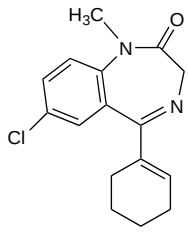
Tetrazepam *(BAN, pINN)*

CB-4261; Tetratsepaami; Tétrazépam; Tetrazepám; Tetrazepamas; Tetrazepamum. 7-Chloro-5-(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2*H*-1,4-benzodiazepin-2-one.

Тетразепам

$C_{16}H_{17}ClN_2O$ = 288.8.
CAS — 10379-14-3.
ATC — M03BX07.
ATC Vet — QM03BX07.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Tetrazepam). A light yellow or yellow crystalline powder. Practically insoluble in water; soluble in acetonitrile; freely soluble in dichloromethane. Protect from light.

Profile
Tetrazepam is a benzodiazepine with general properties similar to those of diazepam (p.986). It is used for its muscle relaxant properties in the treatment of muscle spasm (p.1887). The usual initial dose is 25 to 50 mg orally increased, if necessary, to 150 mg or more daily.

Pharmacokinetics. References.

1. Bun H, *et al.* Plasma levels and pharmacokinetics of single and multiple dose of tetrazepam in healthy volunteers. *Arzneimittelforschung* 1987; **37:** 199–202.

Porphyria. Tetrazepam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

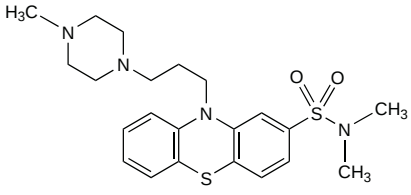
Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Myolastan; ***Belg.:*** Epsipam; Myolastan; ***Cz.:*** Myolastan; ***Fr.:*** Megavix; Myolastan; Panos; ***Ger.:*** Mobiforton; Musapam; Musaril; Muskelat†; Myospasmal; Rilex; Spasmorelax; Tethexal†; Tetra-saar; Tetramdura; Tetrazep; ***Mex.:*** Miolastan; ***Pol.:*** Miozepam; Myolastan; Myopam; Tetratio; ***Spain:*** Myolastan.

Thioproperazine Mesilate *(BANM, rINNM)*

Mesilato de tioproperazina; RP-7843; SKF-5883; Thioproperazine Dimethanesulphonate; Thiopropérazine, Mésilate de; Thioproperazine Mesylate; Thioproperazine Methanesulphonate; Thioproperazini Mesilas. *NN*-Dimethyl-10-[3-(4-methylpiperazin-1-yl)propyl]phenothiazine-2-sulphonamide dimethanesulphonate.

Тиопроперазина Мезилат

$C_{22}H_{30}N_4O_2S_2,2CH_4O_3S$ = 638.8.
CAS — 316-81-4 (thioproperazine); 2347-80-0 (thioproperazine mesilate).
ATC — N05AB08.
ATC Vet — QN05AB08.



(thioproperazine)

Pharmacopoeias. In *Fr.*

Profile
Thioproperazine is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It has a piperazine sidechain. It is used in the treatment of schizophrenia (p.955), mania (see Bipolar Disorder, p.372), and other psychoses. Thioproperazine is given as the mesilate although doses are expressed in terms of the base; thioproperazine mesilate 7.2 mg is equivalent to about 5 mg of thioproperazine. Initial daily doses of 5 mg are given orally, increased as necessary; the usual effective dosage is 30 to 40 mg daily. In severe or resistant cases daily doses of 90 mg or more have been given.

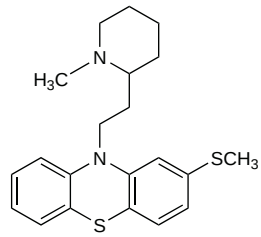
Preparations
Proprietary Preparations (details are given in Part 3)
Canad.: Majeptil; ***Gr.:*** Majeptil; ***Mex.:*** Majeptil†; ***Rus.:*** Majeptil (Мажептил); ***Spain:*** Majeptil; ***Venez.:*** Majeptil†.

