ABPI COMPENDIUM OF DATA SHEETS AND SUMMARIES OF PRODUCT CHARACTERISTICS 1998–99

With The Code of Practice for the Pharmaceutical Industry

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THE COMPENDIUM

This is the second edition of the Compendium in which summaries of product characteristics (SPCs) appear. New requirements came into effect in 1995 replacing data sheets with SPCs for new products and those products coming up for licence renewal. There will be a period of about five years during which data sheets will coexist with SPCs and this edition of the Compendium reflects that fact.

Both data sheets and SPCs are prepared by the individual companies concerned and, in consequence, vary somewhat in style, but all follow either the requirements laid down by 'The Medicines (Data Sheet) Regulations 1972' (for data sheets) or the European Commission's Committee for Proprietary Medicinal Products (CPMP) Note for Guidance (for SPCs).

Participation in the Compendium is open to all companies supplying medicinal products intended for use under medical supervision.

Data sheets and SPCs are intended for members of the medical and pharmaceutical professions and are written with them in mind. Any member of the public who reads them should bear in mind the need to take professional advice before making any decision affecting his or her own medication based upon their contents.

DATE OF PREPARATION

The data sheets included in this Compendium were finalised during the third quarter of 1997 and the Compendium itself was published in January 1998. Summaries of product characteristics have individual dates of approval/revision.

REVISED DATA SHEETS/SPCs

Individual participating companies may issue loose leaf data sheets/summaries of product characteristics (SPCs) which supersede those included in this Compendium.

It is advisable to retain any such revised data sheets/SPCs which are received and to indicate that fact on the corresponding data sheets or SPCs in the Compendium.

LEGAL CATEGORY

The following abbreviations are used under the heading 'Legal category' in data sheets and summaries of product characteristics in the Compendium.

GSL A preparation which is included in the General Sale List.

P A pharmacy sale medicine which can be sold only from a retail pharmacy.

POM A prescription only medicine.

CD A preparation controlled by the Misuse of Drugs Act 1971 and Regulations. The CD is followed by (Sch 1), (Sch 2), (Sch 3), (Sch 4) or (Sch 5) depending on the schedule to the Misuse of Drugs Regulations 1985, as amended, in which the preparation is included.

Doctors are reminded that certain of the particulars must be in their own handwriting on prescriptions for preparations coming within Schedule 2 and Schedule 3 (except phenobarbitone) to the Misuse of Drugs Regulations 1985, as amended.

SYMBOLS AND ABBREVIATIONS

An asterisk (*) by the name of a product indicates that the name is a trade mark. The company symbols which appear in certain participants' sections are also trade marks.

An inverted triangle (▼) by the name of a product indicates that that product is newly introduced and there are special requirements as to the reporting of adverse reactions (see page iv).

OP in the 'Package quantities' section of a data sheet indicates that the pack is an 'original pack'.

FURTHER INFORMATION

The regulations which relate to data sheets restrict the scope of the material which may be given under the heading 'Further information' and require insertion of the word 'Nil' in any data sheet where there is no entry under that heading. Companies are, of course, none the less always willing to provide additional information on their products upon request.

Enquiries should be directed to the companies concerned. Addresses and telephone numbers are provided in the Directory of Participants in the coloured section at the end of the Compendium.

nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Beta-adrenoceptor blocking drugs may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-adrenoceptor blocking drug should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-adrenoceptor blocking drug therapy, the introduction of beta-adrenoceptor blocking drugs should be delayed for several days after clonidine administration has stopped.

Digitalis glycosides, in association with beta-adrenoceptor blocking drugs, may increase atrio-ventricular conduction time.

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-adrenoceptor blocking drugs.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

Concomitant use of prostaglandin synthetase inhibiting drugs, e.g. ibuprofen or indomethacin, may decrease the hypotensive effects of beta-adrenoceptor blocking drugs.

Anaesthesia: Caution must be exercised when using anaesthetic agents with Tenormin. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-adrenoceptor blocking drugs with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Pregnancy: Tenormin crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Tenormin in the first trimester and the possibility of foetal injury cannot be excluded. Tenormin has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Tenormin to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of Tenormin in women who are, or may become pregnant, requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-endreoceptor blocking agents, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Lactation: There is significant accumulation of Tenormin in breast milk. Caution should be exercised when Tenormin is administered to a nursing woman.

