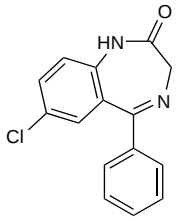
Nordazepam *(rINN)*

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

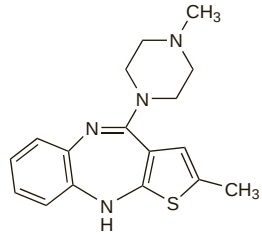
Proprietary Preparations (details are given in Part 3)
Belg.: Calmday; ***Fr.:*** Nordaz; ***Ger.:*** Tranxilium N; ***Ital.:*** Madar; ***Port.:*** Sopax; ***Singapore:*** Nordaz.

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

for 1 month.[2] Olanzapine was continued but carbamazepine was added; there was no recurrence of the seizure.

1. Lee JW, *et al.* Seizure associated with olanzapine. *Ann Pharmacother* 1999; **33:** 554–6.
2. Bonelli RM. Olanzapine-associated seizure. *Ann Pharmacother* 2003; **37:** 149–50.

Effects on the pancreas. There have been isolated reports of pancreatitis associated with olanzapine.[1-3] See also under Clozapine, p.982.

1. Doucette DE, *et al.* Olanzapine-induced acute pancreatitis. *Ann Pharmacother* 2000; **34:** 1128–31.
2. Hagger R, *et al.* Olanzapine and pancreatitis. *Br J Psychiatry* 2000; **177:** 567.
3. Waage C, *et al.* Olanzapine-induced pancreatitis: a case report. *JOP* 2004; **5:** 388–91.

Effects on sexual function. Priapism has been reported[1,2] in 2 patients receiving olanzapine.

1. Deirmenjian JM, *et al.* Olanzapine-induced reversible priapism: a case report. *J Clin Psychopharmacol* 1998; **18:** 351–3.
2. Songer DA, Barclay JC. Olanzapine-induced priapism. *Am J Psychiatry* 2001; **158:** 2087–8.

Extrapyramidal disorders. There have been isolated reports[1,2] of tardive dyskinesia associated with olanzapine treatment. However, the incidence of extrapyramidal effects (p.971) is generally lower with atypical than classical antipsychotics.

1. Herrán A, Vázquez-Barquero JL. Tardive dyskinesia associated with olanzapine. *Ann Intern Med* 1999; **131:** 72.
2. Bella VL, Piccoli F. Olanzepine-induced tardive dyskinesia. *Br J Psychiatry* 2003; **182:** 81–2.

Mania. Although olanzapine is used in the treatment of bipolar disorder, it has been associated with reports of mania in both schizophrenic and bipolar patients.[1-4] A report sponsored by the manufacturers noted that no association was seen in pooled data from 2 placebo-controlled studies involving 254 bipolar patients.[5]

1. Lindenmayer J-P, Klebanov R. Olanzapine-induced manic-like syndrome. *J Clin Psychiatry* 1998; **59:** 318–19.
2. Fitz-Gerald MJ, *et al.* Olanzapine-induced mania. *Am J Psychiatry* 1999; **156:** 1114.
3. Aubry J-M, *et al.* Possible induction of mania and hypomania by olanzapine or risperidone: a critical review of reported cases. *J Clin Psychiatry* 2000; **61:** 649–55.
4. Henry C, Demotes-Mainard J. Olanzapine-induced mania in bipolar disorders. *J Psychiatry Neurosci* 2002; **27:** 200–201.
5. Baker RW, *et al.* Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord* 2003; **73:** 147–53.

Neuroleptic malignant syndrome. Cases of neuroleptic malignant syndrome (p.972) have been associated with olanzapine therapy.[1-4]

1. Filice GA, *et al.* Neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 1998; **32:** 1158–9.
2. Nyfort-Hansen K, Alderman CP. Possible neuroleptic malignant syndrome associated with olanzapine. *Ann Pharmacother* 2000; **34:** 667.
3. Suh H, *et al.* Neuroleptic malignant syndrome and low-dose olanzapine. *Am J Psychiatry* 2003; **160:** 796.
4. Kogoj A, Velikonja I. Olanzapine induced neuroleptic malignant syndrome–a case review. *Hum Psychopharmacol* 2003; **18:** 301–9.

