Moclobemide *(BAN, USAN, rINN)*

Moclobemida; Moclobémide; Moclobemidum; Moklobemid; Moklobemidi; Ro-11-1163; Ro-11-1163/000. 4-Chloro-*N*-(2-morpholinoethyl)benzamide.

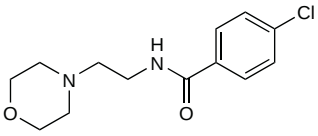
Моклобемид

$C_{13}H_{17}ClN_2O_2$ = 268.7.

CAS — 71320-77-9.

ATC — N06AG02.

ATC Vet — QN06AG02.



Pharmacopoeias. In *Chin.* and *Swiss*.

Adverse Effects

Adverse effects reported to occur with moclobemide include sleep disturbances, dizziness, agitation, feelings of anxiety, restlessness, irritability, and headache. Gastrointestinal disturbances include dry mouth, diarrhoea, constipation, and nausea and vomiting. Paraesthesia, visual disturbances, and oedema have also been reported, and skin reactions include rash, pruritus, urticaria, and flushing. Confusional states have been observed that disappear rapidly on stopping the drug. Raised liver enzymes and galactorrhoea have been reported rarely.

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

Effects on the cardiovascular system. Hypertension has been reported[1,2] rarely in patients taking moclobemide, some of whom were also taking other drugs although moclobemide was suspected to be the cause. Blood pressure usually returned to normal after stopping moclobemide.

1. Coulter DM, Pillans PI. Hypertension with moclobemide. *Lancet* 1995; **346:** 1032.
2. Boyd IW. Hypertension with moclobemide. *Lancet* 1995; **346:** 1498.

Effects on the endocrine system. A prescription-event monitoring study found that galactorrhoea is significantly associated with the use of moclobemide.[1]

1. Dunn NR, *et al.* Galactorrhoea with moclobemide. *Lancet* 1998; **351:** 802.

Effects on the liver. An 85-year-old woman developed intrahepatic cholestasis after taking moclobemide for about 1 week;[1] she had previously been taking fluoxetine and was switched to moclobemide without a washout period. She died 12 days after the onset of jaundice despite prompt moclobemide withdrawal.

1. Timmings P, Lamont D. Intrahepatic cholestasis associated with moclobemide leading to death. *Lancet* 1996; **347:** 762–3.

Overdosage. Several case series[1-3] have suggested that moclobemide is relatively safe when taken alone in overdose; symptoms such as gastrointestinal irritation, agitation, aggression, behavioural disturbances, and tachycardia have been noted. However, fatalities have been reported, particularly when taken with other serotonergic drugs.[3,4]

1. Hetzel W. Safety of moclobemide taken in overdose for attempted suicide. *Psychopharmacology (Berl)* 1992; **106:** S127–S129.
2. Myrenfors PG, *et al.* Moclobemide overdose. *J Intern Med* 1993; **233:** 113–15.
3. Isbister GK, *et al.* Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity. *Br J Clin Pharmacol* 2003; **56:** 441–50.
4. Giroud C, *et al.* Death following acute poisoning by moclobemide. *Forensic Sci Int* 2004; **140:** 101–7.

Precautions

Moclobemide is contra-indicated in patients with acute confusional states and in those with phaeochromocytoma. It should be avoided in excited or agitated patients, unless used with a sedative. Manic episodes may be provoked in patients with bipolar disorder. Care is also required in patients with thyrotoxicosis as moclobemide may theoretically precipitate a hypertensive reaction. Reduced doses should be used in patients with severe hepatic impairment.

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.

Although impairment of mental alertness is generally not expected with moclobemide, caution should be exercised with respect to driving or operating machinery until individual reactions have been assessed.

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

Breast feeding. In a study[1] of the distribution of moclobemide into the breast milk of 6 mothers given a single 300-mg dose of moclobemide, a mean of 0.057% of the dose appeared in breast milk as moclobemide and 0.031% as Ro-12-8095, its major metabolite, within 24 hours of a dose. It was considered that this small amount of moclobemide was unlikely to be hazardous to breast-fed infants. UK licensed drug information advises caution and consideration of the benefits of moclobemide therapy to the mother against possible risks to the infant.

1. Pons G, *et al.* Moclobemide excretion in human breast milk. *Br J Clin Pharmacol* 1990; **29:** 27–31.

Children. Moclobemide has not been adequately studied for the treatment of depression in children and its use is not recommended in UK licensed product information. 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. UK licensed drug information recommends that moclobemide should only be used during pregnancy if the benefits to the mother outweigh any possible risks to the fetus.

A patient who took at least 300 mg daily of moclobemide throughout her pregnancy delivered a healthy, full-term infant after an uncomplicated pregnancy.[1] The infant was monitored from birth, and psychomotor and somatic development for the first 14 months was found to be normal.

1. Rybakowski JK. Moclobemide in pregnancy. *Pharmacopsychiatry* 2001; **34:** 82–3.

Withdrawal. Withdrawal symptoms may occur if an antidepressant such as moclobemide is suddenly stopped after regular use for 8 weeks or more; the *BNF* recommends that the dose should be tapered gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

Despite reducing the dose of moclobemide over 3 days, symptoms such as muscle cramps, shivering, headache, nausea, and hot flushes developed in a 47-year-old woman on the day that moclobemide was completely stopped.[1] The patient had been taking moclobemide for about 15 months.

