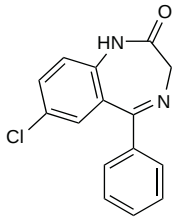
Nordazepam *(rINN)*

A-101; Demethyldiazepam; Desmethyldiazepam; *N*-Desmethyldiazepam; Nordazépam; Nordazepamum; Nordiazepam; Ro-5-2180. 7-Chloro-1,3-dihydro-5-phenyl-2*H*-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

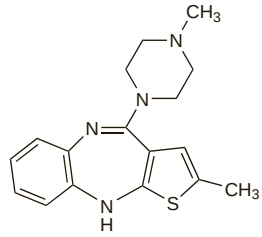
Proprietary Preparations (details are given in Part 3)
Belg.: Calmday; ***Fr.:*** Nordaz; ***Ger.:*** Tranxilium N; ***Ital.:*** Madar; ***Port.:*** Sopax; ***Singapore:*** Nordaz.

Olanzapine *(BAN, USAN, rINN)*

LY-170053; Olantsapiini; Olanzapin; Olanzapina; Olanzapinum. 2-Methyl-4-(4-methyl-1-piperazinyl)-10*H*-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 homoeostasis 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.

1. Beasley CM, *et al.* Safety of olanzapine. *J Clin Psychiatry* 1997; **58** (suppl 10): 13–17.
2. Biswasl 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 study[1] 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.

1. 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 review[1] 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.

1. Tolosa-Vilella C, *et al.* Olanzapine-induced agranulocytosis: a case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 411–4.
2. Flynn SW, *et al.* Prolongation of clozapine-induced granulocytopenia associated with olanzapine. *J Clin Psychopharmacol* 1997; **17:** 494–5.
3. Bogunovic O, Viswanathan R. Thrombocytopenia possibly associated with olanzapine and subsequently with benztropine mesylate. *Psychosomatics* 2000; **41:** 277–88.
4. 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 hypothermia. In one report[1] 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.

1. 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.

1. Haberfellner EM, Rittmannsberger H. Weight gain during long-term treatment with olanzapine: a case series. *Int Clin Psychopharmacol* 2004; **19:** 251–3.
2. Hennen J, *et al.* Weight gain during treatment of bipolar I patients with olanzapine. *J Clin Psychiatry* 2004; **65:** 1679–87.
3. 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.

1. Bettinger TL, *et al.* Olanzapine-induced glucose dysregulation. *Ann Pharmacother* 2000; **34:** 865–7.
2. Roefaro J, Mukherjee SM. Olanzapine-induced hyperglycemic nonketonic coma. *Ann Pharmacother* 2001: **35:** 300–302.
3. Bonanno DG, *et al.* Olanzapine-induced diabetes mellitus. *Ann Pharmacother* 2001; **35:** 563–5.
4. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. *Ann Pharmacother* 2001; **35:** 1556–8.
5. Koller E, *et al.* Atypical antipsychotic drugs and hyperglycemia in adolescents. *JAMA* 2001; **286:** 2547–8.
6. CSM. Olanzapine (Zyprexa) and diabetes. *Current Problems* 2002; **28:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 21/08/08)
7. 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.
8. 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 man[2] and in a 22-year-old man[3] after 10 weeks and after 6 months of olanzapine therapy, respectively. Both patients recovered and were switched to another atypical antipsychotic.

1. Hägg S, *et al.* Olanzapine and venous thromboembolism. *Int Clin Psychopharmacol* 2003; **18:** 299–300.
2. Waage IM, Gedde-Dahl A. Pulmonary embolism possibly associated with olanzapine treatment. *BMJ* 2003; **327:** 1384.
3. 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-mps/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.

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

Effects on the liver. A report[1] of acute hepatocellular cholestatic jaundice that developed in a 78-year-old woman 13 days after starting treatment with olanzapine.

1. 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