Profile

Tianeptine sodium is an antidepressant reported to act by increasing (rather than inhibiting) the presynaptic reuptake of serotonin. It is given in oral doses of 12.5 mg three times daily in the treatment of depression (p.373). Doses should be reduced to a total of 25 mg daily in elderly patients; for details of dosage in those with renal impairment, see below.

Isolated cases of hepatitis have been reported during treatment with tianeptine.

Abuse. Reports of misuse of tianeptine.[1,2]

1. Leterme L, *et al.* Usage détourné de tianeptine: à propos de cinq cas de surconsommation. *Ann Med Interne (Paris)* 2003; **154:** 2S58–2S63.
2. Kisa C, *et al.* Is it possible to be dependent to tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; **31:** 776–8.

Administration in renal impairment. Licensed product information recommends that oral doses of tianeptine sodium should not exceed a total of 25 mg daily in patients with renal impairment.

Asthma. Tianeptine has been reported to improve symptoms in patients with asthma.[1] It was thought that reduction of raised levels of free serotonin found in such patients contributed to the beneficial effect of tianeptine.

1. Lechin F, *et al.* The serotonin uptake-enhancing drug tianeptine suppresses asthmatic symptoms in children: a double-blind, crossover, placebo-controlled study. *J Clin Pharmacol* 1998; **38:** 918–25.

Depression. References to the use of tianeptine in patients with depression (p.373) are given below.

1. Wilde MI, Benfield P. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* 1995; **49:** 411–39.
2. Ginestet D. Efficacy of tianeptine in major depressive disorders with or without melancholia. *Eur Neuropsychopharmacol* 1997; **7** (suppl 3): S341–S345.
3. Wagstaff AJ, *et al.* Tianeptine: a review of its use in depressive disorders. *CNS Drugs* 2001; **15:** 231–59.
4. Kasper S, Olie JP. A meta-analysis of randomized controlled trials of tianeptine versus SSRI in the short-term treatment of depression. *Eur Psychiatry* 2002; **17** (suppl 3): 331–40.
5. Waintraub L, *et al.* Efficacy and safety of tianeptine in major depression: evidence from a 3-month controlled clinical trial versus paroxetine. *CNS Drugs* 2002; **16:** 65–75.
6. Nickel T, *et al.* Clinical and neurobiological effects of tianeptine and paroxetine in major depression. *J Clin Psychopharmacol* 2003; **23:** 155–68.

Pharmacokinetics. References.

1. Royer RJ, *et al.* Tianeptine and its main metabolite: pharmacokinetics in chronic alcoholism and cirrhosis. *Clin Pharmacokinet* 1989; **16:** 186–91.
2. Carlhant D, *et al.* Pharmacokinetics and bioavailability of tianeptine in the elderly. *Drug Invest* 1990; **2:** 167–72.
3. Demotes-Mainard F, *et al.* Pharmacokinetics of the antidepressant tianeptine at steady state in the elderly. *J Clin Pharmacol* 1991; **31:** 174–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Stablon; ***Austria:*** Stablon; ***Braz.:*** Stablon; ***Cz.:*** Coaxil; ***Fr.:*** Stablon; ***Hung.:*** Coaxil; ***India:*** Stablon; ***Indon.:*** Stablon; ***Malaysia:*** Stablon; ***Mex.:*** Stablon; ***Philipp.:*** Stablon; ***Pol.:*** Coaxil; ***Port.:*** Stablon; ***Rus.:*** Coaxil (Коаксил); ***Singapore:*** Stablon; ***Thai.:*** Stablon; ***Turk.:*** Stablon; ***Venez.:*** Stablon.

Tranylcypromine Sulfate *(rINNM)*

SKF-385; Sulfato de tranilcipromina; Transamine Sulphate; Tranylcypromine, Sulfate de; Tranylcypromine Sulphate *(BANM)*; Tranylcypromini Sulfas. (±)-*trans*-2-Phenylcyclopropylamine sulphate.

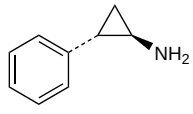
Транилципромина Сульфат

$(C_9H_{11}N)_2,H_2SO_4$ = 364.5.

CAS — 155-09-9 (tranylcypromine); 13492-01-8 (tranylcypromine sulfate).

ATC — N06AF04.

ATC Vet — QN06AF04.



(tranylcypromine)

Pharmacopoeias. In *Br.*
BP 2008 (Tranylcypromine Sulphate). A white or almost white crystalline powder; odourless or with a faint odour of cinnamaldehyde. Soluble in water; very slightly soluble in alcohol and in ether; insoluble in chloroform.