Overdosage. A 2½-year-old boy was found sleeping and difficult to arouse after taking one or two 7.5-mg olanzapine tablets.[1] His reported symptoms included agitation, aggressive behaviour, miosis, hypersalivation, tachycardia, and ataxia; he recovered after 24 hours. Symptoms suggestive of diabetes insipidus, together with mild CNS depression, have also been reported,[2] in an adolescent who took 75 mg of olanzapine with a small quantity of prazepam. The polyuria responded to desmopressin. A review[3] identified 29 fatalities associated with olanzapine overdose, but evidence of a direct causative relationship was limited.

1. Yip L, *et al.* Olanzapine toxicity in a toddler. *Pediatrics* 1998; **102:** 1494.
2. Etienne L, *et al.* Polyuria after olanzapine overdose. *Am J Psychiatry* 2004; **161:** 1130.
3. Chue P, Singer P. A review of olanzapine-associated toxicity and fatality in overdose. *J Psychiatry Neurosci* 2003; **28:** 253–61.

Parkinsonism. Worsening of motor function has been reported[1-4] in patients with parkinsonism after use of olanzapine.

1. Graham JM, *et al.* Olanzapine in the treatment of hallucinosis in idiopathic Parkinson's disease: a cautionary note. *J Neurol Neurosurg Psychiatry* 1998 **65:** 774–7.
2. Molho ES, Factor SA. Worsening of motor features of parkinsonism with olanzapine. *Mov Disord* 1999; **14:** 1014–16.
3. Goetz CG, *et al.* Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. *Neurology* 2000; **55:** 789–94.
4. Manson AJ, *et al.* Low-dose olanzapine for levodopa induced dyskinesias. *Neurology* 2000; **55:** 795–9.

Pregnancy. The manufacturer has reviewed both prospective and retrospective cases of pregnancies that have been exposed to olanzapine treatment.[1] Of the 37 prospective pregnancies, there were 14 therapeutic abortions (with no reported abnormality in the fetus), 3 spontaneous abortions (again with no reported abnormality in the fetus), and 1 still-birth. The remaining 19 pregnancies included 16 normal births without complications and 1 premature birth; the 2 other births were complicated by post-term deliveries. Eleven retrospective cases were also identified and included 2 cases of major malformation (dysplastic kidney and Down's syndrome), 1 case of fetal death following an overdose by the mother, and 1 case each of neonatal convulsion and sudden infant death. For comments on the use of some atypical antipsychotics, including olanzapine, during pregnancy, see under Precautions of Clozapine, p.983.

1. Goldstein DJ, *et al.* Olanzapine-exposed pregnancies and lactation: early experience. *J Clin Psychopharmacol* 2000; **20:** 399–403.

Speech disorders. Although olanzapine may be used in the treatment of stuttering, it has also been associated with reports of the development of the disorder, see under Uses and Administration, below.

Interactions

The central effects of other CNS depressants, including alcohol, may be enhanced by olanzapine. Olanzapine may antagonise the effects of dopaminergics. Neutropenia may be more common when olanzapine is given with valproate. Use with valproate or lithium has also been associated with an increased incidence of tremor, dry mouth, increased appetite, and weight gain.There is a theoretical risk of QT prolongation when olanzapine is given with other drugs that are known to cause this effect.

Drugs that induce hypotension, bradycardia, or respiratory depression should be used with caution in patients given intramuscular olanzapine. Parenteral benzodiazepine treatment should be given at least 1 hour after intramuscular olanzapine as it is recommended that they are not given together.

The metabolism of olanzapine is mediated to some extent by the cytochrome P450 isoenzyme CYP1A2. Use with drugs that inhibit, induce, or act as a substrate to this isoenzyme may affect plasma concentrations of olanzapine and a dose adjustment of olanzapine may be required. The CYP1A2 inhibitor fluvoxamine significantly inhibits the metabolism of olanzapine. The clearance of olanzapine is increased by tobacco smoking and carbamazepine.

Valproate. In a study of 4 patients, valproate reduced plasma concentrations of olanzapine by 32.3 to 78.8% (mean 53.6%).[1]

1. Bergemann N, *et al.* Valproate lowers plasma concentrations of olanzapine. *Pharmacopsychiatry* 2005; **38:** 44.

Pharmacokinetics

Olanzapine is well absorbed from the gastrointestinal tract after oral doses but undergoes considerable first-pass metabolism. Peak plasma concentrations are achieved about 5 to 8 hours after oral doses and about 15 to 45 minutes after an intramuscular dose. Olanzapine is about 93% bound to plasma proteins. It is extensively metabolised in the liver, primarily by direct glucuronidation and by oxidation mediated through the cytochrome P450 isoenzymes CYP1A2, and, to a lesser extent, CYP2D6. The 2 major metabolites 10-*N*-glucuronide and 4′-*N*-desmethyl olanzapine appear to be inactive. About 57% of a dose is excreted in the urine, mainly as metabolites, and about 30% appears in the faeces. The mean plasma elimination half-life has been variously reported to be about 30 to 38 hours; half-lives tend to be longer in female than in male patients. Olanzapine is distributed into breast milk.

