Metirosine *(BAN, rINN)*

L-588357-0; Metirosiini; Metirosin; Metirosina; Métirosine; Metirosinum; Metyrosine *(USAN)*; MK-781. (–)-α-Methyl-L-tyrosine; 4-Hydroxy-α-methylphenylalanine.

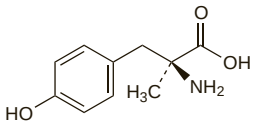
Метирозин

$C_{10}H_{13}NO_3$ = 195.2.

CAS — 672-87-7 (metirosine); 620-30-4 (racemetirosine).

ATC — C02KB01.

ATC Vet — QC02KB01.



NOTE. The term α-methyltyrosine (α-MPT; α-MT; α-methyl-*p*-tyrosine) is used below since although metirosine, the (–)-isomer, is the active form the manufacturers state that some racemate (racemetirosine; (±)-α-methyl-DL-tyrosine) is produced during synthesis but that the material supplied contains mainly (–)-isomer with a small amount of (+)-isomer.

The code name MK-781, applied to earlier investigational material, may have described a racemate or a preparation containing a smaller proportion of (–)-isomer than the product now available commercially.

Potency of the proprietary preparation (*Demser*) is expressed in terms of metirosine.

Pharmacopoeias. In *US*.

Adverse Effects

Sedation occurs in almost all patients receiving α-methyltyrosine. Other adverse effects include extrapyramidal symptoms, such as trismus and frank parkinsonism; anxiety, depression, and psychic disturbances including hallucinations, disorientation, and confusion; and diarrhoea, which may be severe. Crystalluria, transient dysuria, and haematuria have been seen in a few patients. There have also been occasional reports of slight swelling of the breast, galactorrhoea, nasal congestion, decreased salivation, gastrointestinal disturbances, headache, impotence or failure of ejaculation, and hypersensitivity reactions. Eosinophilia, raised serum aspartate aminotransferase, and peripheral oedema have been reported rarely.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome occurred after the use of the dopamine-depleting drugs tetrabenazine and α-methyltyrosine in a patient with Huntington's chorea.[1]

1. Burke RE, *et al*. Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington disease. *Neurology* 1981; **31:** 1022–6.

Precautions

To minimise the risk of crystalluria, patients receiving α-methyltyrosine should have a fluid intake sufficient to maintain a urine volume of at least 2 litres daily and their urine should be examined regularly for the presence of crystals.

α-Methyltyrosine has sedative effects and patients should be warned of the hazards of driving a motor vehicle or operating machinery while receiving the drug. Symptoms of psychic stimulation and insomnia may occur when α-methyltyrosine is withdrawn.

When α-methyltyrosine is used pre-operatively in patients with phaeochromocytoma, blood pressure and the ECG should be monitored continuously during surgery as the danger of hypertensive crises and arrhythmias is not eliminated. Concomitant alpha blockade (e.g. with phentolamine) may be required; a beta blocker or lidocaine may be needed for the management of arrhythmias. Blood volume must be maintained during and after surgery, particularly if an alpha blocker is used, to avoid hypotension.

Interactions

The sedative effects of α-methyltyrosine may be potentiated by alcohol and other CNS depressants. Use with phenothiazines or haloperidol may exacerbate extrapyramidal effects.

Pharmacokinetics

α-Methyltyrosine is well absorbed from the gastrointestinal tract and is excreted mainly unchanged by the kidneys. A plasma half-life of 3.4 to 7.2 hours has been reported. Less than 1% of a dose may be excreted as the metabolites α-methyldopa, α-methyldopamine, α-methylnoradrenaline, and α-methyltyramine.

Uses and Administration

α-Methyltyrosine is an inhibitor of the enzyme tyrosine hydroxylase, and consequently of the synthesis of catecholamines. It is used to control the symptoms of excessive sympathetic stimulation in patients with phaeochromocytoma (p.1179) and decreases the frequency and severity of hypertensive attacks and related symptoms in most patients. It may be given for pre-operative preparation, or for long-term management in those for whom surgery is contra-indicated or who have malignant phaeochromocytoma.

In the management of phaeochromocytoma, α-methyltyrosine is given orally in a dose of 250 mg four times daily, increased daily by 250 mg or 500 mg to a maximum of 4 g daily in divided doses. The optimum dose, achieved by monitoring clinical symptoms and catecholamine excretion, is usually in the range of 2 to 3 g daily and when used pre-operatively it should be given for at least 5 to 7 days before surgery. The use of alpha blockers may also be necessary.

α-Methyltyrosine is not effective in controlling essential hypertension.

