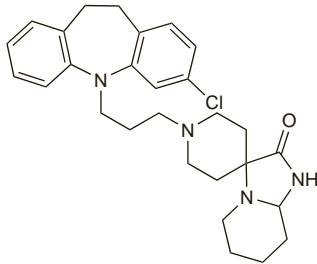


Mosapramine (rINN)

Clospiramine; Mosapramina; Mosapraminum; Y-516. (±)-1'-[3-(3-Chloro-10,11-dihydro-5H-dibenz[*b,f*]azepin-5-yl)propyl]hexahydrospiro[imidazo[1,2-*a*]pyridine-3(2H),4'-piperidin]-2-one.

Мозапрамин
C₂₈H₃₅ClN₄O = 479.1.
CAS — 89419-40-9.
ATC — N05AX10.
ATC Vet — QN05AX10.

**Profile**

Mosapramine is an antipsychotic that has been tried in the treatment of schizophrenia.

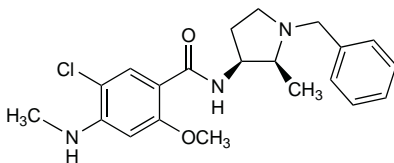
◇ References.

- Ishigooka J, *et al.* Pilot study of plasma concentrations of mosapramine, a new iminodibenzyl antipsychotic agent, after multiple oral administration in schizophrenic patients. *Curr Ther Res* 1994; **55**: 331-42.
- Takahashi N, *et al.* Comparison of risperidone and mosapramine addition to neuroleptic treatment in chronic schizophrenia. *Neuropsychobiology* 1999; **39**: 81-5.

Nemonapride (rINN)

Emonapride; Nemonaprida; Némonapride; Nemonapridum; YM-09151-2. (±)-*cis*-N-(1-Benzyl-2-methyl-3-pyrrolidiny)-5-chloro-4-(methylamino)-*o*-anisamide.

Немонаприд
C₂₁H₂₆ClN₃O₂ = 387.9.
CAS — 93664-94-9.

**Profile**

Nemonapride is a substituted benzamide antipsychotic with general properties similar to those of sulpiride (p.1028). It is given orally in the treatment of schizophrenia in usual doses of 9 to 36 mg daily in divided doses; up to 60 mg daily may be given if necessary.

◇ References.

- Satoh K, *et al.* Effects of nemonapride on positive and negative symptoms of schizophrenia. *Int Clin Psychopharmacol* 1996; **11**: 279-81.

Preparations

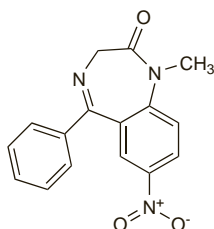
Proprietary Preparations (details are given in Part 3)

Jpn: Emilace.

Nimetazepam (rINN)

Menifazepam; Nimetazéepam; Nimetazepamum; S-1530. 1,3-Dihydro-1-methyl-7-nitro-5-phenyl-1,4-benzodiazepin-2-one.

Ниметазепам
C₁₆H₁₃N₃O₃ = 295.3.
CAS — 2011-67-8.

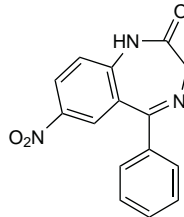
**Profile**

Nimetazepam is a benzodiazepine with the general properties of diazepam (p.986). It has been given orally for the short-term management of insomnia. It appears to have been subject to abuse, especially in South East Asia.

Nitrazepam (BAN, USAN, rINN)

Nitratsepaami; Nitrazéepam; Nitrazepám; Nitrazepamas; Nitrazepamum; NSC-58775; Ro-4-5360; Ro-5-3059. 1,3-Dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one.

Нитразепам
C₁₅H₁₁N₃O₃ = 281.3.
CAS — 146-22-5.
ATC — N05CD02.
ATC Vet — QN05CD02.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of nitrazepam: Don; Moggies; Moogles; Nitro's; The Don.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, and *Jpn.*

Ph. Eur. 6.2 (Nitrazepam). A yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◇ For the purpose of withdrawal regimens, 5 mg of nitrazepam may be considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Effects on the digestive system. Two children given nitrazepam as part of their antiepileptic therapy developed drooling, eating difficulty, and aspiration pneumonia; symptoms improved in one patient when the dosage of nitrazepam was reduced.¹ Manometric studies indicated that the onset of normal cricopharyngeal relaxation in swallowing was delayed in these patients until after hypopharyngeal contraction, resulting in impaired swallowing and spillover of material into the trachea. Other workers² have found similar effects on swallowing and cricopharyngeal relaxation in children given nitrazepam. The deaths of 6 epileptic children under 5 years of age who were treated with nitrazepam have been reported.³ Three of the deaths were unexpected, and in view of the previous reports of swallowing difficulties and aspiration, it was recommended that the use of nitrazepam in young children be restricted to those in whom seizure control fails to improve with other antiepileptics. Another study⁴ also found an apparently increased risk of death, especially in young patients with intractable epilepsy, associated with nitrazepam therapy.

