Lorazepam *(BAN, USAN, rINN)*

Loratsepaami; Lorazépam; Lorazepám; Lorazepamas; Lorazepamum; Wy-4036. 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1,4-benzodiazepin-2-one.

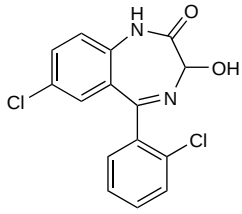
Лоразепам

$C_{15}H_{10}Cl_2N_2O_2$ = 321.2.

CAS — 846-49-1.

ATC — N05BA06.

ATC Vet — QN05BA06.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of lorazepam:
Benzo; Somnios.

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Lorazepam). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; sparingly or slightly soluble in dichloromethane. Store in airtight containers. Protect from light.
USP 31 (Lorazepam). A white or practically white, practically odourless powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform. Store in airtight containers. Protect from light.

Incompatibility. Visual incompatibility has been noted with lorazepam and sargramostim[1] or aztreonam.[2]

1. Trissel LA, *et al.* Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; **49:** 402–6.
2. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; **52:** 1086–90.

Solubility. The solubility of lorazepam in fluids for intravenous use (water, glucose injection, lactated Ringer's injection, and sodium chloride injection) was greatest in glucose injection (5%) at 62 micrograms/mL and lowest in sodium chloride injection (0.9%) at 27 micrograms/mL;[1] these differences in solubility appeared to be pH related. Commercial injections are reported to contain polyethylene glycol in propylene glycol to overcome this poor solubility. However, precipitation has been noted[2] in solutions prepared by dilution of lorazepam injection with sodium chloride injection (0.9%) to a concentration of 500 micrograms/mL. One group of workers[3] have reported that they had overcome such problems with precipitation by using glucose injection (5%) as a diluent and by avoiding final concentrations of lorazepam between 0.08 mg/mL and 1 mg/mL. It was suggested that the propylene glycol in the mixture might account for the unusual concentration effect. Such recommendations have been adopted by another group[4] although they observed that precipitation occurred if a formulation of lorazepam containing 4 mg/mL was used to prepare the injection; no precipitation was noted when a formulation containing 2 mg/mL was used. The group also commented that, in the USA, licensed product information for lorazepam injection advises that admixtures should be prepared with the 2 mg/mL formulation only.

1. Newton DW, *et al.* Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* 1983; **40:** 424–7.
2. Boullata JI, *et al.* Precipitation of lorazepam infusion. *Ann Pharmacother* 1996; **30:** 1037–8.
3. Volles DF, *et al.* More on usability of lorazepam admixtures for continuous infusion. *Am J Health-Syst Pharm* 1996; **53:** 2753–4.
4. Levanda M. Noticeable difference in admixtures prepared from lorazepam 2 and 4 mg/ml. *Am J Health-Syst Pharm* 1998; **55:** 2305.

Sorption. Significant loss of lorazepam has been reported from solutions stored in PVC[1] or polypropylene[2] giving equipment; polyolefin[3-5] or glass[6] equipment appears to be more suitable.

1. Hoey LL, *et al.* Lorazepam stability in parenteral solutions for continuous intravenous administration. *Ann Pharmacother* 1996; **30:** 343–6.
2. Stiles ML, *et al.* Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. *Am J Health-Syst Pharm* 1996; **53:** 1583–8.
3. Trissel LA, Pearson SD. Storage of lorazepam in three injectable solutions in polyvinyl chloride and polyolefin bags. *Am J Hosp Pharm* 1994; **51:** 368–72.
4. Norenberg JP, *et al.* Stability of lorazepam in 0.9% sodium chloride stored in polyolefin bags. *Am J Health-Syst Pharm* 2004; **61:** 1039–41.
5. Trissel LA, *et al.* Drug compatibility with new polyolefin infusion solution containers. *Am J Health-Syst Pharm* 2006; **63:** 2379–82.
6. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 500 micrograms of lorazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. Pain and a sensation of burning have occurred following injection of lorazepam.

