Antidepressants, particularly MAOIs, should be withdrawn gradually to reduce the risk of withdrawal symptoms.

◊ Reviews.

1. Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev* 2003; **9:** 97–140.

Administration in hepatic impairment. UK licensed drug information states that doses of moclobemide in patients with severe hepatic impairment may need to be reduced to half or one-third of the recommended dose (see above).

Anxiety disorders. The use of MAOIs in general in the management of anxiety disorders is discussed under Phenelzine on p.420. For a discussion of the overall treatment of anxiety disorders, see p.952.

References.

1. Noyes R, *et al.* Moclobemide in social phobia: a controlled dose-response trial. *J Clin Psychopharmacol* 1997; **17:** 247–54.
2. Neal LA, *et al.* An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol* 1997; **12:** 231–7.
3. Schneier FR, *et al.* Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry* 1998; **172:** 70–7.
4. Tiller JW, *et al.* Moclobemide and fluoxetine for panic disorder. *Eur Arch Psychiatry Clin Neurosci* 1999; **249** (suppl 1): S7–S10.
5. Stein DJ, *et al.* Moclobemide is effective and well tolerated in the long-term pharmacotherapy of social anxiety disorder with or without comorbid anxiety disorder. *Int Clin Psychopharmacol* 2002; **17:** 161–70.

Depression. As discussed on p.373 there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effects. The traditional MAOIs such as phenelzine are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide offer a safer alternative to the irreversible non-selective MAOIs and fewer dietary restrictions are necessary.

References.

1. Fitton A, *et al.* Moclobemide: a review of its pharmacological properties and therapeutic use in depressive illness. *Drugs* 1992; **43:** 561–96.
2. Angst J, Stabl M. Efficacy of moclobemide in different patient groups: a meta-analysis of studies. *Psychopharmacology (Berl)* 1992; **106** (suppl): S109–S113.
3. Lonnqvist J, *et al.* Moclobemide and fluoxetine in atypical depression: a double-blind trial. *J Affect Disord* 1994; **32:** 169–77.
4. Norman TR, Burrows GD. A risk-benefit assessment of moclobemide in the treatment of depressive disorders. *Drug Safety* 1995; **12:** 46–54.
5. Roth M, *et al.* Moclobemide in elderly patients with cognitive decline and depression: an international double-blind, placebo-controlled trial. *Br J Psychiatry* 1996; **168:** 149–57.
6. Lotufo-Neto F, *et al.* Meta-analysis of the reversible inhibitors of monoamine oxidase type A moclobemide and brofaromine for the treatment of depression. *Neuropsychopharmacology* 1999; **20:** 226–47.

Smoking cessation. In a preliminary double-blind, placebo-controlled parallel-group study in 88 smokers, moclobemide facilitated smoking cessation (p.2354) in highly dependent smokers.[1]

1. Berlin I, *et al.* A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. *Clin Pharmacol Ther* 1995; **58:** 444–52.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Aurorix†; ***Austral.:*** Amira; Arima; Aurorix; Clobemix; Maosig; Mohexal; ***Austria:*** Aurobemid; Aurorix; ***Belg.:*** Aurorix; ***Braz.:*** Aurorix; ***Canad.:*** Manerix; ***Chile:*** Aurorix; Inpront; ***Cz.:*** Apo-Moclob; Aurorix; ***Denm.:*** Aurorix; Moclostad; ***Fin.:*** Aurorix; ***Fr.:*** Moclamine; ***Ger.:*** Aurorix; Moclix†; Moclobeta; Moclodura; Moclonorm†; ***Gr.:*** Aurorix; ***Hong Kong:*** Aurorix; ***Hung.:*** Aurorix; Maorex; Moclopharm; Mocrim; ***India:*** Rimarex; ***Indon.:*** Aurorix; ***Irl.:*** Manerix; ***Israel:*** Mobemide; ***Malaysia:*** Aurorix; ***Mex.:*** Aurorex; Feraken; ***Neth.:*** Aurorix; ***Norw.:*** Aurorix; ***NZ:*** Aurorix†; ***Philipp.:*** Aurorix; ***Pol.:*** Aurorix; Mobemid; Mocloxil; Moklar; ***Port.:*** Aurorix; ***S.Afr.:*** Aurorix; Clorix; Depnil; ***Singapore:*** Aurorix†; Mobemide; ***Spain:*** Manerix; ***Swed.:*** Aurorix; ***Switz.:*** Aurorix; Moclo A; ***Thai.:*** Aurorix; ***Turk.:*** Aurorix; Lobem; ***UK:*** Manerix.