- Wyllie E, *et al.* The mechanism of nitrazepam-induced drooling and aspiration. *N Engl J Med* 1986; **314**: 35-8.
- Lim HCN, *et al.* Nitrazepam-induced cricopharyngeal dysphagia, abnormal esophageal peristalsis and associated bronchospasm: probable cause of nitrazepam-related sudden death. *Brain Dev* 1992; **14**: 309-14.
- Murphy JV, *et al.* Deaths in young children receiving nitrazepam. *J Pediatr* 1987; **111**: 145-7.
- Rintahaka PJ, *et al.* Incidence of death in patients with intractable epilepsy during nitrazepam treatment. *Epilepsia* 1999; **40**: 492-6.

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

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Nitrazepam is fairly readily absorbed from the gastrointestinal tract, although there is some individual variation. It is about 87% bound to plasma proteins. It crosses the blood-brain and the placental barriers and traces are found in breast milk. Nitrazepam is metabolised in the liver, mainly by nitroreduction followed by

acetylation; none of the metabolites possess significant activity. It is excreted in the urine in the form of its metabolites (free or conjugated) with only small amounts of a dose appearing unchanged. Up to about 20% of an oral dose is found in the faeces. Mean elimination half-lives of 24 to 30 hours have been reported.

Distribution into breast milk. A mean milk-to-plasma ratio of 0.27 was obtained after giving nitrazepam 5 mg for 5 nights to 9 puerperal women.¹ The accumulation of nitrazepam in milk over the study period was similar to that in plasma.

- Matheson I, *et al.* Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30**: 787-93.

Hepatic impairment. The pharmacokinetics of intravenous nitrazepam in 12 patients with cirrhosis of the liver has been compared with 9 healthy subjects aged 22 to 49 years and 8 healthy elderly subjects aged 67 to 76 years.¹ The mean elimination half-life of nitrazepam was 26 hours in young and 38 hours in elderly subjects, the difference, which was not significant, being chiefly due to the greater volume of distribution in elderly subjects. Although there was also no significant difference between young and elderly subjects in percentage of unbound nitrazepam (13.0 and 13.9% respectively) there was a substantially higher unbound fraction in the patients with cirrhosis, the mean value being 18.9%, and clearance of unbound nitrazepam was reduced relative to healthy subjects.

- Jochems R, *et al.* Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. *Br J Clin Pharmacol* 1983; **15**: 295-302.

Metabolism. Although the acetylation of the reduced metabolite of nitrazepam has been reported to be controlled by acetylator phenotype,¹ no significant differences between either half-life or residual effects of nitrazepam were observed in slow and fast acetylators.²

- Karim AKMB, Price Evans DA. Polymorphic acetylation of nitrazepam. *J Med Genet* 1976; **13**: 17-19.
- Swift CG, *et al.* Acetylator phenotype, nitrazepam plasma concentrations and residual effects. *Br J Clin Pharmacol* 1980; **9**: 312P-313P.

Uses and Administration

Nitrazepam is an intermediate-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 is reported to act in 30 to 60 minutes to produce sleep lasting for 6 to 8 hours. Nitrazepam has also been used in epilepsy, notably for infantile spasms (see below).

The usual oral dose for insomnia is 5 mg at night, although 10 mg may be required in some patients. Elderly or debilitated patients should not be given more than half of the normal adult dose.