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

Free lorazepam concentrations in the breast milk of 4 mothers ranged from 8 to 9 nanograms/mL four hours after receiving a 3.5-mg oral dose.[2] This represented about 15 to 26% of the concentration in plasma, and was probably sufficiently low to cause no adverse effects in breast-fed infants.

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. Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; **57:** 1042–3.

Effects on the blood. A case of pancytopenia associated with oral lorazepam was reported[1] in 1988; only 5 instances of thrombocytopenia and none of leucopenia had been reported to the UK CSM or the UK manufacturers over the previous 13 years.

1. El-Sayed S, Symonds RP. Lorazepam induced pancytopenia. *BMJ* 1988; **296:** 1332.

Effects on fluid and electrolyte homoeostasis. Inappropriate secretion of antidiuretic hormone related to ingestion of lorazepam was considered to be the cause of hyponatraemia in an 81-year-old woman.[1]

1. Engel WR, Grau A. Inappropriate secretion of antidiuretic hormone associated with lorazepam. *BMJ* 1988; **297:** 858.

Effects on the nervous system. For reference to extrapyramidal disorders associated with use of lorazepam, see Diazepam, p.988.

The elderly. For discussion of the need for reduced dosage of benzodiazepines in elderly patients, including mention of lorazepam, see Diazepam, p.989.

Formulation. There have been reports of toxicity, presumed to be due to polyethylene glycol[1,2] or propylene glycol,[3] after prolonged parenteral use of lorazepam; polyethylene glycol in propylene glycol is included as a solubiliser in lorazepam solutions. Diarrhoea in an infant given large enteral doses of lorazepam or diazepam solutions may have been due to the combined osmotic effect of polyethylene glycol and propylene glycol in these preparations.[4]

1. Laine GA, *et al.* Polyethylene glycol nephrotoxicity secondary to prolonged high-dose intravenous lorazepam. *Ann Pharmacother* 1995; **29:** 1110–4.
2. Tayar J *et al.* Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam. *N Engl J Med* 2002; **346:** 1253–4.
3. Seay RE, *et al.* Possible toxicity from propylene glycol in lorazepam infusion. *Ann Pharmacother* 1997; **31:** 647–8. Woycik CL, Walker PC. Correction and comment: possible toxicity from propylene glycol in injectable drug preparations. *ibid.*: 1413.
4. Marshall JD, *et al.* Diarrhea associated with enteral benzodiazepine solutions. *J Pediatr* 1995; **126:** 657–9.

Hepatic impairment. Lorazepam is contra-indicated in severe hepatic impairment; patients with mild to moderate impairment may require reduced doses. Although the elimination half-life of lorazepam was increased in 13 patients with alcoholic cirrhosis compared with 11 control subjects, this was not associated with an impairment in systemic plasma clearance.[1] With the exception of a modest decrease in the extent of plasma protein binding, acute viral hepatitis had no effect on the disposition kinetics of lorazepam.

1. Kraus JW, *et al.* Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; **24:** 411–19.

Local reactions. Of 40 patients given a single intravenous dose of lorazepam 4 mg three had local thrombosis 2 to 3 days later and 6 had local thrombosis 7 to 10 days later.[1] The incidence was lower than in those given diazepam [in solution].

1. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *BMJ* 1977; **2:** 1384–5.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Lorazepam is readily absorbed from the gastrointestinal tract after oral doses, with a bioavailability of about 90%; peak plasma concentrations are reported to occur about 2 hours after an oral dose. The absorption profile after intramuscular injection is similar to that after oral dosage.

Lorazepam is about 85% bound to plasma proteins. It crosses the blood-brain barrier and the placenta; it is also distributed into breast milk. Lorazepam is metabolised in the liver to the inactive glucuronide, and excreted in urine. The elimination half-life has been reported to range from about 10 to 20 hours.

◊ References.