α-Methyltyrosine has also been tried in patients with schizophrenia.

Preparations

USP 31: Metyrosine Capsules.

Proprietary Preparations (details are given in Part 3)
USA: Demser.

Metolazone *(BAN, USAN, rINN)* ⊗

Metolatsoni; Metolazon; Metolazona; Métolazone; Metolazonum; SR-720-22. 7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolylquinazoline-6-sulphonamide.

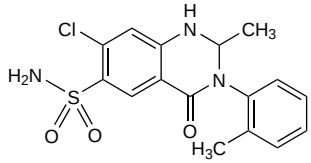
Метолазон

$C_{16}H_{16}ClN_3O_3S$ = 365.8.

CAS — 17560-51-9.

ATC — C03BA08.

ATC Vet — QC03BA08.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Metolazone). A white or slightly yellowish, crystalline powder. It exhibits polymorphism. Very slightly soluble in water and dichloromethane; sparingly soluble in methyl alcohol; slightly soluble in ethyl acetate. Protect from light.

USP 31 (Metolazone). Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Hydrochlorothiazide, p.1307. Metolazone has also been reported to cause palpitations, chest pain, and chills.

Effects on the blood. Profound neutropenia was seen in a 58-year-old woman within 10 days of starting treatment with metolazone.[1] Neutropenia persisted for a further 10 days after metolazone was withdrawn. No other haematological abnormalities were seen.

1. Donovan KL. Neutropenia and metolazone. *BMJ* 1989; **299:** 981.

Effects on the nervous system. Two patients had acute muscle cramps with impairment of consciousness and epileptiform movements after taking metolazone 5 mg (single dose) or 2.5 mg daily for 3 days.[1]

1. Fitzgerald MX, Brennan NJ. Muscle cramps, collapse, and seizures in two patients taking metolazone. *BMJ* 1976; **1:** 1381–2.

Precautions

As for Hydrochlorothiazide, p.1309.

Interactions

As for Hydrochlorothiazide, p.1309. Severe electrolyte disturbances may occur when metolazone and furosemide are used together.

ACE inhibitors. Deterioration in renal function occurred in a 65-year-old woman when metolazone 5 mg [daily] was added to *captopril*, furosemide, spironolactone, and digoxin for heart failure.[1] An interaction between captopril and metolazone was suspected and both drugs were stopped with a subsequent return to normal renal function. It was suggested that natriuresis and a fall in blood pressure caused by the diuretic may have compromised an already low renal perfusion pressure when autoregulatory mechanisms were blocked by captopril.

1. Hogg KJ, Hillis WS. Captopril/metolazone induced renal failure. *Lancet* 1986; **i:** 501–2.

Antidiabetics. Hypoglycaemia occurred in a patient with type 2 diabetes mellitus controlled with *glibenclamide* 40 hours after starting therapy with metolazone 5 mg daily.[1] Studies of protein binding *in vitro* did not reveal any evidence of displacement of glibenclamide from binding sites.

1. George S, *et al*. Possible protein binding displacement interaction between glibenclamide and metolazone. *Eur J Clin Pharmacol* 1990; **38:** 93–5.

Ciclosporin. An increase in serum-creatinine concentration in a renal transplant patient was attributed to a toxic drug interaction between metolazone and ciclosporin.[1] Serum-creatinine concentrations returned to pretreatment values when metolazone was stopped.

1. Christensen P, Leski M. Nephrotoxic drug interaction between metolazone and cyclosporin. *BMJ* 1987; **294:** 578.

Pharmacokinetics

Metolazone is slowly and incompletely absorbed from the gastrointestinal tract. An average of about 65% of a dose has been reported to be absorbed after oral doses in healthy subjects, and an average of about 40% in patients with cardiac disease. In some countries a formulation with enhanced bioavailability is available. About 95% of the drug is bound in the circulation: about 50 to 70% to the red blood cells and between 15 and 33% to plasma proteins. The half-life has been reported to be 8 to 10 hours in whole blood, and 4 to 5 hours in plasma, but the diuretic effect persists for up to 24 hours or more. About 70 to 80% of the amount of metolazone absorbed is excreted in the urine, of which 80 to 95% is excreted unchanged. The remainder is excreted in the bile and some enterohepatic circulation has been reported. Metolazone crosses the placenta and is distributed into breast milk.

◊ References.

1. Tilstone WJ, *et al*. Pharmacokinetics of metolazone in normal subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther* 1974; **16:** 322–9.

Uses and Administration

Metolazone is a diuretic with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1310) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Unlike thiazides in general, metolazone is reported to be effective in patients with a glomerular filtration rate of less than 20 mL/minute. Diuresis starts in about 1 hour, reaches a peak in about 2 hours, and lasts for 12 to 24 hours depending on the dose.