Epilepsy. Benzodiazepines are sometimes employed in the management of epilepsy (p.465), but their long-term use is limited by problems of sedation, dependence, and tolerance to the antiepileptic effects. Nitrazepam has perhaps been most useful in the treatment of infantile spasms (as for example in West's syndrome) and the so-called infantile myoclonic seizures. The *BNFC* suggests that those aged from 1 month to 2 years may be given initial oral doses of 125 micrograms/kg twice daily, adjusted according to response over 2 to 3 weeks to 250 micrograms/kg twice daily (maximum 500 micrograms/kg, but not exceeding 5 mg, twice daily); the same total daily dose may also be given in 3 divided doses. There has been concern, however, over swallowing difficulties with subsequent aspiration and reports of unexpected death associated with the use of nitrazepam in young children (see Effects on the Digestive System under Adverse Effects, above).

Preparations

BP 2008: Nitrazepam Oral Suspension; Nitrazepam Tablets.

Proprietary Preparations (details are given in Part 3)

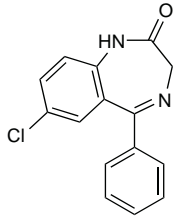
Austral.: Alodorm; Mogadon; **Austria:** Mogadon; **Belg.:** Mogadon; **Braz.:** Nitrapan; Nitrazepol; Sonebon; **Canad.:** Mogadon; Nitrazadon; **Denm.:** Apodorm; Mogadon; Pacisyn; **Fin.:** Insomin; **Fr.:** Mogadon; **Ger.:** Dormalon; Dormo-Puren; Eatan N; Imeson; Mogadon; Novanox; Radedorm; **Hong Kong:** Mogadon; **Hung.:** Eunoctin; **India:** Hypnotex; Nitavan; Nitratravet; **Indon.:** Dumolid; **Irl.:** Mogadon; Somnite†; **Israel:** Numbon; **Ital.:** Mogadon; **Malaysia:** Mogadon†; **Neth.:** Mogadon; **Norw.:** Apodorm; Mogadon; **NZ:** Insoma; Nitrados; **Rus.:** Eunoctin (Эуноктин); Nitrosun (Нитросун); Radedorm (Радеаорм); **S.Afr.:** Arem; Mogadon; Ormodon; Paxadorm; **Singapore:** Dima; Nitrados; **Swed.:** Apodorm; Mogadon; **Switz.:** Mogadon; **Thai.:** Alodorm†; Nitrados†; **UK:** Mogadon; Remnos; Somnite; **Venez.:** Onirema.

Multi-ingredient: Arg.; Cavodan†.

Nordazepam (*nINN*)

A-101; Demethyl diazepam; Desmethyl diazepam; N-Desmethyl diazepam; Nordazepam; Nordazepamum; Nordiazepam; Ro-5-2180. 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one.

Нордазепам
 $C_{15}H_{11}ClN_2O = 270.7$
 CAS — 1088-11-5.
 ATC — N05BA16.
 ATC Vet — QN05BA16.

**Profile**

Nordazepam is a long-acting benzodiazepine with the general properties of diazepam (p.986). It is the principal active metabolite of a number of benzodiazepines and has a half-life of 2 to 5 days. It is given in oral doses of up to 15 mg daily for the short-term treatment of anxiety disorders (p.952) and insomnia (p.957).

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

Preparations

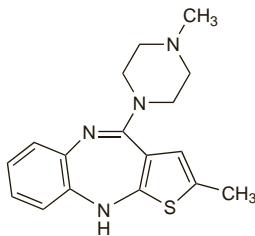
Proprietary Preparations (details are given in Part 3)

Belg.: Calmday; **Fr.:** Nordaz; **Ger.:** Tranxilium N; **Ital.:** Madar; **Port.:** Sopax; **Singapore:** Nordaz.

Olanzapine (BAN, USAN, *nINN*)

LY-170053; Olantsapiini; Olanzapin; Olanzapina; Olanzapinum. 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.

Оланзапин
 $C_{17}H_{20}N_4S = 312.4$
 CAS — 132539-06-1.
 ATC — N05AH03.
 ATC Vet — QN05AH03.



Stability. A suspension of olanzapine 1 mg/mL, made by crushing olanzapine tablets and suspending the powder in a syrup-based mixture containing carboxymethylcellulose preserved with methyl hydroxybenzoate and propyl hydroxybenzoate (Guy's Hospital paediatric base formula), was considered to be stable for 2 weeks when stored in a refrigerator.¹

1. Harvey EJ, *et al.* The preparation and stability of a liquid olanzapine preparation for oral administration in hospitals. *Pharm J* 2000; **265**: 275–6.