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p.415).

Tranylcypromine has a stimulant action and insomnia is a common adverse effect if it is taken in the evening.

Hypertensive reactions are more likely to occur with tranylcypromine than with other MAOIs, but severe liver damage occurs less frequently.

Dependence. Dependence on tranylcypromine with tolerance has been reported in patients receiving high doses with or without a history of previous substance abuse. For further details, see Withdrawal under Precautions in Phenelzine, p.417.

Effects on the cardiovascular system. Although orthostatic hypotension is more common, hypertension can occur with MAOIs. A hypertensive crisis has been described in 2 patients after only one dose of tranylcypromine.[1,2] In the first case it was thought possible that an autointeraction may have occurred between tranylcypromine and amfetamine to which it is partly metabolised. In the second case the provocation of hypertension led to the finding of a previously undiagnosed phaeochromocytoma and it was suggested this may have been a possibility in previous reports of hypertension induced by MAOIs.

1. Gunn J, *et al.* Hypertensive crisis and broad complex bradycardia after a single dose of monoamine oxidase inhibitor. *BMJ* 1989; **298:** 964.
2. Cook RF, Katritsis D. Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma. *BMJ* 1990; **300:** 614.

Porphyria. Tranylcypromine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Interactions

For interactions associated with MAOIs, see Phenelzine, p.417.

The use of clomipramine with tranylcypromine is particularly hazardous.

Pharmacokinetics

Tranylcypromine is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 1 to 3 hours after ingestion. It is excreted in the urine mainly in the form of metabolites. Tranylcypromine has a reported plasma elimination half-life of about 2.5 hours.

◊ In 9 depressed patients, tranylcypromine absorption was rapid after oral dosing.[1] Absorption was biphasic in 7. Elimination was also rapid, with an elimination half-life of 1.54 to 3.15 hours. From 2 to 7 hours after dosing, standing systolic and diastolic blood pressures were lowered, and standing pulse was raised. The onset of the effect on standing systolic blood pressure correlated with the time of peak plasma tranylcypromine concentration. Maximum orthostatic drop of blood pressure and rise in pulse rate occurred 2 hours after dosing. Mean plasma-tranylcypromine concentrations correlated with mean orthostatic drop of systolic blood pressure and rise of pulse rate. Patients experiencing clinically significant hypotensive reactions to tranylcypromine may benefit from changes in their dose regimen aimed at minimising peak concentrations.

1. Mallinger AG, *et al.* Pharmacokinetics of tranylcypromine in patients who are depressed: relationship to cardiovascular effects. *Clin Pharmacol Ther* 1986; **40:** 444–50.

Uses and Administration

Tranylcypromine, a cyclopropylamine derivative, is an MAOI with actions and uses similar to those of phenelzine (p.419). It produces a less prolonged inhibition of the enzymes than phenelzine.

Tranylcypromine is used in the treatment of depression, but as discussed on p.373 the risks associated with traditional non-selective MAOIs such as tranylcypromine usually mean that other antidepressants are preferred. It is given orally as the sulfate although doses are expressed in terms of the base. Tranylcypromine sulfate 13.7 mg is equivalent to about 10 mg of tranylcypromine.

The usual initial dose is equivalent to tranylcypromine 10 mg in the morning and 10 mg in the afternoon; if the response is inadequate after a week, the afternoon dose may be increased to 20 mg or alternatively, 10 mg may be given additionally at midday. A dosage of 30 mg daily should only be exceeded with caution, although in the USA a maximum dose of 60 mg daily is allowed. Once a satisfactory response has been obtained the dosage may be gradually reduced for maintenance; some patients may continue to respond to 10 mg daily.

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

Preparations

BP 2008: Tranylcypromine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Parnate†; ***Austral.:*** Parnate; ***Braz.:*** Parnate; ***Canad.:*** Parnate; ***Cz.:*** Parnate†; ***Ger.:*** Jatrosom N; ***Irl.:*** Parnate; ***NZ:*** Parnate; ***S.Afr.:*** Parnate; ***Spain:*** Parnate; ***USA:*** Parnate.

Multi-ingredient: ***Arg.:*** Cuait D; Stelapar; ***Braz.:*** Stelapar†; ***Ital.:*** Parmodalin.

Trazodone Hydrochloride

(BANM, USAN, rINNM)

AF-1161; Hidrocloruro de trazodona; Trazodon Hidroklorür; Trazodone, Chlorhydrate de; Trazodoni Hydrochloridum. 2-[3-(4-*m*-Chlorophenylpiperazin-1-yl)propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.