A preparation with enhanced bioavailability, which is effective in lower doses than conventional formulations, is available in some countries. Doses given in *Martindale* refer to the conventional tablet formulation unless otherwise stated.

In the treatment of **oedema** the usual dose is 5 to 10 mg daily; in some cases doses of 20 mg or more may be required. No more than 80 mg should be given in any 24-hour period. In refractory cases, metolazone has been used with furosemide or other loop diuretics, but the electrolyte balance should be monitored closely.

In the treatment of **hypertension** the usual dose is 2.5 to 5 mg daily either alone, or with other antihypertensives. An initial dose of 1.25 mg has also been used. The dosage may be adjusted after 3 to 4 weeks according to response. A maintenance dose of 5 mg on alternate days may be used.

Formulations with enhanced bioavailability are given in doses of 0.5 to 1 mg daily in the treatment of hypertension. They are not bioequivalent to the conventional tablet formulation and should not be used interchangeably.

Preparations

USP 31: Metolazone Oral Suspension; Metolazone Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Zaroxolyn; ***Chile:*** Pavedal; ***Ger.:*** Zaroxolyn†; ***Gr.:*** Metenix; Zaroxolyn†; ***Hong Kong:*** Zaroxolyn; ***India:*** Metoz; ***Israel:*** Zaroxolyn; ***Ital.:*** Zaroxolyn; ***Port.:*** Diulo; ***S.Afr.:*** Zaroxolyn†; ***Switz.:*** Zaroxolyne†; ***UK:*** Metenix; ***USA:*** Mykrox; Zaroxolyn.

Metoprolol *(BAN, USAN, rINN)* ⊗

Métoprolol; Metoprololi; Metoprololum. (±)-1-Isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

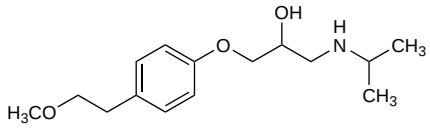
Метопролол

$C_{15}H_{25}NO_3$ = 267.4.

CAS — 54163-88-1; 37350-58-6.

ATC — C07AB02.

ATC Vet — QC07AB02.



Metoprolol Fumarate *(BANM, USAN, rINNM)* ⊗

CGP-2175C; Fumarato de metoprolol; Métoprolol, Fumarate de; Metoprololi Fumaras.

Метопролола Фумарат

$(C_{15}H_{25}NO_3)_2,C_4H_4O_4$ = 650.8.

CAS — 119637-66-0.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *US.*

USP 31 (Metoprolol Fumarate). A 10% solution in water has a pH of between 5.5 and 6.5. Store in airtight containers. Protect from light.

Metoprolol Succinate *(BANM, USAN, rINNM)* ⊗

Métoprolol, succinate de; Metoprolol Süksinat; Metoprololi succinas; Metoprololio sukcinatas; Metoprololisuksinaatti; Metoprololsuccinat; Metoprolol-sukcinát; Metoprolol-szukcinát; Succinato de metoprolol.

Метопролола Суксинат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_4$ = 652.8.

CAS — 98418-47-4.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Metoprolol Succinate). A white or almost white crystalline powder. Freely soluble in water; soluble in methyl alcohol; slightly soluble in alcohol; very slightly soluble in ethyl acetate. A 2% solution in water has a pH of between 7.0 and 7.6. Protect from light.

USP 31 (Metoprolol Succinate). A white to off-white powder. Freely soluble in water; soluble in methyl alcohol; sparingly soluble in alcohol; slightly soluble in isopropyl alcohol. A 6.5% solution in water has a pH of between 7.0 and 7.6. Store in airtight containers at controlled room temperature.

Metoprolol Tartrate *(BANM, USAN, rINNM)* ⊗

CGP-2175E; H-93/26; Metoprolol tartarát; Metoprolol Tartarat; Métoprolol, tartrate de; Metoprololi tartras; Metoprololio tartratas; Metoprololitartraatti; Metoprolol-tartarát; Metoprololtartrat; Tartrato de metoprolol.

Метопролола Тартрат

$(C_{15}H_{25}NO_3)_2,C_4H_6O_6$ = 684.8.

CAS — 56392-17-7.

ATC — C07AB02.

ATC Vet — QC07AB02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US.*

Ph. Eur. 6.2 (Metoprolol Tartrate). A white or almost white crystalline powder or colourless crystals. It exhibits polymorphism. Very soluble in water; freely soluble in alcohol. A 2% solution in water has a pH of between 6.0 and 7.0. Protect from light.