Adverse Effects, Treatment, and Precautions

Although olanzapine may share some of the adverse effects seen with the classical antipsychotics (see Chlorpromazine, p.969), the incidence and severity of such effects may vary. The most frequent adverse effects with olanzapine are somnolence and weight gain; hyperprolactinaemia is also common, but usually asymptomatic. Increased appetite, dizziness, fatigue, elevated plasma glucose, triglyceride, and liver enzyme values, eosinophilia, oedema, orthostatic hypotension, and mild transient antimuscarinic effects such as constipation and dry mouth are also relatively common. More severe abnormalities of glucose homeostasis are

uncommon; severe hyperglycaemia, or exacerbation of pre-existing diabetes, sometimes leading to ketoacidosis, coma, or death, has occurred. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Clinical monitoring of plasma lipids and weight have also been recommended.

Olanzapine is associated with a low incidence of extrapyramidal effects, including tardive dyskinesia, although these effects may be more likely at high doses and in the elderly; the risk of tardive dyskinesia also increases with long-term use. Neuroleptic malignant syndrome has been reported rarely.

Patients receiving olanzapine intramuscularly should be closely observed for 2 to 4 hours for hypotension, bradyarrhythmia, and hypoventilation. Olanzapine should not be given intramuscularly to patients with a history of cardiovascular disease or following heart surgery; caution is recommended when giving olanzapine by mouth to such patients and to those with cerebrovascular disease or conditions predisposing to hypotension. It is recommended that blood pressure is periodically assessed in elderly patients.

The antimuscarinic effects of olanzapine contra-indicate its use in patients with angle-closure glaucoma; caution is also advised in those with conditions such as benign prostatic hyperplasia or paralytic ileus. Olanzapine is also not recommended in Parkinson's disease since its use has commonly been associated with an increase in parkinsonian symptoms and hallucinations. It should be used with caution in patients with hepatic impairment, or a history of blood dyscrasias, bone marrow depression, or myeloproliferative disease. Seizures are rare with olanzapine but it should be used with care in those with a history of seizures or with conditions that lower the seizure threshold.

Olanzapine may affect the performance of skilled tasks such as driving.

Withdrawal symptoms, including sweating, tremor, anxiety, and nausea and vomiting, have occurred rarely when olanzapine has been stopped abruptly; a gradual dose reduction may be appropriate when stopping olanzapine.

◇ References.

- Beasley CM, *et al.* Safety of olanzapine. *J Clin Psychiatry* 1997; **58** (suppl 10): 13–17.
- Biswas PN, *et al.* The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *J Psychopharmacol* 2001; **15**: 265–71.

Breast feeding. From a study¹ of the distribution of olanzapine into breast milk in 7 breast feeding women taking a median dose of 7.5 mg daily, it was estimated that the weight-adjusted median dose ingested by the breast-fed infants was 1.02% of the maternal dose. Olanzapine was not detected in the plasma of the 6 infants from whom a sample was taken; no adverse effects were observed in all 7 infants. However, UK licensed product information states that at steady state the estimated mean exposure of breast-fed infants of mothers taking olanzapine would be 1.8% of the maternal dose and recommends that patients should not breast feed if they are taking olanzapine.

- Gardiner SJ, *et al.* Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *Am J Psychiatry* 2003; **160**: 1428–31.

Dementia. For details of a possibly increased risk of mortality in elderly patients with dementia given olanzapine and other atypical antipsychotics, see under Risperidone, p.1024.

Effects on the blood. A review¹ has described 11 reports of olanzapine-associated haematotoxicity that included 3 cases of agranulocytosis, 6 of neutropenia, and 2 of leucopenia. In most cases, the haematotoxicity developed within the first month of treatment and patients recovered after olanzapine withdrawal. There was a history of clozapine-associated haematotoxicity in 5 patients. It was suggested that white blood cell counts should be monitored periodically during olanzapine treatment.

Olanzapine has also apparently delayed recovery of granulocyte counts in patients with clozapine-induced granulocytopenia who were switched to olanzapine before blood counts had returned to the normal range.²

There have been case reports^{3,4} of thrombocytopenia associated with olanzapine treatment. In one report,³ the patient improved on stopping olanzapine but subsequently had a similar episode associated with benzatropine therapy. In another report,⁴ an elderly patient with pre-existing idiopathic thrombocytopenic purpura died from bleeding complications due to thrombocytopenia

associated with olanzapine treatment; the patient's plasma concentration of olanzapine was reported to be 10 times the usual mean therapeutic value.