Effect on ability to drive or operate machinery: The use of Tenormin is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

Undesirable events: Tenormin is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of atenolol.

The following undesired events, listed by body system, have been reported.

Cardiovascular: bradycardia, heart failure deterioration, postural hypotension which may be associated with syncope, cold extremities. In susceptible patients: precipitation of heart block, intermittent claudication, Raynaud's phenomenon.

CNS: confusion, dizziness, headache, mood changes, nightmares, psychoses and hallucinations, sleep disturbances of the type noted with other beta-adrenoceptor blocking drugs.

Gastrointestinal: dry mouth, gastrointestinal disturbances.

Haematological: purpura, thrombocytopenia.

Integumentary: alopecia, dry eyes, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Neurological: paraesthesia.

Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Special senses: visual disturbances.

Others: fatigue, an increase in ANA (antinuclear antibodies) has been observed, however the clinical relevance of this is not clear.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Overdosage: The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

Pharmaceutical precautions Tenormin Injection should be stored below 25°C, protected from light.

Dilutions of Tenormin Injection in Dextrose Injection BP, Sodium Chloride Injection BP, or Sodium Chloride and Dextrose Injection BP may be used.

Legal category POM.

Package quantities 10 ml ampoules in boxes of 10.

Further information - The narrow dose range and early patient response to Tenormin ensure that the effect of the drug in individual patients is quickly demonstrated. Tenormin is fully compatible with diuretics, other hypotensive agents and antianginals (but see *Warnings*). Since it acts preferentially on beta-adrenergic receptors in the heart, Tenormin may, with care, be used successfully in the treatment of patients with respiratory disease who cannot tolerate non selective beta-adrenoceptor blocking drugs.

Product licence number 12818/0074.

TENORMIN® SYRUP

Presentation Tenormin Syrup is a clear, colourless, lemon and lime flavoured syrup containing 0.5% w/v Atenolol PhEur (equivalent to 25 mg/5 ml). The inactive ingredients are citric acid, flavour, methylhydroxybenzoate, propylhydroxybenzoate, saccharin sodium, sodium citrate, sorbitol and water.

Uses

(a) Management of hypertension.
(b) Management of angina.
(c) Management of cardiac arrhythmias.
(d) Myocardial infarction: early intervention in the acute phase.

Mode of action: Tenormin (atenolol) is a beta-adrenoceptor blocking drug which is beta$_1$-selective (i.e. acts preferentially on beta$_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose. Atenolol is without intrinsic sympathomimetic and membrane stabilising activities, and, as with other beta-adrenoceptor blocking drugs, has negative inotropic effects (and is therefore contra-indicated in uncontrolled heart failure). As with other beta-adrenoceptor blocking drugs, its mode of action in the treatment of hypertension is unclear. It is probably the action of Tenormin in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina. It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Tenormin is effective and well tolerated in most ethnic populations although the response may be less in black patients. Tenormin is compatible with diuretics, other antihypertensive agents and antianginal agents (see *Warnings*).

Early intervention with Tenormin in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Tenormin is an additional treatment to standard coronary care.

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40–50%) with peak plasma concentrations occurring 2–4 hours after dosing. Atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Dosage and administration

Adults: Hypertension: Two or four 5 ml spoonfuls daily i.e. 50 mg or 100 mg in patients unable to take 50 mg or 100 mg tablets.

Most patients respond to 100 mg once daily. Some patients, however, will respond to 50 mg given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining Tenormin with other antihypertensive agents.

Angina: Most patients with angina pectoris will respond to 100 mg (four 5 ml spoonfuls) given orally once a day or 50 mg (two 5 ml spoonfuls) given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Arrhythmias: A suitable initial dose of Tenormin injection is 2.5 mg (5 ml) given intravenously over a 2.5 minute period (i.e. 1 mg/minute). (See prescribing information for Tenormin Injection). This may be repeated at 5 minute intervals until a response is observed up to a maximum dosage of 10 mg. If Tenormin injection is given by infusion, 150 micrograms/kg bodyweight may be administered over a 20 minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the arrhythmias, a suitable oral maintenance dosage is 50–100 mg (two to four 5 ml spoonfuls) of Tenormin Syrup daily given as a single dose.