USP 31 (Metoprolol Tartrate). A white crystalline powder. Very soluble in water; freely soluble in alcohol, in chloroform, and in dichloromethane; slightly soluble in acetone; insoluble in ether. A 10% solution in water has a pH of between 6.0 and 7.0. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Stability. Metoprolol tartrate 400 micrograms/mL in glucose 5% or sodium chloride 0.9% was stable for 36 hours when stored at 24° in PVC bags.[1]

1. Belliveau PP, *et al.* Stability of metoprolol tartrate in 5% dextrose injection or 0.9% sodium chloride injection. *Am J Hosp Pharm* 1993; **50:** 950–2.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p.1226.

Breast feeding. Metoprolol is distributed into breast milk and studies[1-3] have shown that the concentration in milk is higher than that in plasma. However, the amount ingested by an infant is likely to be small, and the concentration of metoprolol in infant plasma has been found[3] to be undetectable or very low. No adverse effects have been seen in breast-fed infants whose mothers were given metoprolol and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding.

1. Sandström B, Regårdh C-G. Metoprolol excretion into breast milk. *Br J Clin Pharmacol* 1980; **9:** 518–19.
2. Liedholm H, *et al.* Accumulation of atenolol and metoprolol in human breast milk. *Eur J Clin Pharmacol* 1981; **20:** 229–31.
3. Kulas J, *et al.* Atenolol and metoprolol: a comparison of their excretion into human breast milk. *Acta Obstet Gynecol Scand Suppl* 1984; **118:** 65–9.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Effects on hearing. Loss of hearing in a patient receiving metoprolol appeared to be dose-related;[1] hearing gradually improved over several months once the drug was withdrawn.

1. Fäldt R, *et al.* β Blockers and loss of hearing. *BMJ* 1984; **289:** 1490–2.

Effects on lipid metabolism. Beta blockers may increase serum-triglyceride concentrations. For a report of acute pancreatitis provoked by severe hypertriglyceridaemia in a patient taking atenolol and metoprolol, see p.1227.

Effects on the liver. Acute hepatitis associated with metoprolol has been reported in a 56-year-old woman.[1] The hepatotoxicity could not be explained by deficient oxidation of metoprolol; drug oxidation phenotyping showed she was an extensive metaboliser of debrisoquine and hence metoprolol.

For a discussion of the relationship between polymorphic oxidation of metoprolol and the incidence of adverse effects, see Metabolism, under Pharmacokinetics, below.

1. Larrey D, *et al.* Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. *Ann Intern Med* 1988; **108:** 67–8.

Interactions

The interactions associated with beta blockers are discussed on p.1228.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of metoprolol and that the dose of metoprolol may need to be reduced if used together.

Pharmacokinetics

Metoprolol is readily and completely absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 hours after a single oral dose. It is moderately lipid-soluble.

Metoprolol is widely distributed; it crosses the blood-brain barrier and the placenta, and is distributed into breast milk. It is about 12% bound to plasma protein. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP2D6, and undergoes oxidative deamination, *O*-dealkylation followed by oxidation, and aliphatic hydroxylation. The metabolites are excreted in the urine with only small amounts of unchanged metoprolol. The rate of metabolism by CYP2D6 is determined by genetic polymorphism; the half-life of metoprolol in fast hydroxylators is stated to be 3 to 4 hours, whereas in poor hydroxylators it is about 7 hours.

The elderly. Several studies[1-3] indicate that age-related physiological changes have negligible effects on the pharmacokinetics of metoprolol.

1. Quarterman CP, *et al.* The effect of age on the pharmacokinetics of metoprolol and its metabolites. *Br J Clin Pharmacol* 1981; **11:** 287–94.
2. Regårdh CG, *et al.* Pharmacokinetics of metoprolol and its metabolite α-OH-metoprolol in healthy, non-smoking, elderly individuals. *Eur J Clin Pharmacol* 1983; **24:** 221–6.
3. Larsson M, *et al.* Pharmacokinetics of metoprolol in healthy, elderly, non-smoking individuals after a single dose and two weeks of treatment. *Eur J Clin Pharmacol* 1984; **27:** 217–22.

Metabolism. Metoprolol is metabolised by the cytochrome P450 isoenzyme CYP2D6 and therefore exhibits a debrisoquine-type genetic polymorphism.[1-3] Poor, intermediate, extensive, and ultrarapid metabolisers of metoprolol have been identified, and studies[4-6] have confirmed that plasma-metoprolol concentrations correlate with metaboliser status. However, the clinical relevance of these differences is less clear. A retrospective study[7] found that the proportion of poor metabolisers among patients who had severe adverse effects was higher than expected, but other studies[8,9] have found no correlation between the incidence of adverse effects and metaboliser status. Controlled studies in patients with hypertension[5] and in healthy subjects[4] have found that there is little or no relationship between plasma concentrations or metaboliser status and either the incidence of adverse effects or the response to therapy.

