

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 amnesic 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; Sedativalf; Sidenar; Trapax; Tratenamin†; **Austral.:** Ativan; **Austria:** Merlit; Temesta; **Belg.:** Dozoraz; Lauracalm; Lorazemed; Lorazetop; Loridem; Optisedine; Serenase; Temesta; Vigiten†; **Braz.:** Calmogonol†; 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; Cictetan†; Dorm; Modium; Nifalin; Novhepar; Proneurit†; Tavor; Titus; Trankilium; **Hong Kong:** Ativan†; LAtiven; 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; Loresdal; Rialam; **Rus.:** Lorafen (Лорafen); **S.Afr.:** Ativan; Tranqipam; **Singapore:** Ativan; Lorans; **Spain:** Domix; Idalprem; Orifidal; Placinalor; Sedicepan; **Swed.:** Temesta; **Switz.:** Loratifar; 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)

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

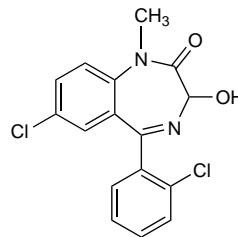
Лорметазепам

$C_{16}H_{12}Cl_2N_2O_2 = 335.2$ .

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.<sup>1</sup>

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; Loretan; Noctamid; **Gr.:** Loramet; **Hong Kong:** Loramet†; **Irl.:** Noctamid; **Ital.:** Axilium; Ipnolor; Luzul; Moxylor; Minias; **Neth.:** Loramet†; Noctamid; **NZ:** Noctamid; **Pol.:** Noctofor; **Port.:** Noctamid†; **S.Afr.:** Loramet; Noctamid; **Singapore:** Loramet; **Spain:** Aldosomnil; Loramet; Noctamid; **Switz.:** Loramet; Noctamid; **Thai.:** Loramet†.

## Loxapine (BAN, USAN, rINN)

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

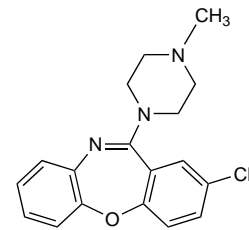
Локсапин

$C_{18}H_{18}ClN_3O = 327.8$ .

CAS — 1977-10-2.

ATC — N05AH01.

ATC Vet — QN05AH01.



## Loxapine Hydrochloride (BANM, rINNM)

Hydrocloruro 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 Сукцинат

$C_{18}H_{18}ClN_3O_4.C_4H_6O_4 = 445.9$ .

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.<sup>1</sup>

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.<sup>1</sup> 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.<sup>1</sup> 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.<sup>1</sup> 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