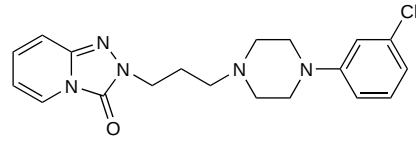
Тразодона Гидрохлорид

$C_{19}H_{22}ClN_5O,HCl$ = 408.3.

CAS — 19794-93-5 (trazodone); 25332-39-2 (trazodone hydrochloride).

ATC — N06AX05.

ATC Vet — QN06AX05.



(trazodone)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of trazodone hydrochloride:
Sleepeasy.

Pharmacopoeias. In *Br.* and *US.*
BP 2008 (Trazodone Hydrochloride). A white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; practically insoluble in ether. A 1% solution in water has a pH of 3.9 to 4.5. Store in airtight containers. Protect from light.
USP 31 (Trazodone Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in chloroform. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

Trazodone has sedative properties although drowsiness usually disappears on continuing treatment. Other adverse effects occasionally reported include dizziness, headache, nausea and vomiting, weakness, weight loss, tremor, dry mouth, bradycardia or tachycardia, orthostatic hypotension, oedema, constipation, diarrhoea, blurred vision, restlessness, confusional states, insomnia, and skin rash. Although some of these effects are typical of antimuscarinic activity it is reported that trazodone has little antimuscarinic activity compared with tricyclic antidepressants. *Animal* studies have also indicated that trazodone is less cardiotoxic than the tricyclics. Priapism has been reported on a number of occasions.

Agranulocytosis, thrombocytopenia, and anaemia have been reported rarely. Adverse effects on hepatic function, including jaundice and hepatocellular damage, which may be severe, have also been reported rarely. There have been occasional reports of serotonin syndrome. Neuroleptic malignant syndrome has occurred rarely.

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

Symptoms of overdosage include drowsiness, dizziness, vomiting, priapism, respiratory arrest, seizures, and ECG changes. The value of gastric decontamination after overdosage is uncertain. However, activated charcoal may be considered in adults who have taken more than 1 g (children more than 150 mg) and present within 1 hour; gastric lavage may also be considered in adults in life-threatening overdoses. Thereafter, symptomatic and supportive therapy should be given as appropriate.

Effects on the cardiovascular system. Although trazodone is considered to cause fewer adverse cardiovascular reactions than the tricyclic antidepressants, they have, nevertheless, been reported in individual patients. In therapeutic doses it has been associated with heart block in a patient with pre-existing cardiovascular disease,[1] as well as in a patient with no ECG abnormalities.[2] Similarly, ventricular arrhythmias have been associated with therapeutic doses of trazodone both in patients with a history of cardiac problems,[3,4] and with no history of cardiac abnor-

malities.[5] Atrial fibrillation has been reported in a patient with ischaemic heart disease.[6]

1. Rausch JL, *et al.* Complete heart block following a single dose of trazodone. *Am J Psychiatry* 1984; **141:** 1472–3.
2. Lippmann S, *et al.* Trazodone cardiotoxicity. *Am J Psychiatry* 1983; **140:** 1383.
3. Janowsky D, *et al.* Ventricular arrhythmias possibly aggravated by trazodone. *Am J Psychiatry* 1983; **140:** 796–7.
4. Vlay SC, Friedling S. Trazodone exacerbation of VT. *Am Heart J* 1983; **106:** 604.
5. Johnson BA. Trazodone toxicity. *Br J Hosp Med* 1985; **33:** 298.
6. White WB, Wong SHY. Rapid atrial fibrillation associated with trazodone hydrochloride. *Arch Gen Psychiatry* 1985; **42:** 424.

Effects on the eyes. A patient receiving clomipramine and trazodone orally noted excessive blinking whenever the dose of trazodone exceeded or equalled that of clomipramine.[1] When trazodone, but not clomipramine, was withdrawn, blinking became normal within 3 weeks.