Nefazodone Hydrochloride *(BANM, USAN, rINNM)*

BMY-13754; Hidrocloruro de nefazodona; MJ-13754-1; Néfazodone, Chlorhydrate de; Nefazodoni Hydrochloridum. 2-{3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl}-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-1,2,4-triazol-3-one monohydrochloride.

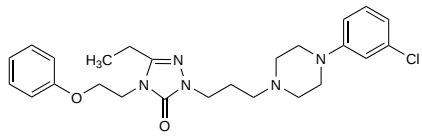
Нефазодона Гидрохлорид

$C_{25}H_{32}ClN_5O_2$,HCl = 506.5.

CAS — 83366-66-9 (nefazodone); 82752-99-6 (nefazodone hydrochloride).

ATC — N06AX06.

ATC Vet — QN06AX06.



(nefazodone)

Pharmacopoeias. In *US.*

USP 31 (Nefazodone Hydrochloride). A non-hygroscopic white powder. Slightly soluble in water and in macrogols; freely soluble in chloroform; soluble in propylene glycol. Store in airtight containers at a temperature between 15° and 30°.

Adverse Effects and Treatment

The most common adverse effects seen with nefazodone are weakness, dry mouth, nausea, constipation, somnolence, dizziness, insomnia, and lightheadedness. Other effects which have occurred less frequently include chills, fever, orthostatic hypotension, incoordination, vasodilatation, arthralgia, paraesthesia, confusion, memory impairment, abnormal dreams, ataxia, and amblyopia and other visual disturbances. Syncope, priapism, and seizures have occurred rarely and there have been reports of sinus bradycardia. Hepatotoxicity has occurred (see below).

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, the symptoms that have been reported most frequently include hypotension, dizziness, nausea, vomiting, and drowsiness. The value of gastric decontamination in the treatment of overdosage is uncertain. Activated charcoal should be considered if more than 1.5 g (in an adult) or 20 mg/kg (in a child) has been taken and treatment is within 1 hour of ingestion. US licensed product information recommends gastric lavage, although this technique is seldom practicable and should not be attempted unless the airway is protected. Supportive therapy should be given as necessary. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

◊ Reviews.

1. Robinson DS, *et al.* The safety profile of nefazodone. *J Clin Psychiatry* 1996; **57** (suppl 2): 31–8.

Effects on the liver. Subfulminant hepatic failure developed in 3 women given nefazodone for depression.[1] Two patients required liver transplantation although this was unsuccessful in one case and the patient died. Hepatitis, positive on rechallenge, has also been reported with nefazodone.[2]

The original US manufacturer (*Bristol-Myers Squibb*) of nefazodone have stated that rare events of raised liver enzymes, hepatitis, hepatic failure and necrosis have been reported since marketing but no causal relationship has been established. In the USA, a reported rate of about 1 case of hepatic failure resulting in death or transplantation per 250 000 to 300 000 patient years of nefazodone treatment has been estimated by the manufacturer; this rate is about 3 to 4 times greater than the background rate of hepatic failure.[3] Onset times for such cases ranged from 2 weeks to 6 months. The Canadian manufacturers have indicated[4] that as of June 2001 there had been 109 reports of serious hepatic adverse events associated with nefazodone from postmarketing surveillance worldwide. These included 23 cases of hepatic failure, of which 16 led to transplantation and/or death. Most cases occurred within 4 months of beginning treatment although a few were after continuous use for up to 2 years. After a review[5] of the data available to December 2002, it was decided to withdraw nefazodone from the Canadian market in November 2003. Subsequently, one manufacturer (*Bristol-Myers Squibb*) withdrew nefazodone worldwide.

