i>General disorders and administration site conditions</i> | <i>Very common</i> | <i>Fatigue</i> <i>Oedema</i> <i>Fever without neutropenia</i> |
| | <i>Common</i> | <i>Weight loss</i> |

Majority of these adverse drug reactions were Grade 1 or 2. Adverse drug reactions Grade 3 or 4 occurring in 5% of patients or more were: nausea, vomiting, fatigue and dyspnoea.

Laboratory abnormality Grade 3 or 4 occurring in 5% of patients or more were: neutropenia (16%) and leucopenia (7%).

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: <http://www.hpra.ie>
e-mail: medsafety@hpra.ie

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/m^2 i.v. every 6 hours. As the time interval between Tomudex 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: 16.1.3 Antineoplastic drugs and immunomodulators. Cytotoxic agents. Antimetabolites.

ATC code: L01BA03

Raltitrexed is a folate analogue belonging to the family of antimetabolites 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.

Clinical Efficacy

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.

Malignant Pleural Mesothelioma

A phase III clinical trial has compared Tomudex in combination with cisplatin with cisplatin alone in the treatment of patients with malignant pleural mesothelioma who had not previously received chemotherapy. Results showed a statistically significant improvement in overall survival with Tomudex and cisplatin compared with cisplatin alone. Refer to efficacy analysis data in Table 5.

Table 5 Efficacy analysis

| | Treatment Group | |
|---|---|-----------------------------------|
| | Cisplatin alone (n=124) ⁽¹⁾ | Tomudex plus cisplatin (n=126) |
| Overall survival (primary endpoint) | | |
| Number of deaths (%) | 108 (87.1) | 102 (81.0) |
| Survival | | |
| Median (months) (95% CI) | 8.8 (7.8-10.8) | 11.4 (10.1-15.0) |
| 1 year survival | | |
| % (95% CI) | 39.6 (30.9-48.3) | 46.2 (37.4-55.0) |
| P value (2 sided logrank test) | p = 0.0483 | |
| Hazard ratio (95% CI) | 0.76 (0.58-1.00) | |
| Primary endpoint following adjustment for prognostic factors ² | Cisplatin alone (n=114) | Tomudex plus cisplatin (n=111) |
| Overall survival (primary endpoint) | | |
| Number of deaths (%) | 100 (87.8) | 91 (82.0) |
| Survival | | |
| Median (months) (95% CI) | 8.8 (7.3-10.7) | 11.0 (8.5-13.9) |
| 1 year survival | | |
| % (95% CI) | 39.3 (30.2-48.5) | 43.7 (34.4-53.0) |
| P value (2 sided logrank test) | p = 0.0828 | |
| Hazard ratio (95% CI) | 0.78 (0.59-1.03) | |
| Progression free survival (secondary endpoint) | | |
| Number of events | 121 (97.6) | 119 (94.4) |
| (progression/death) (%) | | |
| Progression free survival | | |
| Median (months) (95% CI) | 4.0 (3.0-5.0) | 5.3 (4.6-6.6) |
| 1 year progression free survival (%) | 9.7 (4.4-15.1) | 13.5 (7.4-19.6) |
| (95% CI) | | |
| P value (2 sided logrank test) | p = 0.0581 | |
| Hazard ratio (95% CI) | 0.78 (0.61-1.01) | |
| Median follow-up (months) | | |
| Months (95% CI) | 24.8 (22.4-45.8) | 30.2 (21.0-38.5) |
| Range | (0-45.7) | (0-45.9) |

(1) Excludes a patient who erroneously received only cisplatin rather than the allocated Tomudex and cisplatin.

(2) Prognostic factors included interval since diagnosis, platelet count, haemoglobin difference, disease stage and histological subtype. Note this adjustment was provided as exploratory analysis and not protocol defined.

5.2 Pharmacokinetic properties

Following intravenous administration at 3 mg/m² 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:

Summary of mean pharmacokinetic parameters in patients administered 3 mg/m² Raltitrexed by Intravenous Infusion

| C _{max} (ng/ml) | AUC _{0 - ∞} (ng.h/ml) | CL (ml/min) | CL _r (ml/min) | V _{ss} (l) | t _{1/2} β (h) | t _{1/2} Y (h) |
|-----------------------------|-----------------------------------|----------------|-----------------------------|------------------------|---------------------------|---------------------------|
| 656 | 1856 | 51.6 | 25.1 | 548 | 1.79 | 198 |

- KEY:**
C_{max}: Peak plasma concentration
AUC: Area under plasma concentration-time curve
CL: Clearance
CL_r: Renal clearance
V_{ss}: Volume of distribution at steady state
t_{1/2}β Half-life of the second (β) phase
t_{1/2}Y: Terminal Half-life

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%. It was also excreted in the faeces 15% of the dose 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.

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.

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

5.3 Preclinical safety data

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

Acute toxicity

The approximate LD₅₀ 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, 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

Tomudex was not mutagenic in the Ames test or in supplementary tests using *E. coli* or chinese hamster ovary cells. Tomudex 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, Tomudex is capable of causing chromosome damage in the bone marrow.

Reproductive toxicology

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

Carcinogenicity

The carcinogenic potential of Tomudex has not been evaluated.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Mannitol
Dibasic sodium phosphate
Sodium hydroxide

6.2 Incompatibilities

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

6.3 Shelf life

3 years. After reconstitution, use solution within 24 hours.

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton. Once reconstituted, store at 2 - 8°C and use as soon as possible but within 24 hours.

6.5 Nature and contents of container

Tomudex is packed in 5ml or 10ml clear neutral type I glass vials, with a bromobutyl rubber closure and an aluminium crimp seal with a plastic flip - off cover.

The vials are packed in individual cartons.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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 - 250ml 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 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.

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

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8 MARKETING AUTHORISATION NUMBER

PA 0437/062/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th January 1996

Date of last renewal: 8th January 2006

10 DATE OF REVISION OF THE TEXT

December 2015