1. Cooper MA, Dening TR. Excessive blinking associated with combined antidepressants. *BMJ* 1986; **293:** 1243.

Effects on the liver. A mixed hepatocellular-cholestatic liver enzyme pattern has been reported in a patient after about 3 weeks of treatment with trazodone in doses of up to 500 mg daily.[1] The enzyme abnormalities returned to normal 4 weeks after trazodone was stopped but it was suggested that liver enzyme values should be monitored during the first 4 weeks of therapy. A similar case apparently presenting as obstructive jaundice and hepatocellular inflammation, in which the patient had only been receiving 50 mg daily for 2 weeks, has also been described.[2] It was believed that the patient suffered an idiosyncratic drug reaction to trazodone. Further reports of trazodone-induced liver injury include an elderly patient who developed chronic active hepatitis after receiving trazodone 150 mg daily for about 8 months.[3] A case of fatal hepatic necrosis reported in another elderly patient was considered to be due to treatment with trazodone and antipsychotics.[4] The authors of the report[4] noted that up to August 1991 the UK CSM had received 14 reports of adverse effects on the liver associated with trazodone including one episode of fatal hepatic necrosis. In one of 2 later reports of trazodone-induced hepatotoxicity,[5] a female patient with rheumatoid arthritis developed jaundice 18 months after trazodone was added to her existing medications. All drugs were stopped and the patient improved; however, an inadvertent rechallenge with trazodone (without any other medication) led to a recurrence of her symptoms which again resolved following trazodone withdrawal. The second case[6] involved a HIV-positive male who was started on methadone, clonidine, and trazodone as part of a detoxification programme; 4 days later acute hepatitis and cholestasis was noted and trazodone and clonidine were withdrawn with subsequent resolution of symptoms. The authors considered that trazodone was probably the causative agent.

1. Chu AG, *et al.* Trazodone and liver toxicity. *Ann Intern Med* 1983; **99:** 128–9.
2. Sheikh KH, Nies AS. Trazodone and intrahepatic cholestasis. *Ann Intern Med* 1983; **99:** 572.
3. Beck PL, *et al.* Chronic active hepatitis associated with trazodone therapy. *Ann Intern Med* 1993; **118:** 791–2.
4. Hull M, *et al.* Fatal hepatic necrosis associated with trazodone and neuroleptic drugs. *BMJ* 1994; **309:** 378.
5. Fernandes NF, *et al.* Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am J Gastroenterol* 2000; **95:** 532–5.
6. Rettman KS, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother* 2001; **35:** 1559–61.

Effects on mental state. There have been reports of mania,[1,2] and psychosis with hallucinations[3,4] associated with the use of trazodone in depressed patients; delirium[5] in patients with bulimia nervosa and possible psychosis or hypomania[6] in a patient receiving trazodone-tryptophan treatment for aggression have also been reported.

1. Warren M, Bick PA. Two case reports of trazodone-induced mania. *Am J Psychiatry* 1984; **141:** 1103–4.
2. Arana GW, Kaplan GB. Trazodone-induced mania following desipramine-induced mania in major depressive disorders. *Am J Psychiatry* 1985; **142:** 386.
3. Kraft TB. Psychosis following trazodone administration. *Am J Psychiatry* 1983; **140:** 1383–4.
4. Mizoguchi Y, Monji A. Low-dose-trazodone-induced disorganized type psychosis. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 253–4.
5. Damlouji NF, Ferguson JM. Trazodone-induced delirium in bulimic patients. *Am J Psychiatry* 1984; **141:** 434–5.
6. Patterson BD, Srisopark MM. Severe anorexia and possible psychosis or hypomania after trazodone-tryptophan treatment of aggression. *Lancet* 1989; **i:** 1017.

Effects on sexual function. Trazodone is notable for the number of reports of priapism associated with its use.[1,2] In most cases, priapism occurred during treatment with standard doses after 1 to 3 weeks of therapy. Several patients required surgery and recovery was not always complete.[1] A review[3] of priapism induced by psychotropic drugs proposed that the effect was related to blockade of alpha-adrenoceptors in the absence of sufficient antimuscarinic activity, criteria fulfilled by the pharmacological profile of trazodone.

Inhibition of ejaculation,[4] and an increase in libido in women[5] and men[6] have also been reported with trazodone therapy. There have also been reports of trazodone-associated priapism of the clitoris.[7,8]

1. CSM. Priapism and trazodone (Molipaxin). *Current Problems 13* 1984. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024420&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)
2. Anonymous. Priapism with trazodone (Desyrel). *Med Lett Drugs Ther* 1984; **26:** 35.
3. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
4. Jones SD. Ejaculatory inhibition with trazodone. *J Clin Psychopharmacol* 1984; **4:** 279–81.
5. Gartrell N. Increased libido in women receiving trazodone. *Am J Psychiatry* 1986; **143:** 781–2.
6. Sullivan G. Increased libido in three men treated with trazodone. *J Clin Psychiatry* 1988; **49:** 202–3.
7. Pescatori ES, *et al.* Priapism of the clitoris: a case report following trazodone use. *J Urol (Baltimore)* 1993; **149:** 1557–9.
8. Medina CA. Clitoral priapism: a rare condition presenting as a cause of vulvar pain. *Obstet Gynecol* 2002; **100:** 1089–91.

