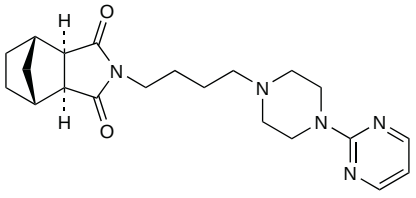
Tandospirone Citrate *(BANM, USAN, rINNM)*

Citrato de tandospirona; Metanopirone Citrate; SM-3997 (tandospirone or tandospirone citrate); Tandospirone, Citrate de; Tandospironi Citras. (1R*,2S*,3R*,4S*)-*N*-{4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl}-2,3-norbornanedicarboximide citrate.

Тандоспирона Цитрат

$C_{21}H_{29}N_5O_2,C_6H_8O_7$ = 575.6.

CAS — 87760-53-0 (tandospirone); 112457-95-1 (tandospirone citrate).



(tandospirone)

Profile

Tandospirone, a partial agonist at serotonin (5-HT) receptors of the 5-HT_{1A} subtype, is an anxiolytic structurally related to buspirone (p.965). It also has antidepressant actions. Tandospirone citrate is given in usual oral doses of 30 mg daily in 3 divided doses up to a maximum of 60 mg daily.

◊ References.

1. Sumiyoshi T, *et al.* The effect of tandospirone, a serotonin(1A) agonist, on memory function in schizophrenia. *Biol Psychiatry* 2001; **49:** 861–8.
2. Yamada K, *et al.* Clinical efficacy of tandospirone augmentation in patients with major depressive disorder: a randomized controlled trial. *Psychiatry Clin Neurosci* 2003; **57:** 183–7.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Sediel.

Temazepam *(BAN, USAN, rINN)*

ER-115; 3-Hydroxydiazepam; K-3917; Ro-5-5345; Tematsepaami; Témazépam; Temazepám; Temazepamas; Temazepamum; Wy-3917. 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-1,4-benzodiazepin-2-one.

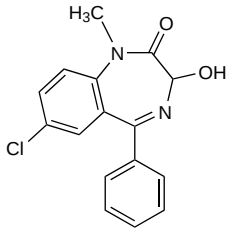
Темазепам

$C_{16}H_{13}ClN_2O_2$ = 300.7.

CAS — 846-50-4.

ATC — N05CD07.

ATC Vet — QN05CD07.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of temazepam: Beans; Egg; Eggs; Jellies; Knockout Pills; Mazzies; Oranges; Rugby Balls; Temazies; Temmies; Terms; Wobbly jellies.

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

Ph. Eur. 6.2 (Temazepam). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane. Protect from light.

USP 31 (Temazepam). A white or nearly white crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 10 mg of temazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Abuse. Liquid-filled temazepam *capsules* (known on the street as 'eggs') were widely abused on the illicit drugs market, the liquid gel lending itself to intravenous injection.[1] This formulation was, therefore, replaced in a number of countries by tablets or by semi-solid gel-filled capsules, which were intended to be difficult to inject even after heating or diluting the gel in various solvents.[2] In spite of this there is evidence of intravenous or intra-arterial abuse of these capsules,[3-5] and there are reports of ischaemia, in some cases necessitating amputation.[6-8] The *tablets* may also be liable to abuse; there has been a report of death after intravenous injection of a solution containing crushed temazepam tablets.[9] The manufacturers of a temazepam *elixir* considered that, because of its viscosity and its low strength relative to the liquid in the capsules, it had a low potential for intravenous abuse.[10] Nonetheless, there have been reports[3] of some drug abusers injecting large quantities of diluted elixir.

For mention of rhabdomyolysis associated with abuse of temazepam, see Effects on Skeletal Muscle, under Diazepam, p.988.

