tains not less than 0.08% of total hypericins, expressed as hypericin ($C_{30}H_{16}O_8$ = 504.4) calculated with reference to the dried drug. Protect from light.

**Ph. Eur. 6.2** (Hypericum for Homoeopathic Preparations; Hypericum Perforatum ad Praeparationes Homoeopathicas). The whole, fresh plant of *Hypericum perforatum*, at the beginning of the flowering period. Protect from light.

**USP 31** (St. John's Wort). The dried flowering tops or aerial parts of *Hypericum perforatum* (Hypericaceae), gathered shortly before or during flowering. It contains not less than 0.04% of the combined total of hypericin ($C_{30}H_{16}O_8$ = 504.4) and pseudohypericin ($C_{30}H_{16}O_9$ = 520.4) and not less than 0.6% of hyperforin ($C_{35}H_{52}O_4$ = 536.8). Store in airtight containers. Protect from light.

## Adverse Effects and Precautions

Adverse effects reported with St John's wort have included gastrointestinal symptoms, dizziness, headache, confusion, urinary frequency, allergic reactions, and fatigue. Photosensitivity has also been reported; hypericin and pseudohypericin are the constituents of St John's wort thought to be responsible for this reaction.

**Effects on the nervous system.** Subacute polyneuropathy after sun exposure developed in a woman who had taken St John's wort for mild depression; she improved after drug withdrawal.[1] Seizures and confusion occurred in a 16-year-old girl after an overdose of St John's wort.[2] She had taken large daily doses for 2 weeks and an overdose just before presentation.

1. Bove GM. Acute neuropathy after exposure to sun in a patient treated with St John's Wort. *Lancet* 1998; **352:** 1121–2.
2. Karalapillai DC, Bellomo R. Convulsions associated with an overdose of St John's wort. *Med J Aust* 2007; **186:** 213–14.

**Effects on the skin.** In addition to photosensitivity reactions associated with St John's wort use,[1] there has been a report of severe erythroderma in a patient who supplemented his regular antidepressant medication (dosulepin) with St John's wort.[2] The reaction was seen on both light-exposed and non-exposed areas, and was thought to be due to the St John's wort although there remained a possibility that it was due to an interaction between the 2 drugs.

1. Lane-Brown MM. Photosensitivity associated with herbal preparations of St John's wort (Hypericum perforatum). *Med J Aust* 2000; **172:** 302.
2. Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; **143:** 1127–8.

**Mania.** There have been a number of cases of mania or hypomania associated with the use of St John's wort.[1-3]

1. Neirenberg AA, *et al.* Mania associated with St John's wort. *Biol Psychiatry* 1999; **46:** 1707–8.
2. Fahmi M, *et al.* A case of mania induced by hypericum. *World J Biol Psychiatry* 2002; **3:** 58–9.
3. Stevinson C, Ernst E. Can St John's wort trigger psychoses? *Int J Clin Pharmacol Ther* 2004; **42:** 473–80.

**Withdrawal.** A 58-year-old woman developed symptoms such as nausea, anorexia, dizziness, dry mouth, thirst, chills, and fatigue the day after stopping St John's wort;[1] she had taken the drug for 32 days. The symptoms, which the authors considered suggestive of a withdrawal syndrome, resolved within 8 days.

1. Dean AJ, *et al.* Suspected withdrawal syndrome after cessation of St John's wort. *Ann Pharmacother* 2003; **37:** 150.

## Interactions

St John's wort has been shown to induce several drug metabolising enzymes including some cytochrome P450 isoenzymes (in particular CYP3A4) and the transport protein P-glycoprotein. Clinically important interactions resulting in decreased plasma concentrations of the interacting drug have been reported with ciclosporin, digoxin, HIV-protease inhibitors, NNRTIs, oral contraceptives, tacrolimus, theophylline, and warfarin. There is also a possibility of an interaction between St John's wort and antiepileptics. In addition, stopping St John's wort may result in increased, and possibly toxic, concentrations of the interacting drug.

In many countries, including the UK and USA, preparations of St John's wort are not required to be licensed as medicines, and the amount of active ingredient may vary widely between preparations. Changing preparations may therefore alter the degree of enzyme induction.

Use of St John's wort with drugs known to act on serotonergic neurotransmitters may result in synergistic interactions and an increased risk of adverse effects may also occur. Examples include the SSRIs and nefazodone (see Antidepressants, p.418) and the selective serotonin (5-$HT_1$) agonists (see under Sumatriptan, p.626) used to treat migraine.

◊ References.