◊ References.

1. Callaghan JT, *et al.* Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999; **37:** 177–93.
2. Markowitz JS, *et al.* Pharmacokinetics of olanzapine after single-dose oral administration of standard tablet versus normal and sublingual administration of an orally disintegrating tablet in normal volunteers. *J Clin Pharmacol* 2006; **46:** 164–71.

Uses and Administration

Olanzapine is a thienobenzodiazepine atypical antipsychotic. It has affinity for serotonin, muscarinic, histamine (H_1), and adrenergic (α_1) receptors as well as various dopamine receptors.

Olanzapine is used for the management of schizophrenia and for the treatment of moderate to severe mania associated with bipolar disorder.

In the UK, the usual initial oral dose for **schizophrenia** is 10 mg daily as a single dose; thereafter dosage adjustments may be made according to response at intervals of not less than 24 hours to within the range of 5 to 20 mg daily. In the USA, the starting dose is 5 to 10 mg daily and it is recommended that dosage adjustments beyond 10 mg daily are made at intervals of not less than 1 week; the daily dosage should be adjusted in steps of 5 mg. However, it is recommended that doses above 10 mg daily should be given only after clinical reassessment.

For the treatment of **acute mixed or manic episodes** in bipolar disorder, a recommended initial oral dose is 10 or 15 mg daily as monotherapy or 10 mg if given as part of combination therapy; the daily dosage may be adjusted in steps of 5 mg if necessary, at intervals of not less than 24 hours to a dose of between 5 and 20 mg daily. If a response is achieved, therapy may continue at the same dosage to prevent recurrence. For **prevention of recurrence** in patients whose manic episodes have responded previously to olanzapine, the recommended starting dose is 10 mg daily.

For the **rapid control of agitation and disturbed behaviour** in patients with schizophrenia or mania, olanzapine may be given intramuscularly in an initial dose of 5 to 10 mg followed by 5 to 10 mg as required after 2 hours. Not more than 3 injections should be given in any 24-hour period and the maximum daily dose, including olanzapine given orally, should not exceed 20 mg. Injections may be given for up to a maximum of 3 days but transfer to oral therapy should be started as soon as possible.

The metabolism of olanzapine might be slower in female, elderly, or non-smoking patients; if more than one of these factors is present, a lower initial dose (e.g. 5 mg daily if given orally) and a more gradual dose escalation should be considered. The intramuscular dose should be reduced by half in the elderly. See below for doses in patients with hepatic or renal impairment.

Administration in hepatic or renal impairment. A starting dose of 5 mg daily of olanzapine orally or by intramuscular injection may be necessary for patients with renal or hepatic impairment; for patients with moderate hepatic insufficiency, the starting dose should only be increased with caution.

Bipolar disorder. Olanzapine is of benefit for the treatment of mania, with or without psychosis, in patients with bipolar disorder (p.372), and the use of atypical antipsychotics in the management of such patients is increasing. However, there have been individual case reports of olanzapine-induced mania (see above). There is also increasing interest in the use of olanzapine for the depressive phase of bipolar disorder, and for other forms of resistant depression. In some countries olanzapine is available as a fixed-dose combination with fluoxetine for use in the former condition.

References.

1. Shelton RC, *et al.* A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001; **158:** 131–4.
2. Rendell JM, *et al.* Olanzapine alone or in combination for acute mania. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 24/05/05).
3. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar I disorder. *Drugs* 2004; **64:** 2709–26.
4. Shelton RC. Olanzapine/fluoxetine combination for bipolar depression. *Expert Rev Neurother* 2006; **6:** 33–9.

Nausea and vomiting. For mention of the use of olanzapine as a second-line drug to control nausea and vomiting in palliative care see p.1700.

Parkinsonism. Olanzapine is associated with a relatively low incidence of extrapyramidal disorders and has been studied[1] for use in the treatment of psychosis in patients with Parkinson's disease (see Disturbed Behaviour, p.954). However, there have been a number of reports of adverse effects including exacerbation of the movement disorder (see Parkinsonism, under Precautions, above).