1. Greenblatt DJ. Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; **6:** 89–105.
2. Swart EL, *et al.* Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol* 2004; **57:** 135–45.

Children. References to the pharmacokinetics of lorazepam in children.

1. Relling MV, *et al.* Lorazepam pharmacodynamics and pharmacokinetics in children. *J Pediatr* 1989; **114:** 641–6.

NEONATES. References to slow elimination of lorazepam by neonates.

1. Cummings AJ, Whitelaw AGL. A study of conjugation and drug elimination in the human neonate. *Br J Clin Pharmacol* 1981; **12:** 511–15.
2. McDermott CA, *et al.* Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992; **120:** 479–83.
3. Reiter PD, Stiles AD. Lorazepam toxicity in a premature infant. *Ann Pharmacother* 1993; **27:** 727–9.

Distribution. Evidence that lorazepam undergoes enterohepatic recirculation with possible first-pass metabolism.[1]

1. Herman RJ, *et al.* Disposition of lorazepam in human beings: enterohepatic recirculation and first-pass effect. *Clin Pharmacol Ther* 1989; **46:** 18–25.

CNS. In a study involving 6 healthy subjects, peak plasma-lorazepam concentrations were reached 5 minutes after the end of a one-minute intravenous injection.[1] CNS effects, as measured by EEG activity, were not maximal until 30 minutes after injection; they declined to baseline values slowly over 5 to 8 hours in a similar manner to plasma concentrations. In contrast, CNS effects of diazepam were maximal immediately after the injection. They also declined more rapidly than lorazepam, but again in a similar way to plasma concentrations. Studies in *mice* suggested that the slow onset of action of lorazepam that has been reported by some is at least partly explained by a delay in passage from systemic blood into brain tissue.

1. Greenblatt DJ, *et al.* Kinetic and dynamic study of intravenous lorazepam; comparison with intravenous diazepam. *J Pharmacol Exp Ther* 1989; **250:** 134–40.

Uses and Administration

Lorazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term treatment of anxiety disorders (p.952), as a hypnotic in the short-term management of insomnia (p.957), and as an anticonvulsant in the management of status epilepticus (p.469). When used in the treatment of status epilepticus lorazepam has a prolonged antiepileptic action and may be the preferred initial treatment if intravenous access is available. It is also used for its sedative and amnestic properties in premedication and as an adjunct in regimens for the control of nausea and vomiting associated with cancer chemotherapy (p.1700).

Lorazepam is usually given orally or by injection as the base although the pivalate is available for oral use in some countries. Sublingual tablets are used in some countries in doses similar to those for standard tablets. The intramuscular route is usually only used when oral or intravenous dosage is not possible. Injections should usually be diluted before use; intravenous injections should be given at a rate of not more than 2 mg/minute into a large vein. Lorazepam should be given in reduced dosage to elderly or debilitated patients; half the usual adult dose, or less, may be sufficient.

The usual oral dose of lorazepam for the treatment of **anxiety disorders** is 1 to 6 mg daily in 2 or 3 divided doses with the largest dose taken at night; up to 10 mg daily has been given. A dose of 25 to

30 micrograms/kg may be given by injection every 6 hours for acute anxiety. Lorazepam has also been used for **panic attacks**. A suggested dose in the *BNF* is 3 to 5 mg daily. A single oral dose of 1 to 4 mg at bedtime may be given for **insomnia** associated with anxiety. However, the MHRA in the UK advises against the use of oral daily doses of lorazepam above 4 mg for anxiety and phobia, and 2 mg for insomnia.

For **premedication** an oral dose of 2 to 3 mg may be given the night before the operation; the *BNF* suggests that this may be followed if necessary the next morning by a smaller dose. Alternatively, 2 to 4 mg may be given 1 to 2 hours before an operation. In the UK, although lorazepam tablets are not licensed for premedication of *children* under 5 years of age, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given orally at least 1 hour before an operation to those aged 1 month to 12 years; the same dose may also be given the night before, in addition to, or to replace the dose before, the operation. Lorazepam may also be given parenterally for premedication; a dose of 50 micrograms/kg may be given 30 to 45 minutes before the operation if given intravenously or 1 to 1½ hours before if given intramuscularly. Again, although unlicensed in the UK for premedication of children under 12 years of age, the *BNFC* suggests that 50 to 100 micrograms/kg (maximum of 4 mg) may be given by slow intravenous injection to those aged 1 month to 18 years.