Myocardial infarction: For patients suitable for treatment with intravenous beta-adrenoceptor blockade and presenting within 12 hours of the onset of the chest pain, Tenormin injection 5–10 mg should be given by slow intravenous administration (1 mg/minute) followed by Tenormin Syrup 50 mg (two 5 ml spoonfuls) orally about 15 minutes later provided no untoward effects occur from the intravenous dose. This should be followed by a further 50 mg orally 12 hours after the intravenous dose and then 12 hours later by 100 mg (four 5 ml spoonfuls) orally to be given once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, Tenormin should be discontinued.

Elderly patients: Dosage requirements may be reduced, especially in patients with impaired renal function.

Children: There is no paediatric experience with Tenormin and for this reason it is not recommended for use in children.

Renal failure: Since Tenormin is excreted via the kidneys dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of Tenormin occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m^2 (normal range is 100–150 ml/min/1.73 m^2). For patients with a creatinine clearance of 15–35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300–600 micromol/litre) the oral dose should be 50 mg daily and the intravenous dose should be 10 mg once every two days. For patients with a creatinine clearance of <15 ml/min/1.73 m^2 (equivalent to serum creatinine of >600 micromol/litre) the oral dose should be 25 mg daily or 50 mg on alternate days and the intravenous dose should be 10 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis: this should be done under hospital supervision as marked falls in blood pressure can occur.

Contra-indications, warnings, etc Tenormin as with other beta-adrenoceptor blocking drugs, should not be used in patients with any of the following conditions: known hypersensitivity to the substance, bradycardia, cardiogenic shock, hypotension, metabolic acidosis, severe peripheral arterial circulatory disturbances, second or third degree heart block, sick sinus syndrome, untreated phaeochromocytoma or uncontrolled heart failure.

Tenormin as with other beta-adrenoceptor blocking drugs:

- although contra-indicated in uncontrolled heart failure (see *Contra-indications*), may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Tenormin is a beta$_1$-selective beta-adrenoceptor blocking drug: consequently, its use may be considered although utmost caution must be exercised.
- although contra-indicated in severe peripheral arterial circulatory disturbances (see *Contra-indications*), may also aggravate less severe peripheral arterial circulatory disturbances.
- due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- may modify the tachycardia of hypoglycaemia.
- may mask the signs of thyrotoxicosis.
- will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.
- should not be discontinued abruptly in patients suffering from ischaemic heart disease.
- may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Although cardioselective (beta$_1$) beta-adrenoceptor blocking drugs may have less effect on lung function than non-selective beta-adrenoceptor blocking drugs, as with all beta-adrenoceptor blocking drugs, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, Tenormin may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients, however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

The label and patient information leaflet for this product state the following warning: "If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor".

Caution must be exercised when prescribing a beta-adrenoceptor blocking drug with Class 1 antiarrhythmic agents such as disopyramide.

Combined use of beta-adrenoceptor blocking drugs and calcium channel blockers with negative inotropic effects e.g. verapamil, diltiazem can lead to an exaggeration of these effects, particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-adrenoceptor blocking drug nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Beta-adrenoceptor blocking drugs may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-adrenoceptor blocking drug should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-adrenoceptor blocking drug therapy, the introduction of beta-adrenoceptor blocking drugs should be delayed for several days after clonidine administration has stopped.

Digitalis glycosides, in association with beta-adrenoceptor blocking drug, may increase atrio-ventricular conduction time.

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-adrenoceptor blocking drugs.

Concomitant use with insulin and oral antidebetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

Concomitant use of prostaglandin synthetase inhibiting drugs, e.g. ibuprofen or indomethacin, may decrease the hypotensive effects of beta-adrenoceptor blocking drugs.