Effects on the skin. Individual reports of adverse dermatological reactions to trazodone have included leucocytoclastic vasculitis,[1] erythema multiforme,[2] and exacerbation of psoriasis.[3]

1. Mann SC, *et al.* Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol* 1984; **10:** 699–70.
2. Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy: case report. *J Clin Psychiatry* 1985; **46:** 294–5.
3. Barth JH, Baker H. Generalized pustular psoriasis precipitated by trazodone in the treatment of depression. *Br J Dermatol* 1986; **115:** 629–30.

Epileptogenic effect. Tonic-clonic seizures related to trazodone therapy have been reported in 2 patients[1,2] with no history of seizure disorders.

1. Bowdan ND. Seizure possibly caused by trazodone hydrochloride. *Am J Psychiatry* 1983; **140:** 642.
2. Lefkowitz D, *et al.* Seizures and trazodone therapy. *Arch Gen Psychiatry* 1985; **42:** 523.

Overdosage. Reviews have indicated that the incidence of serious toxicity from trazodone overdose alone was low compared with tricyclic antidepressant overdose.[1-4]

In a review covering 149 overdose cases,[1] only 10 deaths had been reported and in only 1 case was trazodone the sole agent reported to be ingested; in this case autopsy revealed an acute myocardial infarction after the patient was stable. The remaining 9 patients also had histories of ingestion of unknown quantities of alcohol, benzodiazepines, or other sedative-hypnotics that may have contributed to their demise. In the surviving 139 patients, 2 cases of respiratory arrest, 2 cases of right bundle branch block, and one case each of priapism, seizure, atrioventricular block, and T-wave inversion were reported. The remaining patients had minor CNS-depressant effects.

In a second review[2] of 88 cases of overdose, no fatalities occurred in the 39 cases where trazodone alone was ingested. However 9 deaths occurred in the remaining 49 cases where trazodone was ingested with other drugs or alcohol.

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

1. Hassan E, Miller DD. Toxicity and elimination of trazodone after overdose. *Clin Pharm* 1985; **4:** 97–100.
2. Gamble DE, Peterson LG. Trazodone overdose: four years of experience from voluntary reports. *J Clin Psychiatry* 1986; **47:** 544–6.
3. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.
4. Gallant DM. Antidepressant overdose: symptoms and treatment. *Psychopathology* 1987; **20** (suppl 1): 75–81.

Precautions

Trazodone should be used with caution in patients with cardiovascular disorders, such as ischaemic heart disease, and its use is not recommended in the immediate recovery phase after myocardial infarction. Similarly, it should be used with caution in patients with epilepsy and severe hepatic or renal impairment. Trazodone should be stopped immediately if patients develop signs of hepatic dysfunction or blood dyscrasias. Patients developing inappropriate or prolonged penile erections should also stop trazodone 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.

Drowsiness often occurs at the start of trazodone therapy and patients, if affected, should not drive or operate machinery.

As with other antidepressants, trazodone therapy should be withdrawn gradually.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of trazodone on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antidepressant drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

A study of 6 women each given a single 50-mg dose of trazodone concluded that the exposure of infants to trazodone via breast milk was very small.[2] However, trazodone has been reported to form an active metabolite and it was not known to what extent this metabolite distributed into breast milk.

1. 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 24/11/05)
2. Verbeeck RK, *et al.* Excretion of trazodone in breast milk. *Br J Clin Pharmacol* 1986; **22:** 367–70.

Porphyria. Trazodone hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. UK licensed drug information states that trazodone should be avoided during pregnancy; that for the USA indicates that trazodone should only be used if the benefits to the mother outweigh the risks to the fetus.

For details of outcome in a multicentre study on the use of trazodone during pregnancy, see under Nefazodone, p.412.

Interactions

Trazodone should not be given to patients receiving MAOIs or for at least 14 days afterwards. 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 trazodone therapy. For further details of combination antidepressant therapy, see Antidepressants under Interactions of Phenelzine, p.418.

It is considered unlikely that trazodone will alter the effects of antihypertensives such as guanethidine; some interaction may, however, occur with clonidine. The dose of other antihypertensives may need to be reduced if used with trazodone.