1. Farrell M, Strang J. Misuse of temazepam. *BMJ* 1988; **297:** 1402.
2. Launchbury AP. Temazepam abuse. *Pharm J* 1990; **244:** 749.
3. Ruben SM, Morrison CL. Temazepam misuse in a group of injecting drug users. *Br J Addict* 1992; **87:** 1387–92.
4. Scott RN, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
5. Adiseshiah M, *et al.* Intra-arterial temazepam. *BMJ* 1992; **304:** 1630.
6. Blair SD, *et al.* Leg ischaemia secondary to non-medical injection of temazepam. *Lancet* 1991; **338:** 1393–4.
7. Fox R, *et al.* Misuse of temazepam. *BMJ* 1992; **305:** 253.
8. Feeney GFX, Gibbs HH. Digit loss following misuse of temazepam. *Med J Aust* 2002; **176:** 380.
9. Vella EJ, Edwards CW. Death from pulmonary microembolization after intravenous injection of temazepam. *BMJ* 1993; **307:** 26.
10. Drake J, Ballard R. Misuse of temazepam. *BMJ* 1988; **297:** 1402.

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

Temazepam was detected in breast milk in only one of 10 mothers given temazepam as a bedtime sedative;[2] temazepam was given in a dose of 10 to 20 mg and milk concentrations were measured about 15 hours after a dose. The authors considered that breast-fed neonates would ingest negligible amounts of temazepam.

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 28/04/04)
2. Lebedevs TH, *et al.* Excretion of temazepam in breast milk. *Br J Clin Pharmacol* 1992; **33:** 204–6.

Effects on the skin. Generalised lichenoid drug eruption that had persisted for 5 months in an elderly patient receiving therapy including temazepam resolved within 10 days of stopping the benzodiazepine.[1] Bullous eruptions associated with temazepam overdose have also been reported.[2]

1. Norris P, Sounex TS. Generalised lichenoid drug eruption associated with temazepam. *BMJ* 1986; **293:** 510.
2. Verghese J, Merino J. Temazepam overdose associated with bullous eruptions. *Acad Emerg Med* 1999; **6:** 1071.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, and licensed product information in the UK advises that temazepam should be avoided in severe cases. However, short-acting benzodiazepines such as temazepam may pose less risk in patients with hepatic impairment; in a study of 15 patients with cirrhosis and 16 healthy subjects, liver disease had no significant effect on the pharmacokinetic parameters or pattern of elimination of temazepam.[1]

1. Ghabrial H, *et al.* The effects of age and chronic liver disease on the elimination of temazepam. *Eur J Clin Pharmacol* 1986; **30:** 93–7.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Temazepam is fairly readily absorbed from the gastrointestinal tract, although the exact rate of absorption depends on the formulation. It is about 96% bound to plasma proteins. Mean elimination half-lives of about 8 to 15 hours or longer have been reported. It is excreted mainly in the urine in the form of its inactive glucuronide conjugate together with small amounts of the demethylated derivative, oxazepam, also in conjugated form.

Absorption and plasma concentration. Various oral temazepam formulations have been available worldwide. These included powder-filled hard gelatin capsules, liquid-filled soft gelatin capsules, semi-solid gel-filled soft gelatin capsules, and an elixir. There has been considerable debate over the comparative absorption profiles of temazepam from these formulations which have, in some cases, been modified over the years. It should be noted that pharmacokinetic studies of temazepam do not always clearly state the formulation used.

Temazepam 30 mg was given as a premedicant to 80 patients undergoing surgery in the form of capsules [type not stated] or elixir.[1] Mean peak plasma concentrations of about 800 nanograms/mL occurred 30 minutes after a dose of either formulation although there was wide interindividual variation in plasma concentrations. The evidence corresponded with previous suggestions that a plasma concentration of about 250 nanograms/mL or more was required to ensure sedation. The presence or absence of anxiety did not influence the absorption of the preparations.

1. Hosie HE, Nimmo WS. Temazepam absorption in patients before surgery. *Br J Anaesth* 1991; **66:** 20–4.

Distribution into CSF. A study in 13 male patients showed a correlation between the unbound concentration of temazepam in plasma and the amount of temazepam detected in CSF.[1] The mean CSF to total plasma temazepam concentration ratio was 5.2.

1. Badcock NR. Plasma and cerebrospinal fluid concentrations of temazepam following oral drug administration. *Eur J Clin Pharmacol* 1990; **38:** 153–5.

Metabolism. References.