In the management of **status epilepticus** 4 mg may be given as a single intravenous dose; the *BNF* suggests that this may be repeated once after 10 minutes if seizures recur. A dose of 2 mg has been suggested for *children* by one manufacturer (*Wyeth*). Alternatively, the *BNFC* suggests that neonates and children up to 12 years of age may be given 100 micrograms/kg (maximum of 4 mg) as a single dose sublingually, rectally, or by slow intravenous injection; this may be repeated once after 10 minutes if necessary.

In patients receiving modestly emetogenic chemotherapy, lorazepam 1 to 2 mg orally may be added to antiemetic therapy with domperidone or metoclopramide, for the prophylaxis of **nausea and vomiting**. The addition of lorazepam may be helpful in the prevention of anticipatory symptoms because of its sedative and amnestic effects.

Disturbed behaviour. For a discussion of the management of behaviour disturbances associated with various psychotic disorders and the value of benzodiazepines, see p.954.

References.

1. Bieniek SA, *et al.* A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; **18:** 57–62.

Nausea and vomiting. References.

1. Malik IA, *et al.* Clinical efficacy of lorazepam in prophylaxis of anticipatory, acute, and delayed nausea and vomiting induced by high doses of cisplatin: a prospective randomized trial. *Am J Clin Oncol* 1995; **18:** 170–5.

Premedication and sedation. Lorazepam is used as a premedicant (p.1780) and as a sedative for therapeutic and investigative procedures such as dental treatment (p.956) and endoscopy (p.956), and also in intensive care (p.957).

References.

1. Maltais F, *et al.* A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; **109:** 1195–8.

Substance dependence. Lorazepam has been used in the management of symptoms of alcohol withdrawal (p.1626).

References.

1. D'Onofrio G, *et al.* Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; **340:** 915–9.

Preparations

BP 2008: Lorazepam Injection; Lorazepam Tablets;
USP 31: Lorazepam Injection; Lorazepam Oral Concentrate; Lorazepam Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aplacasse; Calmatron; Emotival; Kalmalin; Lorezan; Microzepam; Nervistop; Sedatival†; Sidenar; Trapax; Tratenamin†; ***Austral.:*** Ativan; ***Austria:*** Merlit; Temesta; ***Belg.:*** Docloraze; Lauracalm; Lorazemed; Lorazetop; Loridem; Optisedine; Serenase; Temesta; Vigiten†; ***Braz.:*** Calmogenol†; Lorapan; Lorax; Lorazefast; Lorazepan†; Max-Pax; Mesmerin; ***Canad.:*** Ativan; Novo-Lorazem; Nu-Loraz; ***Chile:*** Abinol; Amparax; ***Cz.:*** Loram†; Tavor†; ***Denm.:*** Lorabenz; Temesta; ***Fin.:*** Temesta; ***Fr.:*** Equitam†; Temesta; ***Ger.:*** duralozam†; Laubeel; Somagerol; Tavor; Tolid; ***Gr.:*** Aripax; Ativan; Cicletan†; Dorm; Modium; Nifalin; Novhepar; Proneurit†; Tavor; Titus; Trankilium; ***Hong Kong:*** Ativan†; LAtiwen; Lorans; Lorivan; Silence; ***India:*** Ativan; Calmese; Larpose; ***Indon.:*** Ativan; Merlopam; Renaquil; ***Irl.:*** Ativan; ***Israel:*** Lorivan; ***Ital.:*** Control; Loralin; Lorans; Tavor; Zeloram; ***Malaysia:*** Ativan; Lorans; ***Mex.:*** Ativan; Sinestron†; ***Neth.:*** Temesta; ***NZ:*** Ativan; Lorapam†; ***Pol.:*** Lorafen; ***Port.:*** Ansilor; Lorenin; Lorsedal; Rialam; ***Rus.:*** Lorafen (Лорафен); ***S.Afr.:*** Ativan; Tranqipam; ***Singapore:*** Ativan; Lorans; ***Spain:*** Donix; Idalprem; Orfidal; Placinoral; Sedicepan; ***Swed.:*** Temesta; ***Switz.:*** Lorasifar; Sedazin; Temesta; ***Thai.:*** Anta; Anxira; Ativan†; Lonza; Lora; Loramed; Lorapam; Lorazene†; Lorazep; Ora; Razepam†; Tranavan†; ***Turk.:*** Ativan; ***UK:*** Ativan; ***USA:*** Ativan; ***Venez.:*** Ativan.