The sedative effects of trazodone may be enhanced by alcohol or other CNS depressants. The potential for interaction between trazodone and general anaesthetics or muscle relaxants exists and some licensed product information recommends that trazodone should be stopped before elective surgery for as long as clinically feasible.

Trazodone may increase plasma concentrations of digoxin or phenytoin and some product information recommends monitoring their serum concentrations if used with trazodone.

Trazodone is metabolised by the cytochrome P450 isoenzyme CYP3A4 and inhibitors of this isoenzyme may limit the elimination of trazodone. Consequently, trazodone may need to be given in reduced doses with drugs known to be potent inhibitors of CYP3A4 such as the azole antifungals itraconazole and ketoconazole, and the HIV-protease inhibitors. CYP3A4 inducers such as carbamazepine may reduce the plasma concentrations of trazodone.

Anticoagulants. For the effect of trazodone on *warfarin*, see p.1428.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

Trazodone may increase plasma concentrations of *carbamazepine* (see p.474) and *phenytoin* (see p.498). Some licensed product information recommends monitoring concentrations of phenytoin if used with trazodone.

Antivirals. In a small study in 10 subjects, the use of low-dose *ritonavir* (200 mg twice daily for 2 days) with trazodone (50 mg once daily) more than halved the clearance of trazodone resulting in significant increases in its peak plasma concentrations.[1] Adverse reactions were noted in 3 subjects and included dizziness, nausea, hypotension, and syncope.

1. Greenblatt DJ, *et al.* Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol* 2003; **43:** 414–22.

Ginkgo biloba. Coma, reversible by flumazenil, developed in an 80-year-old woman with Alzheimer's disease 3 days after starting to take a preparation of ginkgo biloba with trazodone.[1]

1. Galluzzi S, *et al.* Coma in a patient with Alzheimer's disease taking low dose trazodone and gingko biloba. *J Neurol Neurosurg Psychiatry* 2000; **68:** 679–80.

Pharmacokinetics

Trazodone is readily absorbed from the gastrointestinal tract although absorption is affected by food. When trazodone is taken shortly after a meal there may be an increase in the amount absorbed, a decrease in the maximum concentration, and a lengthening in the time to maximum concentration compared with the fasting state; peak plasma concentrations occur about one hour after a dose when taken on an empty stomach and after about 2 hours when taken with food. Protein binding is reported to be about 89 to 95%.

Trazodone is extensively metabolised in the liver and paths of metabolism include *N*-oxidation and hydroxylation. It is metabolised to its active metabolite *m*-chlorophenylpiperazine via the cytochrome P450 isoenzyme CYP3A4. Trazodone is excreted mainly in the urine almost entirely in the form of its metabolites, either in free or in conjugated form: some is excreted in the faeces via biliary elimination. The elimination of trazodone from the plasma is biphasic, with a terminal elimination half-life of 5 to 9 hours.

Small amounts of trazodone are distributed into breast milk.

◊ References.

1. Bayer AJ, *et al*. Pharmacokinetic and pharmacodynamic characteristics of trazodone in the elderly. *Br J Clin Pharmacol* 1983; **16:** 371–6.
2. Nilsen OG, Dale O. Single dose pharmacokinetics of trazodone in healthy subjects. *Pharmacol Toxicol* 1992; **71:** 150–3.
3. Nilsen OG, *et al*. Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. *Pharmacol Toxicol* 1993; **72:** 286–9.

Uses and Administration

Trazodone is a triazolopyridine antidepressant chemically unrelated to other classes of antidepressants. It blocks the reuptake of serotonin at presynaptic neurones and has an action at 5-HT_1 receptors. Trazodone is also an antagonist at 5-$HT_{2A/2C}$ receptors. Unlike the tricyclic antidepressants, trazodone does not inhibit the peripheral reuptake of noradrenaline, although it may indirectly facilitate neuronal release. Trazodone blocks central α_1-adrenoceptors and appears to have no effect on the central reuptake of dopamine. It does not appear to have very significant antimuscarinic properties, but has a marked sedative action.

For the treatment of **depression** trazodone hydrochloride is given in oral doses of 150 mg daily initially; total daily dosage may be increased by 50 mg every 3 or 4 days up to 300 to 400 mg daily if necessary. The daily dosage may be divided throughout the day after food or be given as a single dose at night. Divided daily dosages of up to 600 mg may be given in severe depression in hospitalised patients. A suggested initial dose in elderly and other susceptible patients is 100 mg daily, and total daily doses above 300 mg are unlikely to be needed in these patients.