1. Curtin F, *et al.* Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *J Psychopharmacol* 2002; **16:** 271–2.

Interactions

The dietary restrictions that need to be followed with selective reversible inhibitors of monoamine oxidase type A such as moclobemide are less stringent than those for non-selective inhibitors of monoamine oxidase types A and B (see under Interactions of Phenelzine, p.417). However, UK licensed drug information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

Medicines containing *sympathomimetics*, *dextromethorphan*, or *anorectics* should not be taken with moclobemide. Moclobemide should not be given with *other antidepressants* although, owing to its short duration of action, a treatment-free period is generally considered unnecessary after its cessation. For further details, see Antidepressants under Interactions of Phenelzine, p.418. Therapy with moclobemide should not be started until at least a week after cessation of a tricyclic or related antidepressant or an SSRI or related antidepressant (2 weeks in the case of paroxetine and sertraline; at least 5 weeks in the case of fluoxetine) or for at least a week after stopping treatment with non-selective MAOIs. CNS excitation or depression may occur if moclobemide is taken with *opioid analgesics*, and there is also a risk of CNS toxicity if taken with *serotonin (5-HT$_1$) agonists*. The metabolism of moclobemide is inhibited by *cimetidine*, leading to increased plasma concentrations and a need for reduced dosage (see below).

Antimigraine drugs. For the effects of moclobemide on *serotonin (5-HT$_1$) agonists*, see under Sumatriptan, p.626.

Cimetidine. Cimetidine 1 g daily for 2 weeks increased the mean maximum plasma concentration of moclobemide in 8 healthy subjects from 575 nanograms/mL to 787 nanograms/mL; several other parameters associated with moclobemide absorption and disposition were also affected.[1] It was suggested that a reduction in the dosage of moclobemide might be required. UK licensed drug information for moclobemide recommends reducing its dose by half in patients also receiving cimetidine.

1. Schoerlin M-P, *et al.* Cimetidine alters the disposition kinetics of the monoamine oxidase-A inhibitor moclobemide. *Clin Pharmacol Ther* 1991; **49:** 32–8.

Dopaminergics. Adverse effects including nausea, vomiting, and dizziness were noted in healthy subjects given moclobemide and *levodopa with benserazide*;[1] however, no significant hypertensive reactions were seen.

Caution is also required when *selegiline* and moclobemide are given together.[1] Dietary restrictions with this combination (see under Phenelzine, p.417) are recommended by one manufacturer of selegiline, whereas another advises that this combination should be avoided (as does the manufacturer of moclobemide).

See also under Selegiline, p.817.

1. Dingemanse J. An update of recent moclobemide interaction data. *Int Clin Psychopharmacol* 1993; **7:** 167–80.

Omeprazole. Omeprazole, which is an inhibitor of cytochrome P450 isoenzyme CYP2C19, increased plasma concentrations and elimination half-life of moclobemide in extensive metabolisers of the drug towards values seen in poor metabolisers.[1] It had little effect on pharmacokinetic parameters in poor metabolisers. The clinical effects were uncertain but extra care might be warranted if the 2 drugs are given together.

1. Yu K-S, *et al.* Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. *Clin Pharmacol Ther* 2001; **69:** 266–73.

Opioid analgesics. Symptoms suggestive of a mild serotonin syndrome (p.416) developed in a 73-year-old woman taking moclobemide, nortriptyline, and lithium after she was given *pethidine* intravenously.[1] Licensed drug information recommends that moclobemide should not be given with pethidine.

1. Gillman PK. Possible serotonin syndrome with moclobemide and pethidine. *Med J Aust* 1995; **162:** 554.

Pharmacokinetics

Moclobemide is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring within about 1 hour of ingestion. Absorption is virtually complete but first-pass metabolism reduces bioavailability of the drug. Moclobemide is widely distributed throughout the body and is 50% bound to plasma proteins. It undergoes extensive metabolism in the liver, in part by the cytochrome P450 isoenzymes CYP2C19 and CYP2D6. Metabolites of moclobemide and a small amount of unchanged drug are excreted in the urine. Moclobemide has a plasma elimination half-life of 2 to 4 hours. Moclobemide is distributed into breast milk.

◊ References.

1. Mayersohn M, Guentert TW. Clinical pharmacokinetics of the monoamide oxidase-A inhibitor moclobemide. *Clin Pharmacokinet* 1995; **29:** 292–332.
2. Gram LF, *et al.* Moclobemide: a substrate of CYP2C19 and an inhibitor of CYP2C19, CYP2D6, and CYP1A2: a panel study. *Clin Pharmacol Ther* 1995; **57:** 670–7.

Uses and Administration

Moclobemide, a benzamide derivative, is a reversible inhibitor of monoamine oxidase type A (RIMA) (see under Phenelzine, p.419) used for the treatment of depression and of social anxiety disorder.

In the treatment of **depression** the usual initial oral dose of moclobemide is 300 mg daily in divided doses. This may be increased up to 600 mg daily according to response. In some patients, a maintenance dose of 150 mg daily may be sufficient.

In the treatment of **social anxiety disorder**, the initial daily dose of moclobemide is 300 mg increased after 3 days to 600 mg given in 2 divided doses. Treatment should be continued for 8 to 12 weeks to assess efficacy; patients should be periodically re-evaluated thereafter to determine the need for further treatment.

Moclobemide should be taken after food.

Reduced doses should be given in hepatic impairment (see below) and in patients also taking cimetidine (see above).

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.

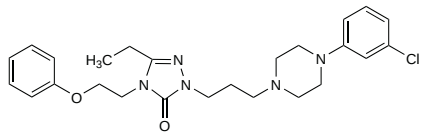
Нефазодона Гидрохлорид

$C_{25}H_{32}ClN_5O_2$,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-