1. Wolters EC, *et al.* Olanzapine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. *Neurology* 1996; **47:** 1085–7.

Psychiatric disorders. The main treatment for *post-traumatic stress disorder* (p.953) is psychotherapy but adjunctive olanzapine may be used in patients refractory to psychotherapy and/or drug treatment with antidepressants. Olanzapine has also been tried for the control of *aggression* in children with autism and conduct disorder (see Disturbed Behaviour, p.954).

Schizophrenia. Studies suggest that olanzapine is as effective as haloperidol against positive symptoms of schizophrenia (p.955) and more effective against negative symptoms in the short-term and possibly in the long-term,[1-5] although a systematic review considered the evidence equivocal.[6] Quality of life has also been judged to be greater in patients treated with olanzapine.[7] In comparative studies, extrapyramidal adverse effects have been less frequent with olanzapine than haloperidol and fewer patients have discontinued treatment with olanzapine. There are

relatively few published comparisons with other atypical antipsychotics, but one systematic review[8] concluded that there was little to differentiate between olanzapine and risperidone apart from their adverse effects; risperidone was particularly associated with movement disorders and sexual dysfunction while olanzapine induced rapid weight gain. Another study has suggested that olanzapine is not inferior to clozapine.[9] Olanzapine's efficacy in the treatment of patients with refractory schizophrenia remains to be determined; a small, randomised study found it to be no more effective than haloperidol.[10]

1. Beasley CM, *et al.* Olanzapine HGAD Study Group. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* 1996; **14:** 111–23.
2. Beasley C, *et al.* Olanzapine versus haloperidol: long-term results of the multi-center international trial. *Eur Neuropsychopharmacol* 1996; **6** (suppl 3): 59.
3. Beasley CM, *et al.* Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* 1997; **7:** 125–37.
4. Tollefson GD, *et al.* Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. *Am J Psychiatry* 1997; **154:** 457–65.
5. Bhana N, *et al.* Olanzapine: an updated review of its use in the management of schizophrenia. *Drugs* 2001; **61:** 111–61.
6. Duggan L, *et al.* Olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 24/05/05).
7. Hamilton SH, *et al.* Olanzapine versus placebo and haloperidol: quality of life and efficacy results of the North American double-blind trial. *Neuropsychopharmacology* 1998; **18:** 41–9.
8. Jayaram MB, *et al.* Risperidone versus olanzapine for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 16/01/07).
9. Naber D, *et al.* Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatr Scand* 2005; **111:** 106–15.
10. Buchanan RW, *et al.* Olanzapine treatment of residual positive and negative symptoms. *Am J Psychiatry* 2005; **162:** 124–9.

Stuttering. Although olanzapine may be of benefit in the treatment of stuttering (p.1001),[1,2] it has been associated with reports of stuttering in 6 adult patients with schizophrenia or depression.[3]

1. Lavid N, *et al.* Management of child and adolescent stuttering with olanzapine: three case reports. *Ann Clin Psychiatry* 1999; **11:** 233–6.
2. Maguire GA, *et al.* Olanzapine in the treatment of developmental stuttering: a double-blind, placebo-controlled trial. *Ann Clin Psychiatry* 2004; **16:** 63–7.
3. Bär KJ, *et al.* Olanzapine- and clozapine-induced stuttering: a case series. *Pharmacopsychiatry* 2004; **37:** 131–4.

Tourette's syndrome. When drug treatment is required for tics and behavioural disturbances in Tourette's syndrome (see Tics, p.954) haloperidol or pimozide are commonly used but atypical antipsychotics, including olanzapine, are increasingly being tried.[1-4]