Thioridazine *(BAN, USAN, rINN)*

Thioridazin; Thioridazinum; Tioridatsiini; Tioridazin; Tioridazina; Tioridazinas; TP-21. 10-[2-(1-Methyl-2-piperidyl)ethyl]-2-methylthiophenothiazine.

Тиоридазин

$C_{21}H_{26}N_2S_2$ = 370.6.
CAS — 50-52-2.
ATC — N05AC02.
ATC Vet — QN05AC02.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Thioridazine). A white or almost white powder. Practically insoluble in water; soluble in alcohol; very soluble in dichloromethane; freely soluble in methyl alcohol. Protect from light.
USP 31 (Thioridazine). A white to slightly yellow crystalline or micronised powder; odourless or having a faint odour. Practically insoluble in water; freely soluble in dehydrated alcohol and in ether; very soluble in chloroform. Protect from light.

Thioridazine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tioridazina; Thioridazin hydrochlorid; Thioridazine, chlorhydrate de; Thioridazini hydrochloridum; Tioridatsiinihydrokloridi; Tioridazinhidroklorid; Tioridazinhydroklorid; Tioridazino hidrochloridas; Tiorydazny chlorowodorek; Tiorydazyny chlorowodorek.

Тиоридазина Гидрохлорид

$C_{21}H_{26}N_2S_2$,HCl = 407.0.
CAS — 130-61-0.
ATC — N05AC02.
ATC Vet — QN05AC02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Thioridazine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in alcohol. A 1% solution in water has a pH of 4.2 to 5.2. Protect from light.
USP 31 (Thioridazine Hydrochloride). A white to slightly yellow granular powder having a slight odour. Freely soluble in water, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 4.2 and 5.2. Store in airtight containers. Protect from light.

Incompatibility. For a warning about incompatibility between thioridazine hydrochloride solution (*Mellaril; Novartis, USA*) and carbamazepine suspension (*Tegretol; Novartis, USA*), see p.471.

Adverse Effects and Treatment
As for Chlorpromazine, p.969.

Thioridazine has been associated with a higher incidence of antimuscarinic effects, but lower incidence of extrapyramidal effects than chlorpromazine. It may also be less sedating. However, it is more likely to induce hypotension and there is an increased risk of cardiotoxicity and dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use has been restricted (see Precautions, and Uses and Administration, below). Sexual dysfunction also appears to be more frequent with thioridazine.

Pigmentary retinopathy characterised by reduced visual acuity, brownish colouring of vision, and impairment of night vision has been seen particularly in patients taking large doses.

Effects on the cardiovascular system. Between 1964 and 2001, the UK CSM received 42 reports of suspected heart rate and rhythm disorders associated with thioridazine.[1] There were 21 fatalities reported out of 39 cases where the outcome was known.

See also under Chlorpromazine, p.970.

1. Committee on Safety of Medicines/Medicines Control Agency. QT interval prolongation with antipsychotics. *Current Problems* 2001; **27:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 12/05/06)

Hypersensitivity. Pruritus and erythematous rash on the genitals of a woman after sexual intercourse were found to be due to thioridazine present in the seminal fluid of her husband, who was taking 100 mg daily at night.[1]

1. Sell MB. Sensitization to thioridazine through sexual intercourse. *Am J Psychiatry* 1985; **142:** 271–2.

Overdosage. Rhabdomyolysis has been reported in a patient after overdosage with thioridazine.[1] Twenty-four hours after taking 9.4 g of thioridazine the patient presented with difficulty in moving and speaking. On examination he had swelling and tenderness over his upper arms, thighs, and calves. Ataxia and transient dysarthria were attributed to generalised muscle weakness. Other effects were consistent with antimuscarinic effects of thioridazine. He had no signs of neuroleptic malignant syndrome but his urine contained myoglobin. The patient was treated with gastric lavage, activated charcoal, and rehydration. Serum biochemistry returned to normal over 1 week and the muscle tenderness and weakness disappeared.

