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.

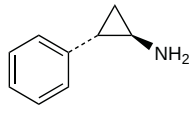
Транилципромина Сульфат

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

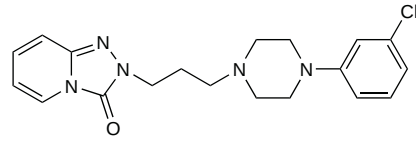
Тразодона Гидрохлорид

$C_{19}H_{22}ClN_5O,HCl$ = 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-