The subject may be further confused by variations in the phenotype between ethnic groups. Although the incidence of the poor metaboliser phenotype in whites of European origin is reported to be about 9%, a study in 138 Nigerians[10] failed to identify evidence of polymorphic metabolism, and the authors caution against extrapolation of data between different racial groups.

1. Lennard MS, *et al.* Defective metabolism of metoprolol in poor hydroxylators of debrisoquine. *Br J Clin Pharmacol* 1982; **14:** 301–3.
2. Lennard MS, *et al.* Oxidation phenotype—a major determinant of metoprolol metabolism and response. *N Engl J Med* 1982; **307:** 1558–60.
3. McGourty JC, *et al.* Metoprolol metabolism and debrisoquine oxidation polymorphism—population and family studies. *Br J Clin Pharmacol* 1985; **20:** 555–66.
4. Kirchheiner J, *et al.* Impact of the ultrarapid metabolizer genotype of cytochrome P450 2D6 on metoprolol pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2004; **76:** 302–12.
5. Zineh I, *et al.* Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. *Clin Pharmacol Ther* 2004; **76:** 536–44.
6. Ismail R, Teh LK. The relevance of CYP2D6 genetic polymorphism on chronic metoprolol therapy in cardiovascular patients. *J Clin Pharm Ther* 2006; **31:** 99–109.
7. Wuttke H, *et al.* Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther* 2002; **72:** 429–37.
8. Clark DWJ, *et al.* Adverse effects from metoprolol are not generally associated with oxidation status. *Br J Clin Pharmacol* 1984; **18:** 965–6.
9. Fux R, *et al.* Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study. *Clin Pharmacol Ther* 2005; **78:** 378–87.
10. Iyun AO, *et al.* Metoprolol and debrisoquin metabolism in Nigerians: lack of evidence for polymorphic oxidation. *Clin Pharmacol Ther* 1986; **40:** 387–94.

Pregnancy. The clearance of metoprolol was increased fourfold in 5 pregnant women during the last trimester, compared with that some months after delivery; this was probably due to enhanced hepatic metabolism in the pregnant state.[1]

The disposition of metoprolol was investigated in neonates of mothers treated with metoprolol 50 to 100 mg twice daily.[2] In 15 of the 17 neonates plasma-metoprolol concentrations increased in the first 2 to 5 hours of the postnatal period, then declined over the next 15 hours; 5 of these infants had no detectable metoprolol concentrations in the umbilical plasma. No infant showed signs of beta blockade.

1. Högstedt S, *et al.* Increased oral clearance of metoprolol in pregnancy. *Eur J Clin Pharmacol* 1983; **24:** 217–20.
2. Lundborg P, *et al.* Disposition of metoprolol in the newborn. *Br J Clin Pharmacol* 1981; **12:** 598–600.

Renal impairment. A single dose of a modified-release tablet of metoprolol produced similar plasma-metoprolol concentrations and values for the area under the concentration/time curve in both normal subjects and those with renal impairment.[1] Mean plasma concentrations of the metabolite α-hydroxymetoprolol were increased two to threefold in subjects with renal impairment compared with normal subjects but such a rise was not considered likely to contribute to beta blockade.

1. Lloyd P, *et al.* The effect of impaired renal function on the pharmacokinetics of metoprolol after single administration of a 14/190 metoprolol OROS system. *Am Heart J* 1990; **120:** 478–82.

Uses and Administration

Metoprolol is a cardioselective beta blocker (p.1225). It is reported to lack intrinsic sympathomimetic activity and to have little or no membrane-stabilising activity.

It is used in the management of hypertension (p.1171), angina pectoris (p.1157), cardiac arrhythmias (p.1160), myocardial infarction (p.1175), and heart failure (p.1165). It is also used in the management of hyperthyroidism (p.2165) and in the prophylactic treatment of migraine (p.616).

Metoprolol is given orally and intravenously as the tartrate. Modified-release tablets usually contain the tartrate or the succinate, but the fumarate has also been used. Doses are usually expressed in terms of the tartrate; 95 mg of metoprolol fumarate or metoprolol succinate is equivalent to about 100 mg of metoprolol tartrate.

The bioavailability of metoprolol is increased if taken with food and it has been recommended that some preparations are taken with or immediately after a meal.

Reduced doses should be given to patients with hepatic impairment.