1. Stamenkovic M, *et al.* Effective open-label treatment of tourette's disorder with olanzapine. *Int Clin Psychopharmacol* 2000; **15:** 23–8.
2. Onofrj M, *et al.* Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. *J Neurol* 2000; **247:** 443–6.
3. Budman CL, *et al.* An open-label study of the treatment efficacy of olanzapine for Tourette's disorder. *J Clin Psychiatry* 2001; **62:** 290–4.
4. Stephens RJ, *et al.* Olanzapine in the treatment of aggression and tics in children with Tourette's syndrome: a pilot study. *J Child Adolesc Psychopharmacol* 2004; **14:** 255–66.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Midax; Zyprexa; ***Austral.:*** Zyprexa; ***Austria:*** Zyprexa; ***Belg.:*** Zyprexa; ***Braz.:*** Zyprexa; ***Canad.:*** Zyprexa; ***Chile:*** Olvin; Zyprexa; ***Cz.:*** Zalasta; Zyprexa; ***Denm.:*** Zyprexa; ***Fin.:*** Zyprexa; ***Fr.:*** Zyprexa; ***Ger.:*** Zyprexa; ***Gr.:*** Zyprexa; ***Hong Kong:*** Zyprexa; ***Hung.:*** Zyprexa; ***India:*** Joyzol; Olexar; Ozapin; Psycholanz; ***Indon.:*** Zyprexa; ***Irl.:*** Zyprexa; ***Israel:*** Zyprexa; ***Ital.:*** Zyprexa; ***Malaysia:*** Zyprexa; ***Mex.:*** Zyprexa; ***Neth.:*** Zyprexa; ***Norw.:*** Zyprexa; ***NZ:*** Zyprexa; ***Philipp.:*** Zyprexa; ***Pol.:*** Olzapin; Zalasta; Zolafren; Zyprexa; ***Port.:*** Olapin; Zalasta; Zolafren; Zyprexa; ***Rus.:*** Zyprexa (Зипрекса); ***S.Afr.:*** Zyprexa; ***Singapore:*** Zyprexa; ***Spain:*** Zyprexa; ***Swed.:*** Zyprexa; ***Switz.:*** Zyprexa; ***Thai.:*** Zyprexa; ***Turk.:*** Zyprexa; ***UK:*** Zyprexa; ***USA:*** Zyprexa; ***Venez.:*** Zyprexa.

Multi-ingredient: ***Arg.:*** Combined†; Symbyax†; ***Chile:*** Symbyax; ***Mex.:*** Symbyax; ***USA:*** Symbyax.

Oxazepam *(BAN, USAN, rINN)*

Oksatsepaami; Oksazeoam; Oksazepam; Oksazepamas; Oxazépam; Oxazepám; Oxazepamum; Wy-3498. 7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2-one.

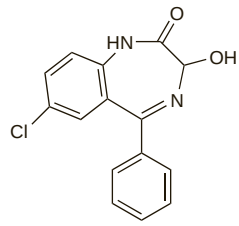
Оксазепам

$C_{15}H_{11}ClN_2O_2$ = 286.7.

CAS — 604-75-1.

ATC — N05BA04.

ATC Vet — QN05BA04.



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

Ph. Eur. 6.2 (Oxazepam). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in alcohol. Protect from light.

USP 31 (Oxazepam). A creamy-white to pale yellow, practically odourless powder. Practically insoluble in water; soluble 1 in 220 of alcohol, 1 in 270 of chloroform, and 1 in 2200 of ether. pH of a 2% suspension in water is between 4.8 and 7.0.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ For the purpose of withdrawal regimens, 15 mg of oxazepam is considered equivalent to about 5 mg of diazepam.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Hepatic impairment. All benzodiazepines should be used with caution in patients with hepatic impairment, but short-acting ones such as oxazepam may be preferred.

Seven patients with acute viral hepatitis, 6 with cirrhosis of the liver, and 16 age-matched healthy control subjects took a single dose of oxazepam 15 or 45 mg orally.[1] Urinary excretion rates and plasma elimination patterns were unaltered in patients with acute and chronic parenchymal liver disease. Oxazepam 15 mg orally was also given three times daily for 2 weeks to 2 healthy subjects and to 2 patients with cirrhosis and did not appear to accumulate in any of the four.

1. Shull HJ, *et al.* Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; **84:** 420–5.

Porphyria. Oxazepam is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Renal impairment. Pharmacokinetic studies suggest that, in general, the dosage of oxazepam does not need adjusting in patients with renal impairment.[1-3]

1. Murray TG, *et al.* Renal disease, age, and oxazepam kinetics. *Clin Pharmacol Ther* 1981; **30:** 805–9.
2. Busch U, *et al.* Pharmacokinetics of oxazepam following multiple administration in volunteers and patients with chronic renal disease. *Arzneimittelforschung* 1981; **31:** 1507–11.
3. Greenblatt DJ, *et al.* Multiple-dose kinetics and dialyzability of oxazepam in renal insufficiency. *Nephron* 1983; **34:** 234–8.

Thyroid disorders. There was a reduction in half-life and an increase in the apparent oral clearance of oxazepam in 7 hyperthyroid patients.[1] In 6 hypothyroid patients there was no overall change in oxazepam elimination, although 5 of the 6 complained of drowsiness despite a relatively low dose (15 mg).