1. Aranda-Michel J, *et al.* Nefazodone-induced liver failure: report of three cases. *Ann Intern Med* 1999; **130:** 285–8.
2. Schrader GD, Roberts-Thompson IC. Adverse effect of nefazodone: hepatitis. *Med J Aust* 1999; **170:** 452.
3. Jody DM [Bristol-Myers Squibb]. Important drug warning including black box information. Available at: http://www.fda.gov/medwatch/SAFETY/2002/serzone_deardoc.PDF (accessed 24/11/05)
4. Bristol-Myers Squibb Canada Inc/Linson Pharama Inc. Important safety information on nefazodone HCl: severe and serious hepatic events (issued June 2001). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)
5. Bristol-Myers Squibb Canada. Important safety information regarding the discontinuation of sales of nefazodone in Canada (issued October 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/bms-nefazodone_hpc-cps-eng.pdf (accessed 14/08/08)

Overdosage. A 27-year-old woman developed no serious toxicity after taking 3 g of nefazodone in a suicide attempt.[1] Somnolence was the most severe effect noted. In another case, a 31-year-old woman attempted suicide with 16.8 g of nefazodone and an unknown quantity of verapamil.[2] The patient was lethargic, and developed significant bradycardia and hypotension; she recovered after supportive therapy. The authors reported that among the 7 cases of overdose occurring during clinical trials, there were no fatalities or permanent sequelae.

In a review of 1338 cases of nefazodone-only overdoses reported to the American Association of Poison Control Centres over a 2-year period, it was found that the majority of cases were either asymptomatic or mild in nature with symptoms such as nausea, vomiting, dizziness, and drowsiness.[3] More severe symptoms were noted in only 2 patients. In one case, an 11-year-old boy with a history of seizures suffered several seizures after starting nefazodone at a dose of 100 mg twice daily; the other case involved a 47-year-old man who developed premature ventricular contractions, bradycardia, agitation, and hypotension after an intentional overdose of an unknown quantity. No deaths were recorded in any of the cases where the outcome was known.

1. Gaffney PW, *et al.* Nefazodone overdose. *Ann Pharmacother* 1998; **32:** 1249–50.
2. Catalano G, *et al.* Nefazodone overdose: a case report *Clin Neuropharmacol* 1999; **22:** 63–5.
3. Benson BE, *et al.* Toxicities and outcomes associated with nefazodone poisoning: an analysis of 1,338 exposures. *Am J Emerg Med* 2000; **18:** 587–92.

Precautions

Treatment with nefazodone should not generally be started in patients with active hepatic disease or elevated baseline serum transaminases. Patients who develop signs or symptoms of hepatic impairment such as jaundice, anorexia, abdominal pain, elevated transaminase levels, or malaise during treatment should be evaluated for hepatic damage and the drug withdrawn if necessary. Nefazodone is contra-indicated in patients previously withdrawn from the drug because of hepatotoxicity.

Nefazodone should be used with caution in patients with epilepsy, or a history of hypomania or mania. It should also be used with caution in cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (for example recent history of myocardial infarction, unstable heart disease, angina, or ischaemic stroke), and in any condition such as dehydration or hypovolaemia that may predispose patients to hypotension.

Since nefazodone is structurally related to trazodone which is known to have caused priapism (see Effects on Sexual Function, p.425), US licensed product information recommends that any patient developing inappropriate or prolonged penile erections should stop nefazodone immediately.

Patients should be closely monitored during early antidepressant therapy until significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

Nefazodone may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Breast feeding. A study[1] in 2 nursing mothers receiving nefazodone for postpartum depression indicated that nefazodone, but not its major active metabolites, was distributed into breast milk in variable amounts; the quantity present did not seem to be dose-related. The calculated exposure of the two women's offspring was 2.2% and 0.4% of the maternal dose respectively. Another report suggested that even such low exposures might result in clinically significant effects:[2] drowsiness, inability to maintain normal body temperature, and poor feeding were reported in the breast-fed infant of a woman receiving nefazodone. After breast feeding was stopped the symptoms resolved, suggesting an association between the two despite a calculated exposure in the infant of only 0.45% of the maternal dose.

1. Dodd S, *et al.* Nefazodone in the breast milk of nursing mothers: a report of two patients. *J Clin Psychopharmacol* 2000; **20:** 717–18.
2. Yapp P, *et al.* Drowsiness and poor feeding in a breast-fed infant: association with nefazodone and its metabolites. *Ann Pharmacother* 2000; **34:** 1269–72.