1. Nankivell BJ, *et al.* Rhabdomyolysis induced by thioridazine. *BMJ* 1994; **309:** 378.

Precautions
As for Chlorpromazine, p.972. Thioridazine should not be used in patients with clinically significant cardiac disorders, uncorrected hypokalaemia or other electrolyte imbalance, with known or suspected QT prolongation or a family history of QT prolongation, or with a history of ventricular arrhythmias including torsade de pointes. Use is also contra-indicated in patients known to have reduced activity of the cytochrome P450 isoenzyme CYP2D6, which is responsible for thioridazine metabolism. Use with drugs liable to interfere with the metabolism of thioridazine, with other drugs known to prolong the QT interval, and with drugs likely to cause electrolyte imbalance should also be avoided (see under Interactions, below).

For all patients starting thioridazine it is recommended that a baseline ECG and electrolyte screening are performed. An ECG should also be repeated before each dose increase, 1 week after the maximum therapeutic dose has been reached, and at 6-monthly intervals in those who continue treatment. Serum electrolyte concentrations should also be monitored periodically during treatment and any imbalance corrected.

Porphyria. Thioridazine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions
As for Chlorpromazine, p.973. The metabolism of thioridazine is mediated by the cytochrome P450 isoenzyme CYP2D6; thioridazine itself is also an inhibitor of CYP2D6. Therefore, there is the potential for interactions between thioridazine and other drugs that inhibit or act as a substrate for this enzyme; such drugs should not be given with thioridazine. Some examples include antiarrhythmics, certain antidepressants including the SSRIs and tricyclics, certain antipsychotics, beta blockers, HIV-protease inhibitors, and opioids.

Use with other drugs known to prolong the QT interval such as class IA and class III antiarrhythmics, tricyclic antidepressants, and some other antipsychotics should also be avoided, as should use with those drugs known to cause electrolyte imbalance.

Pharmacokinetics
The pharmacokinetics of thioridazine appear to be generally similar to those of chlorpromazine (p.975). Thioridazine is metabolised by the cytochrome P450 isoenzyme CYP2D6. Its main active metabolite is mesoridazine (p.1007); another metabolite, sulforidazine, also has some activity. Thioridazine and its active metabolites are reported to be highly bound to plasma proteins (more than 95%). The plasma half-life of thioridazine has been estimated to be about 4 to 10 hours. It also crosses the placenta and is distributed into breast milk.

◊ References.

1. Mårtensson E, Roos B-E. Serum levels of thioridazine in psychiatric patients and healthy volunteers. *Eur J Clin Pharmacol* 1973; **6:** 181–6.
2. Axelsson R, Mårtensson E. Serum concentration and elimination from serum of thioridazine in psychiatric patients. *Curr Ther Res* 1976; **19:** 242–65.

Metabolism. In 10 psychiatric patients stabilised on thioridazine, therapy was replaced by equipotent doses of the side-chain sulfoxide (mesoridazine) and side-chain sulfone (sulforidazine) metabolites of thioridazine.[1] Both metabolites were shown to have an antipsychotic effect, the dose of each required being about two-thirds that of thioridazine. The serum half-lives were thioridazine 21 hours, mesoridazine 16 hours, and sulforidazine 13 hours. Apathy, depression, and restlessness gradually developed during treatment with the 2 metabolites and they could not be used for any length of time. Extrapyramidal symptoms, hypersalivation, and drowsiness were more common with the metabolites; 2 patients had epileptic seizures, and 1 receiving sulforidazine developed probable cholestatic jaundice.

There is some evidence that the metabolism of thioridazine is influenced by debrisoquine hydroxylation phenotype.[2] A single-dose study in 19 healthy male subjects demonstrated slower formation of mesoridazine, and hence higher serum-thioridazine concentrations in poor debrisoquine hydroxylators compared with extensive hydroxylators. Formation of thioridazine ring-