- Tolosa-Viella C, *et al.* Olanzapine-induced agranulocytosis: a case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26**: 411–4.
- Flynn SW, *et al.* Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997; **17**: 494–5.
- Bogunovic O, Viswanathan R. Thrombocytopenia possibly associated with olanzapine and subsequently with benzatropine mesylate. *Psychosomatics* 2000; **41**: 277–88.
- Carrillo JA, *et al.* Thrombocytopenia and fatality associated with olanzapine. *Eur J Clin Pharmacol* 2004; **60**: 295–6.

Effects on body temperature. Olanzapine has been associated with occasional reports of hyperthermia. In one report¹ body temperature fell as low as 33.4° over several days in a woman receiving olanzapine for bipolar disorder. The patient, who also had subclinical hypothyroidism, was asymptomatic, and body temperature returned to normal once olanzapine was stopped; it was unclear whether the endocrine abnormalities had contributed to the condition.

- Blass DM, Chuen M. Olanzapine-associated hypothermia. *Psychosomatics* 2004; **45**: 135–9.

Effects on body-weight. The increased risk of weight gain with some atypical antipsychotics is discussed under Adverse Effects of Clozapine, p.981.

Further references.

- Haberfeller EM, Rittmannerberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004; **19**: 251–3.
- Hennen J, *et al.* Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry* 2004; **65**: 1679–87.
- Hester EK, Thrower MR. Current options in the management of olanzapine-associated weight gain. *Ann Pharmacother* 2005; **39**: 302–10.

Effects on carbohydrate metabolism. The increased risk of glucose intolerance and diabetes mellitus with some atypical antipsychotics, and recommendations on monitoring, are discussed under Adverse Effects of Clozapine, p.981.

Further references for such effects associated with olanzapine use are given below; in some cases the outcome was fatal.

- Bettinger TL, *et al.* Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; **34**: 865–7.
- Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketotic coma. *Ann Pharmacother* 2001; **35**: 300–302.
- Bonanno DG, *et al.* Olanzapine-induced diabetes mellitus. *Ann Pharmacother* 2001; **35**: 563–5.
- Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001; **35**: 1556–8.
- Koller E, *et al.* Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 2001; **286**: 2547–8.
- CSM. Olanzapine (Zyprexa) and diabetes. *Current Problems* 2002; **28**: 3. Also available at: http://www.mhra.gov.uk/home/idcpl?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
- Koro CE, *et al.* Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. *BMJ* 2002; **325**: 243–5.
- Ramaswamy K, *et al.* Risk of diabetic ketoacidosis after exposure to risperidone or olanzapine. *Drug Safety* 2007; **30**: 589–99.

Effects on the cardiovascular system. Two of 3 elderly patients who developed venous thromboembolism shortly after starting treatment with olanzapine also had symptoms of pulmonary embolism.¹ There have been 2 further isolated cases^{2,3} of pulmonary embolism associated with olanzapine therapy; it had been reported in a 28-year-old man² and in a 22-year-old man³ after 10 weeks and after 6 months of olanzapine therapy, respectively. Both patients recovered and were switched to another atypical antipsychotic.

- Hägg S, *et al.* Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol* 2003; **18**: 299–300.
- Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ* 2003; **327**: 1384.
- Health Canada. Olanzapine (Zyprexa): suspected association with pulmonary embolism. *Can Adverse React News* 2005; **15** (1): 5. Also available at: http://www.hc-sc.gc.ca/dhp-mpps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/08/08)

Effects on lipid metabolism. The increased risk of hyperlipidaemia with some atypical antipsychotics is discussed under Adverse Effects of Chlorpromazine, p.970. See also Effects on Carbohydrate Metabolism under Adverse Effects of Clozapine, p.981.

Further references.

- Osser DN, *et al.* Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry* 1999; **60**: 767–70.

Effects on the liver. A report¹ of acute hepatocellular cholestatic jaundice that developed in a 78-year-old woman 13 days after starting treatment with olanzapine.

- Jadallah KA, *et al.* Acute hepatocellular-cholestatic liver injury after olanzapine therapy. *Ann Intern Med* 2003; **138**: 357–8.

Effects on the nervous system. A 31-year-old woman with a complicated medical history suffered three generalised tonic-clonic seizures after 13 days of therapy with olanzapine.¹ She recovered after treatment with phenytoin. Another patient with Huntington's disease also suffered a severe generalised tonic-clonic seizure following treatment with olanzapine 30 mg daily