Children. US licensed product information considers that the safety and efficacy of nefazodone have not been established for the treatment of depression in adolescents and children. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in these patients (see Effects on Mental State, under Fluoxetine, p.392).

Pregnancy. Licensed drug information states that nefazodone should only be used during pregnancy if the benefits to the mother outweigh the risks to the fetus.

In a multicentre study of 147 women who took either nefazodone or trazodone in at least the first trimester of pregnancy there were 121 live births, 20 spontaneous abortions, 6 therapeutic abortions, and 2 reports of major malformations (Hirschsprung disease and neural tube defect);[1] no still-births were recorded. There were no significant differences in pregnancy outcome in the nefazodone/trazodone group when compared to the 2 control groups (women with depression taking non-teratogenic antidepressants and women taking non-teratogenic drugs). The rate of spontaneous abortions was non-significantly higher in both the antidepressant groups than in the other control group. It was sug-

gested that the rate of major malformations in all 3 groups was not greater than the baseline rate of 1 to 3%.

1. Einarson A, *et al.* A multicentre prospective controlled study to determine the safety of trazodone and nefazodone use during pregnancy. *Can J Psychiatry* 2003; **48:** 106–10.

Interactions

Nefazodone should not be given to patients receiving MAOIs or for at least 14 days after they are stopped; it has also been recommended that any drug liable to provoke a serious reaction (e.g. phenelzine) should not be given within one week of stopping nefazodone therapy. For further details on the combined use of antidepressants, see Antidepressants under Interactions of Phenelzine, p.418.

Orthostatic hypotension can be a problem with nefazodone, and therefore caution is required for any patient also on antihypertensive therapy.

Nefazodone is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 responsible for the metabolism of some benzodiazepines, and consequently it may produce clinically important increases in their plasma concentrations. Use with astemizole, cisapride, pimozide, and terfenadine (which are metabolised by the same isoenzyme) is best avoided because the potential also exists for increased plasma concentrations of these drugs, with the risk of inducing ventricular arrhythmias. Other substrates for this isoenzyme may also interact with nefazodone: atorvastatin, lovastatin, and simvastatin should be used with caution with nefazodone since there have been rare reports of rhabdomyolysis with such combinations. Increased serum concentrations of ciclosporin or tacrolimus, both substrates for CYP3A4, have been reported in patients also receiving nefazodone. Monitoring of serum ciclosporin or tacrolimus levels is recommended when either of these two drugs is given with nefazodone.

Plasma concentrations of digoxin are increased by nefazodone, and because of digoxin's narrow therapeutic index, plasma concentrations of digoxin should be monitored if use with nefazodone is necessary.

Caution should be exercised when haloperidol is given with nefazodone as the clearance of haloperidol may be reduced. Plasma concentrations of carbamazepine are also increased when used with nefazodone. More importantly, carbamazepine may reduce nefazodone plasma concentrations to subtherapeutic levels and therefore use together is not recommended. Giving buspirone with nefazodone significantly increases the serum concentrations of buspirone; the manufacturers of nefazodone recommend that the initial dose of buspirone is reduced if these drugs are given together.

The potential for interaction between nefazodone and general anaesthetics exists and the manufacturer recommends that nefazodone should be stopped before elective surgery for as long as clinically feasible.

Benzodiazepines. For further details of interactions between nefazodone and benzodiazepines, see Diazepam, p.990.

Pharmacokinetics

Nefazodone is readily absorbed from the gastrointestinal tract and peak plasma concentrations have been obtained within about 2 hours after oral doses. Absorption is delayed and reduced by food but this is not considered to be clinically significant. Nefazodone undergoes extensive first-pass metabolism and is more than 99% bound to plasma proteins; it is widely distributed. It is extensively metabolised by *N*-dealkylation and hydroxylation in the liver to several metabolites, two of which, hydroxynefazodone and *m*-chlorophenylpiperazine, are known to be pharmacologically active. Excretion is mainly as metabolites via the urine (about 55%) and the faeces (20 to 30%). The plasma elimination half-life is 2 to 4 hours. Pharmacokinetic parameters are reported to be non-linear with increasing doses. Nefazodone is distributed in small amounts into breast milk (see Breast Feeding, above).