In the treatment of **anxiety** (p.952), trazodone hydrochloride is given in an initial oral dose of 75 mg daily increasing to 300 mg daily if necessary.

As with other antidepressants, trazodone should be withdrawn gradually.

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 effect profile. Trazodone has a different biochemical profile from both the tricyclics and the SSRIs.

References.

1. Weisler RH, *et al*. Comparison of bupropion and trazodone for the treatment of major depression. *J Clin Psychopharmacol* 1994; **14:** 170–9.

Disturbed behaviour. Trazodone has produced beneficial results[1-3] when tried in various disorders for the control of symptoms such as agitation, aggression, and disruptive behaviour (see p.954). Some[4] also consider that, in the management of dementia, trazodone might be worth trying in nonpsychotic patients with disturbed behaviour, especially those with mild symptoms or those intolerant of or unresponsive to antipsychotics. However, the evidence for such use is poor; a systematic review on the use of trazodone in the treatment of behavioural and psychological symptoms of dementia found that the evidence from randomised, placebo-controlled studies was insufficient for any recommendations to be made.[5] The risk of adverse effects such as sedation and orthostatic hypotension, which may be particularly problematic in the elderly, should also be considered.[4]

1. Pasion RC, Kirby SG. Trazodone for screaming. *Lancet* 1993; **341:** 970.
2. Lebert F, *et al*. Behavioral effects of trazodone in Alzheimer's disease. *J Clin Psychiatry* 1994; **55:** 536–8.
3. Sultzer DL, *et al*. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. *Am J Geriatr Psychiatry* 1997; **5:** 60–9.
4. Rabins PV, *et al*. APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
5. Martinon-Torres G, *et al*. Trazodone for agitation in dementia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 24/11/05).

Sexual dysfunction. Priapism can occur as an adverse effect of trazodone (see Effects on Sexual Function in Adverse Effects, above) and this has led to trials of oral trazodone for the treatment of erectile dysfunction (p.2179). Positive responses have been reported, both with yohimbine[1] and alone.[2] However, there appear to have been few controlled studies and a systematic review[3] considered some of these to be either small, brief, or methodologically weak. Meta-analysis[3] of data from 6 studies did not find trazodone to be superior to placebo but subgroup analysis possibly suggested a better outcome in patients with psychogenic erectile dysfunction and in those given doses of 150 to 200 mg daily.

1. Montorsi F, *et al*. Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study. *Urology* 1994; **44:** 732–6.
2. Lance R, *et al*. Oral trazodone as empirical therapy for erectile dysfunction: a retrospective review. *Urology* 1995; **46:** 117–20.
3. Fink HA, *et al*. Trazodone for erectile dysfunction: a systematic review and meta-analysis. *BJU Int* 2003; **92:** 441–6.

Substance dependence. The antidepressant, anxiolytic, and sedative properties of trazodone have been reported to have been useful when tried in patients having withdrawal syndromes from a variety of substances including alcohol (p.1626),[1] cocaine (p.1860),[2] and benzodiazepines (p.987).[3-5]

1. Le Bon O, *et al*. Double-blind, placebo-controlled study of the efficacy of trazodone in alcohol post-withdrawal syndrome: polysomnographic and clinical evaluations. *J Clin Psychopharmacol* 2003; **23:** 377–83.
2. Small GW, Purcell JJ. Trazodone and cocaine abuse. *Arch Gen Psychiatry* 1985; **42:** 524.
3. Ansseau M, De Roeck J. Trazodone in benzodiazepine dependence. *J Clin Psychiatry* 1993; **54:** 189–91.
4. Rickels K, *et al*. Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology (Berl)* 1999; **141:** 1–5.
5. Petrovic M, *et al*. A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. *Int J Geriatr Psychiatry* 1999; **14:** 754–60.

Preparations

USP 31: Trazodone Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Taxagon; ***Austria:*** Trittico; ***Belg.:*** Nestrolan; Trazolan; ***Braz.:*** Donaren; ***Canad.:*** Desyrel; Trazorel†; ***Chile:*** Diapresan; Trant; Trittico; Tronsalan; ***Cz.:*** Trittico AC; ***Fin.:*** Azona; ***Ger.:*** Thombran; ***Gr.:*** Trittico; ***Hong Kong:*** Trittico; ***Hung.:*** Depsan†; Trittico; ***Irl.:*** Molipaxin; ***Israel:*** Depyrel†; Trazodil; Trittico; ***Ital.:*** Trittico; ***Mex.:*** Sideril; ***Neth.:*** Trazolan; ***Pol.:*** Trittico; ***Port.:*** Trazone; Triticum; ***Rus.:*** Trittico (Триттико); ***S.Afr.:*** Molipaxin; ***Singapore:*** Trittico; ***Spain:*** Deprax; ***Switz.:*** Trittico; ***Thai.:*** Desirel; Trazo; ***Turk.:*** Desyrel; ***UK:*** Molipaxin; ***USA:*** Desyrel†; ***Venez.:*** Trittico.