Anaesthesia: Caution must be exercised when using anaesthetic agents with Tenormin. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-adrenoceptor blocking drugs with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Pregnancy: Tenormin crosses the placental barrier and appears in the cord blood. No studies have been performed on the use of Tenormin in the first trimester and the possibility of foetal injury cannot be excluded. Tenormin has been used under close supervision for the treatment of hypertension in the third trimester. Administration of Tenormin to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of Tenormin in women who are, or may become pregnant, requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-adrenoceptor blocking agents in general have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, immature and premature deliveries.

Lactation: There is significant accumulation of Tenormin in breast milk. Caution should be exercised when Tenormin is administered to a nursing woman.

Effect on ability to drive or operate machinery: The use of Tenormin is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

Undesirable events: Tenormin is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of atenolol.

The following undesired events, listed by body system, have been reported.

Cardiovascular: bradycardia, heart failure deterioration, postural hypotension which may be associated with syncope, cold extremities. In susceptible patients: precipitation of heart block, intermittent claudication, Raynaud's phenomenon.

CNS: confusion, dizziness, headache, mood changes, nightmares, psychoses and hallucinations, sleep disturbances of the type noted with other beta-adrenoceptor blocking drugs.

Gastrointestinal: dry mouth, gastrointestinal disturbances.

Haematological: purpura, thrombocytopenia.

Integumentary: alopecia, dry eyes, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes.

Neurological: paraesthesia.

Respiratory: bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Special senses: visual disturbances.

Others: fatigue, an increase in ANA (antinuclear antibodies) has been observed, however the clinical relevance of this is not clear.

Discontinuance of the drug should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Overdosage: The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1–2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1–10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

Pharmaceutical precautions Tenormin Syrup should be stored below 25°C, protected from light.

Legal category POM.

Package quantities 300 ml bottle (OP).

Further information Tenormin Syrup is intended for patients unable to swallow Tenormin tablets. Tenormin is effective for at least 24 hours after once daily dosing with 10 ml or 20 ml Tenormin Syrup. Tenormin Syrup facilitates compliance by its acceptability to patients and the once-daily dosing regimen. The narrow dose range and early patient response ensure that the effect of the drug in individual patients is quickly demonstrated. Tenormin is compatible with diuretics, other hypotensive agents and antianginals (but see *Warnings*). Since it acts preferentially on beta-adrenergic receptors in the heart, Tenormin may, with care, be used successfully in the treatment of patients with respiratory disease who cannot tolerate non-selective beta-adrenoceptor blocking drugs.

Product licence number 12819/0075.

TOMUDEX® ▼

Qualitative and quantitative composition Tomudex contains 2 mg raltitrexed in each vial.

Pharmaceutical form Powder for intravenous injection.

Clinical particulars

Therapeutic indications: The palliative treatment of advanced colorectal cancer where 5-fluorouracil and folinic acid based regimens are either not tolerated or is appropriate.

Posology and method of administration

Adults: The dose of Tomudex is calculated on the basis of the body surface area. The recommended dose is 3 mg/m^2 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/m^2 is not recommended, since higher doses have been associated with an increased incidence of life-threatening or fatal toxicity.

Prior to the initiation of treatment and before each subsequent treatment a full blood count (including a differential count and platelets), liver transaminases, serum bilirubin and serum creatinine measurements should be performed. The total white cell count should be greater than 4,000/mm^3, the neutrophil count greater than 2,000/mm^3 and the platelet count greater than 100,000/mm^3 prior to treatment. In the event of toxicity the next scheduled dose should be withheld until signs of toxic effects regress. In particular, signs of gastrointestinal toxicity (diarrhoea or mucositis) and haematological toxicity (neutropenia or thrombocytopenia) should have 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 (neutropaenia 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 pre-clinical data suggest that consideration should be given to the administration of folinic acid. From clinical experience with other antifolates folinic acid 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 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: Dosage and administration as for adults. However, as with other cytotoxics, Tomudex should be used with caution in elderly patients (see *Warnings/Precautions*).

Children: Tomudex 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. 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/m^2*	*Dosing interval*
>65 ml/min	Full dose	3-weekly
25 to 65 ml/min	50%	3-weekly
<25 ml/min	No therapy	Not applicable

See Contra-indications 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 *Pharmacokinetic properties*), and that these patients usually form a poor prognosis group, patients with

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