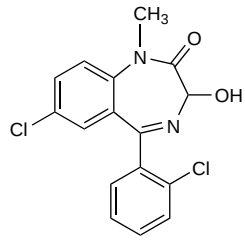
Multi-ingredient: ***Austria:*** Somnium†; ***Switz.:*** Somnium.

Lormetazepam *(BAN, USAN, rINN)*

Lormetatsepaami; Lormétazépam; Lormetazepamum; Wy-4082. (*RS*)-7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-1-methyl-1,4-benzodiazepin-2-one.

Лорметазепам

$C_{16}H_{12}Cl_2N_2O_2$ = 335.2.
CAS — 848-75-9.
ATC — N05CD06.
ATC Vet — QN05CD06.



Pharmacopoeias. In *Br.*
BP 2008 (Lormetazepam). A white crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

Dependence and Withdrawal
As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 0.5 to 1 mg of lormetazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions
As for Diazepam, p.987.

Interactions
As for Diazepam, p.989.

Pharmacokinetics
Lormetazepam is rapidly absorbed from the gastrointestinal tract and metabolised to the inactive glucuronide. The terminal half-life is reported to be about 11 hours.

◊ A brief review of the pharmacokinetics of lormetazepam.[1]

1. Greenblatt DJ, *et al.* Clinical pharmacokinetics of the newer benzodiazepines. *Clin Pharmacokinet* 1983; **8:** 233–52.

Uses and Administration
Lormetazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is mainly used as a hypnotic in the short-term management of insomnia (p.957) in usual oral doses of 0.5 to 1.5 mg at night. A dose of 500 micrograms is recommended for elderly or debilitated patients. Lormetazepam is also used in some countries for premedication (p.1780).

Preparations
BP 2008: Lormetazepam Tablets.

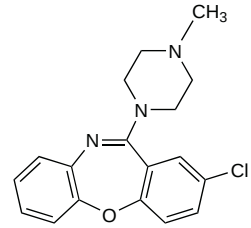
Proprietary Preparations (details are given in Part 3)
Arg.: Dilamet†; ***Austria:*** Noctamid; ***Belg.:*** Doclormeta; Keladormet; Loramet; Loranka; Lormetamed; Metatop; Noctacalm; Noctamid; Octonox; Sedaben; Stilaze; ***Chile:*** Nocton; ***Denm.:*** Pronoctan; ***Fr.:*** Noctamide; ***Ger.:*** Ergocalm; Loretam; Noctamid; ***Gr.:*** Loramet; ***Hong Kong:*** Loramet†; ***Irl.:*** Noctamid; ***Ital.:*** Axilium; Ipnolor; Luzul; Mexylor; Minias; ***Neth.:*** Loramet†; Noctamid; ***NZ:*** Noctamid; ***Pol.:*** Noctofer; ***Port.:*** Noctamid†; ***S.Afr.:*** Loramet; Noctamid; ***Singapore:*** Loramet; ***Spain:*** Aldosomnil; Loramet; Noctamid; ***Switz.:*** Loramet; Noctamid; ***Thai.:*** Loramet†.