Trimipramine *(BAN, USAN, rINN)*

IL-6001; 7162-RP; Trimeprimine; Trimipramiini; Trimipramin; Trimipramina; Trimipraminum. Dimethyl{3-(10,11-dihydro-5*H*-dibenz[*b*,*f*]azepin-5-yl-2-methyl)propyl}amine.

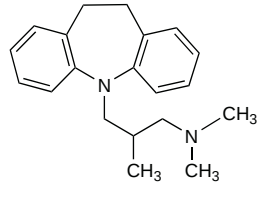
Тримипрамин

$C_{20}H_{26}N_2$ = 294.4.

CAS — 739-71-9.

ATC — N06AA06.

ATC Vet — QN06AA06.



Trimipramine Maleate *(BANM, USAN, rINNM)*

Maleato de trimipramina; Trimipramiinimaleaatti; Trimipramin maleinát; Trimipramine Hydrogen Maleate; Trimipramine, maléate de; Trimipramini maleas; Trimipraminmaleat; Trimipramin-maleát; Trimipramino maleatas.

Тримипрамина Малеат

$C_{20}H_{26}N_2,C_4H_4O_4$ = 410.5.

CAS — 521-78-8.

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

Ph. Eur. 6.2 (Trimipramine Maleate). A white or almost white crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

USP 31 (Trimipramine Maleate). A white to almost white crystalline powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

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

Porphyria. Trimipramine 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

Trimipramine is readily absorbed after oral doses, peak plasma concentrations being obtained in 2 hours. It is metabolised in the liver to its major metabolite desmethyltrimipramine, which is active. Trimipramine is excreted in the urine mainly in the form of its metabolites. It is about 95% bound to plasma proteins. The plasma elimination half-life is reported to be about 23 hours.

◊ References.

1. Maurer H. Metabolism of trimipramine in man. *Arzneimittelforschung* 1989; **39:** 101–3.
2. Musa MN. Nonlinear kinetics of trimipramine in depressed patients. *J Clin Pharmacol* 1989; **29:** 746–7.

Uses and Administration

Trimipramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It has marked antimuscarinic and sedative properties.

Trimipramine is given orally as the maleate although doses are expressed in terms of the base. Trimipramine maleate 34.9 mg is equivalent to about 25 mg of trimipramine. In the treatment of depression, the usual initial dose is the equivalent of trimipramine 50 to 75 mg daily, gradually increased as necessary to 150 to 300 mg daily. The recommended initial dose for the elderly in the UK is 30 to 75 mg daily, gradually increased as necessary. In the USA, the elderly and adolescents may be given 50 mg daily initially followed by gradual increments as necessary up to a maximum of 100 mg daily. Trimipramine may be given in divided doses during the day, but since it has a prolonged half-life, once-daily dosage regimens are also suitable and usually given at night.

Trimipramine has also been given orally as the hydrochloride and the mesilate; the mesilate has also been given intramuscularly.

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

Preparations

BP 2008: Trimipramine Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Surmontil; ***Canad.:*** Apo-Trimip; Novo-Tripramine†; Rhotrimine; Surmontil†; ***Denm.:*** Surmontil; ***Fin.:*** Surmontil; ***Fr.:*** Surmontil; ***Ger.:*** Eldoral†; Herphonal; Stangyl; Trimidura; Trimineurin; ***Hong Kong:*** Surmontil; ***Hung.:*** Sapilent; ***India:*** Surmontil†; ***Irl.:*** Surmontil; ***Israel:*** Surmontil; ***Ital.:*** Surmontil; ***Neth.:*** Surmontil†; ***Norw.:*** Surmontil; ***NZ:*** Surmontil; Tripress; ***Philipp.:*** Surmontil; ***Port.:*** Surmontil; ***S.Afr.:*** Surmontil; Tydamine; ***Spain:*** Surmontil; ***Swed.:*** Surmontil; ***Switz.:*** Surmontil; Trimine; ***UK:*** Surmontil; ***USA:*** Surmontil; ***Venez.:*** Surmontil†.