◊ Reviews.

1. Greene DS, Barbhaiya RH. Clinical pharmacokinetics of nefazodone. *Clin Pharmacokinet* 1997; **33:** 260–75.

Uses and Administration

Nefazodone is a phenylpiperazine antidepressant structurally related to trazodone (see p.424). It blocks the reuptake of serotonin at presynaptic neurones and is an antagonist at postsynaptic 5-HT_2 receptors. Unlike trazodone, nefazodone inhibits the reuptake of noradrenaline. It blocks α_1-adrenoceptors but has no apparent effect on dopamine receptors. Nefazodone does not appear to have very significant antimuscarinic properties compared with tricyclic antidepressants.

Nefazodone hydrochloride has been given for the treatment of depression. One manufacturer (*Bristol-Myers Squibb*) has withdrawn nefazodone worldwide (see also Effects on the Liver, above); however, nefazodone remains available in the USA, and possibly some other countries, as a generic preparation. The usual initial oral dose is 100 mg twice daily increased if necessary, in increments of 100 to 200 mg at intervals of at least a week, to a maximum of 300 mg twice daily. Doses are restricted in elderly patients: a recommended initial dose is 50 mg twice daily.

Antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Nefazodone has been tried in anxiety disorders, but other drugs may now be preferred.

Preparations

USP 31: Nefazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Deprefax†; ***Austral.:*** Serzone†; ***Braz.:*** Serzone†; ***Cz.:*** Serzone†; ***Gr.:*** Nefirel†; ***Hong Kong:*** Serzone†; ***Israel:*** Serzonil†; ***Mex.:*** Serzone†; ***NZ:*** Serzone†; ***S.Afr.:*** Serzone†; ***Singapore:*** Serzone†; ***USA:*** Serzone†.

Nortriptyline Hydrochloride

(BANM, USAN, rINNM)

38489; Hidrocloruro de nortriptilina; Nortriptilin-hidroklorid; Nortriptilino hidrochloridas; Nortriptyliinihydrokloridi; Nortriptyline, chlorhydrate de; Nortriptylin-hydrochlorid; Nortriptylinhydroklorid; Nortriptylini hydrochloridum; Nortryptyliny chlorowodorek. 3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene) propyl(methyl)amine hydrochloride.

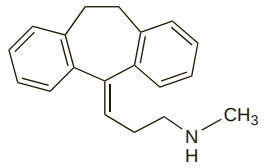
Нортриптилина Гидрохлорид

$C_{19}H_{21}N,HCl$ = 299.8.

CAS — 72-69-5 (nortriptyline); 894-71-3 (nortriptyline hydrochloride).

ATC — N06AA10.

ATC Vet — QN06AA10.



(nortriptyline)

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

Ph. Eur. 6.2 (Nortriptyline Hydrochloride). A white or almost white powder. Sparingly soluble in water; soluble in alcohol and in dichloromethane. Protect from light.

USP 31 (Nortriptyline Hydrochloride). A white to off-white powder having a slight characteristic odour. Soluble 1 in 90 of water, 1 in 30 of alcohol, 1 in 20 of chloroform, and 1 in 10 of methyl alcohol; practically insoluble in ether, in benzene, and in most other organic solvents. pH of a 1% solution in water is about 5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on ventilation. Severe hyperventilation developed in a 61-year-old man with end-stage renal disease after receiving nortriptyline 125 mg daily;[1] mechanical ventilation was necessary to correct severe respiratory alkalosis.

1. Sunderrajan S, *et al.* Nortriptyline-induced severe hyperventilation. *Arch Intern Med* 1985; **145:** 746–7.

Porphyria. Nortriptyline is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Nortriptyline is the principal active metabolite of amitriptyline (p.381). Nortriptyline has been reported to have a longer plasma half-life than amitriptyline. Nortriptyline is subject to extensive first-pass metabolism in the liver to 10-hydroxynortriptyline, which is active.