Loxapine *(BAN, USAN, rINN)*

CL-62362; Loksapiini; Loxapin; Loxapina; Loxapinum; Oxilapine; SUM-3170. 2-Chloro-11-(4-methylpiperazin-1-yl)dibenz[*b,f*]-[1,4]oxazepine.

Локсапин

$C_{18}H_{18}ClN_3O$ = 327.8.
CAS — 1977-10-2.
ATC — N05AH01.
ATC Vet — QN05AH01.



Loxapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de loxapina; Loxapine, Chlorhydrate de; Loxapini Hydrochloridum.

Локсапина Гидрохлорид

$C_{18}H_{18}ClN_3O,HCl$ = 364.3.
ATC — N05AH01.
ATC Vet — QN05AH01.

Loxapine Succinate *(BANM, USAN, rINNM)*

CL-71563; Loxapine, Succinate de; Loxapini Succinas; Succinato de loxapina.

Локсапина Суксинат

$C_{18}H_{18}ClN_3O,C_4H_6O_4$ = 445.9.
CAS — 27833-64-3.
ATC — N05AH01.
ATC Vet — QN05AH01.

Pharmacopoeias. In *US.*
USP 31 (Loxapine Succinate). A white to yellowish, odourless, crystalline powder. Store in airtight containers.

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

Other adverse effects reported include nausea and vomiting, seborrhoea, dyspnoea, ptosis, headache, paraesthesia, facial flush, weight gain or loss, and polydipsia.

Abuse. There has been a report of 3 cases of loxapine succinate abuse.[1]

1. Sperry L, *et al.* Loxapine abuse. *N Engl J Med* 1984; **310:** 598.

Effects on carbohydrate metabolism. Reversible nonketotic hyperglycaemia, coma, and delirium developed in a patient receiving loxapine 150 mg daily in addition to lithium therapy.[1] Symptoms improved on stopping loxapine, but subsequently recurred when the patient was given amoxapine. The causative agent may have been 7-hydroxyamoxapine, a common metabolite of both amoxapine and loxapine.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Mania. A patient, initially diagnosed as having schizophrenia, developed manic symptoms after receiving loxapine.[1] The diagnosis was revised to schizoaffective disorder but it was suspected that loxapine had a role in the emergence of the affective symptoms. As loxapine shares common metabolites with the antidepressant amoxapine it was suggested that an antidepressant effect might have precipitated the manic symptoms.

1. Gojer JAC. Possible manic side-effects of loxapine. *Can J Psychiatry* 1992; **37:** 669–70.

Overdosage. An 8-year-old child was treated with activated charcoal within 30 minutes of being given 375 mg of loxapine by accident.[1] The child became drowsy and was asleep but arousable 1 hour after ingestion. The degree of sedation appeared to peak after 3.75 hours and the child was discharged about 20 hours after ingestion.

1. Tarricone NW. Loxitane overdose. *Pediatrics* 1998; **101:** 496.

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

Interactions
As for Chlorpromazine, p.973.

Pharmacokinetics
Loxapine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 2 hours. It is very rapidly and extensively metabolised and there is evidence for a first-pass effect. It is mainly excreted in the urine, in the form of its conjugated metabolites, with smaller amounts appearing in the faeces as unconjugated metabolites; a substantial proportion of a dose is excreted in the first 24 hours. The major metabolites of loxapine are the active 7- and 8-hydroxyloxapine, which are conjugated to the glucuronide or sulfate; other metabolites include hydroxyloxapine-*N*-oxide, loxapine-*N*-oxide, and hydroxydesmethylloxapine (hydroxyamoxapine). Loxapine is widely distributed and is thought, on the basis of *animal* studies, to cross the placenta and be distributed into breast milk.

Uses and Administration
Loxapine is a dibenzoxazepine with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It is given orally as the succinate and by intramuscular injection as the base