1. Locniskar A, Greenblatt DJ. Oxidative versus conjugative biotransformation of temazepam. *Biopharm Drug Dispos* 1990; **11:** 499–506.

Sex differences. The elimination half-life was significantly longer at 16.8 hours among 17 women given temazepam 30 mg compared with 12.3 hours among 15 men.[1] The total clearance was also lower among women. After correction for differences in protein binding, unbound clearance was still lower in women than men but there was no significant effect of age on this parameter. Time to peak plasma concentration and volume of distribution were not affected by the age or sex of the subjects.

1. Divoll M, *et al.* Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981; **70:** 1104–7.

Uses and Administration

Temazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used as a hypnotic in the short-term management of insomnia (p.957) and for premedication before surgical or investigative procedures (p.1780).

A usual oral dose for insomnia is 10 to 20 mg at night; exceptionally, doses up to 40 mg may be required. For premedication the usual oral dose is 20 to 40 mg given half to one hour beforehand. The *BNFC* states that children aged 1 year and over may be given 1 mg/kg orally for premedication, to a maximum total dose of 30 mg.

Temazepam should be given in reduced dosage to elderly or debilitated patients; one-half the usual adult dose, or less, may be sufficient.

Administration. For reference to the various formulations of oral temazepam that have been used, see Abuse under Adverse Effects, Treatment, and Precautions, above.

Administration in the elderly. In a small study[1] a 7.5-mg dose of temazepam was found to be adequate for the short-term management of insomnia in elderly patients.

1. Vgontzas AN, *et al.* Temazepam 7.5 mg: effects on sleep in elderly insomniacs. *Eur J Clin Pharmacol* 1994; **46:** 209–13.

Preparations

BP 2008: Temazepam Oral Solution; Temazepam Tablets;
USP 31: Temazepam Capsules.

Proprietary Preparations (details are given in Part 3)

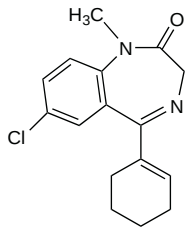
Austral.: Euhypnos†; Nocturne†; Normison; Temaze; Temtabs; ***Austria:*** Levanxol; Remestan†; ***Belg.:*** Euhypnos†; Normison†; ***Canad.:*** Restoril; ***Fin.:*** Normison; Tenox; ***Fr.:*** Normison; ***Ger.:*** Norkotral Tema; Planum; Pronervon T; Remestan; Temazep; ***Gr.:*** Normison; ***Hung.:*** Signopam; ***Irl.:*** Euhypnos†; Insomniger; Normison†; Nortem; Tenox; ***Ital.:*** Euipnos; Normison; ***Neth.:*** Normison; ***NZ:*** Euhypnos; Normison; Somapam†; ***Pol.:*** Signopam; ***Port.:*** Normison; ***Rus.:*** Signopam (Сигнопам); ***S.Afr.:*** Normison; ***Switz.:*** Normison; ***Thai.:*** Euhypnos; ***USA:*** Restoril.

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.

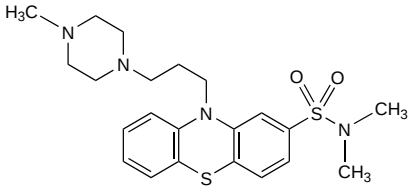
Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Myolastan; ***Belg.:*** Epsipam; Myolastan; ***Cz.:*** Myolastan; ***Fr.:*** Megavix; Myolastan; Panos; ***Ger.:*** Mobiforton; Musapam; Musaril; Muskelat†; Myospasmal; Rilex; Spasmorelax; Tethexal†; Tetra-saar; Tetramdura;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

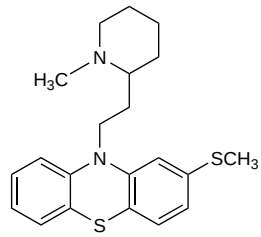
Preparations
Proprietary Preparations (details are given in Part 3)
Canad.: Majeptil; ***Gr.:*** Majeptil; ***Mex.:*** Majeptil†; ***Rus.:*** Majeptil (Мажептил); ***Spain:*** Majeptil; ***Venez.:*** Majeptil†.

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-