1. Roby CA, *et al.* St John's Wort: effect on CYP3A4 activity. *Clin Pharmacol Ther* 2000; **67:** 451–7.
2. CSM/MCA. Reminder: St John's Wort (Hypericum perforatum) interactions. *Current Problems* 2000; **26:** 6–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
3. Dürr D, *et al.* St John's Wort induces intestinal p-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. *Clin Pharmacol Ther* 2000; **68:** 598–604.
4. Wang Z, *et al.* The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001: **70:** 317–26.
5. Hennessy M, *et al.* St John's Wort increases expression of P-glycoprotein: implications for drug interactions. *Br J Clin Pharmacol* 2002 **53:** 75–82.
6. Henderson L, *et al.* St John's wort (*Hypericum perforatum*): drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002; **54:** 349–56.
7. Mills E, *et al.* Interaction of St John's wort with conventional drugs: systematic review of clinical trials. *BMJ* 2004; **329:** 27–30.
8. Mannel M. Drug interactions with St John's wort: mechanisms and clinical implications. *Drug Safety* 2004; **27:** 773–97.
9. Whitten DL, *et al.* The effect of St John's wort extracts on CYP3A: a systematic review of prospective clinical trials. *Br J Clin Pharmacol* 2006; **62:** 512–26.

**Analgesics.** For details of a possible interaction between St John's wort and the opioid analgesic *methadone*, see p.84.

**Anticoagulants.** For mention of a possible interaction between St John's wort and *warfarin*, see p.1432.

**Antiepileptics.** There is a possibility of an interaction between St John's wort and antiepileptics such as *carbamazepine* (see p.474), *phenobarbital* (see p.493), and *phenytoin* (see p.498).

**Antineoplastics.** St John's wort may interact with some antineoplastics; examples include *aminolevulinic acid* (see p.679), *imatinib* (see p.734), and *irinotecan* (see p.737).

**Antivirals.** For details of a possible interaction between St John's wort and *HIV-protease inhibitors* such as indinavir, see p.883.

**Cardiac glycosides.** For details of a possible interaction between St John's wort and *digoxin*, see p.1261.

**Immunosuppressants.** For details of possible interactions between St John's wort and *ciclosporin* or *tacrolimus*, see p.1826 and p.1845, respectively.

**Oral contraceptives.** For reports of a possible interaction between St John's wort and oral contraceptives, see p.2068.

**Verapamil.** For details of a possible interaction between St John's wort and verapamil, see p.1423.

**Xanthines.** For details of a possible interaction between St John's wort and *theophylline*, see p.1143.

## Uses and Administration

Herbal preparations containing St John's wort are used, frequently for self-medication, in the treatment of depression. Such preparations are also promoted for the treatment of other nervous disorders such as insomnia and anxiety, particularly if associated with the menopause. St John's wort oil has also been used as an astringent. Hypericin, a major constituent of St John's wort, has been investigated as an antiviral in the treatment of HIV infection and AIDS (but see Antiviral Action, below).

The amount of active constituents can vary between different preparations and doses depend on the preparation being used.

**Homoeopathy.** St John's wort has been used in homoeopathic medicines under the following names: Hypericum; Hypericum perforatum; Hypericum perforatum ex herba; Hypericum, herba; Hyper.

◊ References.

1. McIntyre M. A review of the benefits, adverse events, drug interactions, and safety of St John's Wort (Hypericum perforatum): the implications with regard to the regulation of herbal medicines. *J Altern Complement Med* 2000; **6:** 115–24.

**Antiviral action.** A study involving 30 HIV-infected patients suggested that hypericin, given intravenously or by mouth, produced significant phototoxicity and had no effect on virological markers or CD4 cell count.[1]

1. Gulick RM, *et al.* Phase I studies of hypericin, the active compound in St John's Wort, as an antiretroviral agent in HIV-infected adults. *Ann Intern Med* 1999; **130:** 510–14.

**Depression.** St John's wort extracts are widely used in some countries for the treatment of depression (p.373).

Two systematic reviews[1,2] of randomised controlled studies found St John's wort extracts to be more effective than placebo in the treatment of mild to moderate depressive disorders. However, the results of the more recent review[2] also suggested that St John's wort extracts were only of minor benefit in patients with major depression and probably of no benefit in those with a prolonged history of the condition; in addition, there was no evidence of effectiveness in severe depression. The authors of this review commented that recent placebo-controlled studies tended to show less favourable results for St John's wort than older studies. It was considered that the heterogeneous findings were due partly to overestimation of effects in some smaller, older studies, and partly to the variable efficacy of St John's wort extracts in different patient populations; non-publication of negative studies was not thought to have played a major role.