Metabolism. Individuals with a poor debrisoquine hydroxylation phenotype may be at greater risk of confusional states when taking nortriptyline.[1] This was thought to be because the polymorphic hydroxylation of debrisoquine and nortriptyline are mediated by similar enzymatic mechanisms [the cytochrome P450 isoenzyme CYP2D6], with poor oxidisers having higher plasma nortriptyline concentrations.[2,3] A nonlinear (dose-dependent) relationship between dose and plasma-nortriptyline concentrations has been observed during therapeutic drug monitoring[4] in subjects who were considered to be extensive metabolisers of debrisoquine; nonlinearity did not appear to occur in poor metabolisers. There was no significant correlation between hydroxylation phenotype and amitriptyline concentrations, suggesting that demethylation and hydroxylation of tricyclic antidepressants are mediated by different cytochrome P450 isoenzymes.[5]

The pharmacokinetics and pharmacological actions of 10-hydroxynortriptyline, the major active metabolite of nortriptyline, have been reviewed.[3]

1. Park BK, Kitteringham NR. Adverse reactions and drug metabolism. *Adverse Drug React Bull* 1987; **122:** 456–9.
2. Nordin C, *et al.* Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients—relationship to the debrisoquine hydroxylation metabolic ratio. *Br J Clin Pharmacol* 1985; **19:** 832–5.
3. Nordin C, Bertilsson L. Active hydroxymetabolites of antidepressants: emphasis on E-10-hydroxy-nortriptyline. *Clin Pharmacokinet* 1995; **28:** 26–40.
4. Jerling M, Alván G. Nonlinear kinetics of nortriptyline in relation to nortriptyline clearance as observed during therapeutic drug monitoring. *Eur J Clin Pharmacol* 1994; **46:** 67–70.
5. Bertilsson L, *et al.* Metabolism of various drugs in subjects with different debrisoquine and sparteine oxidation phenotypes. *Br J Clin Pharmacol* 1982; **14:** 602P.

Therapeutic plasma concentrations. Nortriptyline appears to have an optimum antidepressant effect at plasma concentrations between 50 and 150 nanograms/mL. Outside this range, there is a poor clinical response. Plasma concentration measurements are unequivocally useful in problem patients who do not respond to usual oral doses or in high-risk patients for whom, because of age or medical illness, it is especially important to use the lowest possible effective dose of the drug.[1]

It has been suggested[2] that within this window of total nortriptyline concentrations there is a probability of an antidepressant response of 68% or more with free concentrations of 7 to 10 nanograms/mL.

For reference to dose-dependent kinetics of nortriptyline observed in individuals with an extensive debrisoquine hydroxylation phenotype, see under Metabolism, above.

1. Task Force on the Use of Laboratory Tests in Psychiatry. Tricyclic antidepressants—blood level measurements and clinical outcome: an APA task force report. *Am J Psychiatry* 1985; **142:** 155–62.
2. Perry PJ, *et al.* The relationship of free nortriptyline levels to antidepressant response. *Drug Intell Clin Pharm* 1984; **18:** 510.

Uses and Administration

Nortriptyline is a dibenzocycloheptadiene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is the principal active metabolite of amitriptyline. Nortriptyline is one of the less sedating tricyclics and its antimuscarinic effects are mild.

Nortriptyline is given orally as the hydrochloride although doses are expressed in terms of the base; nortriptyline hydrochloride 113.8 mg is equivalent to about 100 mg of nortriptyline. In the treatment of **depression** a low starting dose is given gradually increasing to the equivalent of 75 to 100 mg daily in 3 or 4 divided doses. Up to a maximum of 150 mg daily may be required in patients with severe depression. Licensed drug information recommends that plasma concentrations of nortriptyline should be monitored when doses above 100 mg daily are given; however, the *BNF* considers that the evidence of any practical value is uncertain. Adolescents and the elderly may be given 30 to 50 mg daily in divided doses. Since nortriptyline has a prolonged half-life, once-daily dosage regimens are also suitable, usually given at night.

Nortriptyline is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Suggested doses are:

- 10 mg for children aged 6 to 7 years (20 to 25 kg)
- 10 to 20 mg for children aged 8 to 11 years (25 to 35 kg)
- 25 to 35 mg for children aged over 11 years (35 to 54 kg)

The dose should be given 30 minutes before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Nortriptyline should be withdrawn gradually to reduce the risk of withdrawal symptoms.