The efficacy of St John's wort compared with standard antidepressants has also been reviewed and found to be comparable.[2] However, this finding should be interpreted with caution, not least because doses of the standard antidepressants used were at the lower end of the range in some studies.

The mechanism of action of St John's wort extracts in the treatment of depression remains unclear. Extracts contain at least 10 active principles. Hypericin, one of the major constituents of St John's wort, was first thought responsible for the antidepressant effect since it had an inhibitory action on monoamine oxidase *in vitro*. However it was later shown that this action was, at best, weak and it is now generally believed that monoamine oxidase inhibition is not responsible for the antidepressant effect of St John's wort. More recent studies have suggested that hyperforin may be one of the major constituents responsible for the antidepressant effect.[3] Although the evidence is mainly from *in vitro* studies, hyperforin inhibits the reuptake of several major neurotransmitters including serotonin, dopamine, and noradrenaline.[4]

1. Stevinson C, Ernst E. Hypericum for depression: an update of the clinical evidence. *Eur Neuropsychopharmacol* 1999; **9:** 501–5.
2. Linde K, *et al.* St John's wort for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 24/11/05).
3. Laakmann G, *et al.* St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998: **31** (suppl.): 54–9.
4. Chatterjee SS, *et al.* Hyperforin as a possible antidepressant component of hypericum extracts. *Life Sci* 1998; **63:** 499–510.

## Preparations

***Ph. Eur.:*** St John's Wort Dry Extract, Quantified.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Amenicil; Felis†; Herbaccion Motivante†; Hipax; Hiperinat; Remotiv†; ***Austral.:*** Bioglan Stress-Relax; Hyperiforte†; Remotiv; ***Austria:*** Esbericum; Felis†; Helarium; Hyperiforce; Jarsin; Johanicum; Johni; Kira; Lunare; Perikan; Psychotonin; Remotiv; Solaguttae; ***Belg.:*** Hyperiplant; Milperinol; Perika; ***Braz.:*** Adprex†; Ciperico; Emotival†; Equilibra†; Fiotan; Fitovital; Hiperex; Hipericin; Hiperico; Hiperifarma†; Hiperil†; Hipersac; Hyperico†; Hyperigreen; Iperisan; Jarsin†; Motiven; Prazen; Remotiv; Triativ; ***Canad.:*** Kira; Movana†; ***Chile:*** Anxium; Ciplazin†; Edual†; Remotiv†; ***Cz.:*** Cesradyston†; Deprim†; Esbericum†; Felisio; Helarium; Hyperikan; Jarsin; Kira†; Laif; Lubovnik†; Nat Trezalky; Psychotonin Forte†; Remotiv; Trezalka v Nalevovych Sacchich; Trezalkova Nat; Trezalkovy Caj; Turineurin†; ***Fr.:*** Bains Romains; Dermum†; Mildac; Procalmil; ***Ger.:*** aar brain N†; Aristo; Aristoforat; Cesradyston; dysto-lux; Esbericum; Felis; Helarium; Herbaneurin†; Hewepsychon uno; Hyperforat; Hypericaps†; Hyperimerck; Hyperpur; Jarsin; Jo-Sabona†; Kira; Kytta-Modal†; Laif; Libertin†; Lomahypericum†; Nervei; Neuroplant; Neurosporal; Neurovegetalin; Psychotonin; Psychotonin M†; Remotiv; Sedovegan†; Syxal†; Texx; Tonizin; Turineurin; Viviplus†; ***Gr.:*** Neukan; ***Hung.:*** Helarium; Hyperikan; Klosterfrau Sedinal; Myrall; Remotiv; ***Indon.:*** Preso; ***Israel:*** Remotiv; ***Ital.:*** Nervaxon; Proserem; Quiens; Remotive; ***Mex.:*** Hiperikan; Nutegen H†; Procalm†; Remotiv; ***Pol.:*** Apatinac; Deprim; Hyperherba; Hyperosedat; Perhip; Remotiv; Silenil; ***Port.:*** Alacre; ***Rus.:*** Deprim (Деприм); Doppelherz Nervotonik (Доппельгерц Нервотоник); Helarium (Гелариум); Negrustin (Негрустин); Novo-Passit (Ново-Пассит); ***S.Afr.:*** Remotiv†; ***Spain:*** Animic; Arkocapsulas Hiperico; Hiperico; Hyneurin; Perika; Quetzal; Vitalium; ***Switz.:*** Hyperforat†; Hypericettes†; Hyperiforce; HyperiMed; Hyperiplant; Hyperval; Jarsin; Libertin†; Lucilium; ReBalance; Remotiv; Solevita; Yakona; ***Turk.:*** Felis; ***UK:*** Hyperi-Calm; Kira; ***Venez.:*** Hyperikan; Kira†; Qual†.

**Multi-ingredient:** ***Austral.:*** Bioglan 3B Beer Belly Buster; Cimicifuga Compound; Feminine Herbal Complex; Infant Tonic†; Joint & Muscle Cream; Nappy Rash Relief Cream; Nevaton; Skin Healing Cream†; ***Austria:*** Eryval; Magentee St Severin; Nerventee St Severin; Remifemin plus; Species nervinae; Vulpuran; Wechseltee St Severin; ***Cz.:*** Alvisan Neo; Cajova Smes pri Redukcni Diete†; Cicaderma; Eugastrin†; Fytokliman Planta; Naturidentt; Novo-Passit; Species Nervinae Planta; Stomaran; Zaludecni Cajova Smes; ***Fr.:*** Cicaderma; ***Ger.:*** Allya†; anabol-loges; Anisan†; Arthrodynat P†; Befelka-Oel; Cheirantho†; Dolo-cyl; Gastritol; Gastrol S†; Gutnacht†; Hewepsychon duo†; Hyperesa; Hyperforat-forte†; JuDorm†; JuViton†; Marianon†; Me-Sabona plus†; Neurapas; Oxacant N†; Phytogran†; Presselin Arterien K 5 P†; Presselin Nerven K 1 N†; Psychotonin-sed; Remifemin plus; Rhoival†; Sedariston Konzentrat; Sedariston plus; Venacton†; ***Hung.:*** Remifemin Plus; ***Ital.:*** Controller; Hiperogyn; Mithen; Skab 2; ***Malaysia:*** Gyno-Plus; ***Mex.:*** Nordimenty; ***Pol.:*** Cholesol; Diges-Tonic; Fortestomachicae; Gastrobonisol; Guttae Stomachicae; Herbogastrin; Krople Zoladkowe; Melisal; Melissed; Nervomix; Perfocrat; Prostapol; Psychotonisol; Sedomix; Uroprost; ***Port.:*** Cicaderma; ***Rus.:*** Prostanorm (Простанорм); Sibectan (Сибектан); ***Spain:*** Natusor Gastrolen†; Natusor Somnisedan†; ***Switz.:*** Gel a la consoude; Huile de millepertuis A. Vogel (huile de St. Jean); Hyperiforce comp; Keppur; Kytta Gel†; Malvedrin; Saltrates Rodell†; Saltrates†; The a l'avoine sauvage de Vollmer; Yakona N†; Ziegella; ***UK:*** St Johnswort Compound; Tranquil; ***Venez.:*** Biomicovo†.

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## Tianeptine Sodium *(rINNM)*

Natrii Tianeptinum; Taneptinum Natricum; Tianeptiininatrium; Tianeptin sodná sůl; Tianeptin Sodyum; Tianeptina sódica; Tianeptine sodique; Tianeptinnatrium; Tianeptin-nátrium; Tianeptino natrio druska; Tianeptinum natricum. The sodium salt of 7-[(3-chloro-6,11-dihydro-6-methyldibenzo[*c*,*f*][1,2]thiazepin-11-yl)amino]heptanoic acid *S*,*S*-dioxide.

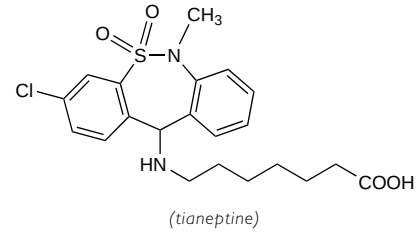
Натрий Тианептин

$C_{21}H_{24}ClN_2NaO_4S$ = 458.9.

*CAS — 66981-73-5 (tianeptine).*

*ATC — N06AX14.*

*ATC Vet — QN06AX14.*




*(tianeptine)*

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

**Ph. Eur. 6.2** (Tianeptine Sodium). A white or yellowish, very hygroscopic, powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. Store in airtight containers.

### 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.

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## Tranylcypromine Sulfate *(rINNM)*

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

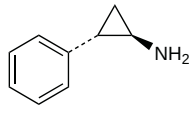
Транилципромина Сульфат

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

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## 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.

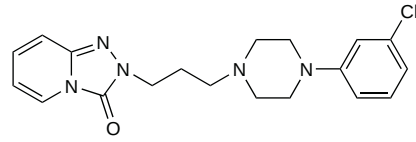
Тразодона Гидрохлорид

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