1. Scott AK, *et al.* Oxazepam pharmacokinetics in thyroid disease. *Br J Clin Pharmacol* 1984; **17:** 49–53.

Interactions

As for Diazepam, p.989.

Pharmacokinetics

Oxazepam is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations about 2 hours after ingestion. It crosses the placenta and has been detected in breast milk. Oxazepam is about 85 to 97% bound to plasma proteins and has been reported to have an elimination half-life ranging from about 3 to 21 hours. It is largely metabolised to the inactive glucuronide which is excreted in the urine.

Pregnancy. The placental passage of oxazepam and its metabolism in 12 women given a single dose of oxazepam 25 mg during labour has been studied.[1] Oxazepam was readily absorbed and peak plasma concentrations were in the same range as those reported in healthy males and non-pregnant females given the same dose, although the plasma half-life (range 5.3 to 7.8 hours in 8 subjects studied) was shorter than that reported for non-pregnant subjects. Oxazepam was detected in the umbilical vein of all 12 patients with the ratio between umbilical to maternal vein concentration of oxazepam reaching a value of about 1.35 and remaining constant beyond a dose-delivery time of 3 hours. All of the babies had a normal Apgar score value. The oxazepam plasma half-life in the newborns was about 3 to 4 times that of the mothers, although in 3 the plasma concentration of oxazepam conjugate rose during the first 6 to 10 hours after delivery indicating the ability of the neonate to conjugate oxazepam.

1. Tomson G, *et al.* Placental passage of oxazepam and its metabolism in mother and newborn. *Clin Pharmacol Ther* 1979; **25:** 74–81.

Uses and Administration

Oxazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term management of anxiety disorders (p.952) and insomnia (p.957) associated with anxiety. Oxazepam is also used for the control of symptoms associated with alcohol withdrawal (p.1626). Oxazepam is usually given as the base but the hemisuccinate has been used in some multi-ingredient preparations.

The usual oral dose of oxazepam for the treatment of anxiety or for control of symptoms of alcohol withdrawal is 15 to 30 mg three or four times daily. A suggested initial dose for elderly or debilitated patients is 10 mg three times daily increased if necessary up to 10 to 20 mg three or four times daily. For the treatment of insomnia associated with anxiety oxazepam 15 to 25 mg may be given one hour before retiring; up to 50 mg may occasionally be necessary.

Administration in renal impairment. For a suggestion that dosage adjustment of oxazepam may not be necessary in patients with renal impairment, see Renal Impairment, above.

Preparations

BP 2008: Oxazepam Tablets;
USP 31: Oxazepam Capsules; Oxazepam Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Pausafren T; ***Austral.:*** Alepam; Murelax; Serepax; ***Austria:*** Adumbran; Anxiolit; Oxahexal; Praxiten; ***Belg.:*** Seresta; Tranquo; ***Chile:*** Serepax†; ***Denm.:*** Alopam; Oxabenz; Oxapax; Serepax; ***Fin.:*** Alopam†; Opamox; Oxamin; Oxepam†; ***Fr.:*** Seresta; ***Ger.:*** Adumbran; Azutranquil†; durazepam; Mirfudorm; Noctazepam†; Oxa; Praxiten; Sigacalm†; Uskan; ***India:*** Serepax; ***Israel:*** Vaben; ***Ital.:*** Limbial; Serpax; ***Neth.:*** Seresta; ***Norw.:*** Alopam; Sobril; ***NZ:*** Ox-Pam; ***Pol.:*** Oxam; ***Port.:*** Serenal; ***Rus.:*** Tazepam (Тазепам); ***S.Afr.:*** Medopam; Noripam; Purata; Serepax; ***Spain:*** Adumbran†; ***Swed.:*** Oxascand; Sobril; ***Switz.:*** Anxiolit; Seresta; ***USA:*** Serax; ***Venez.:*** Anastil†.

Multi-ingredient: ***Arg.:*** Cavodan†; Pankreoflat Sedante†; ***Austria:*** Anxiolit plus; ***Chile:*** Novalona; ***Port.:*** Sedioton†; ***Spain:*** Novo Aerofil Sedante†; Suxidina; ***Venez.:*** Vuscobras.

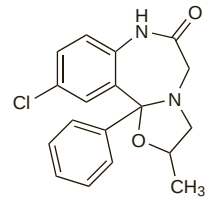
Oxazolam *(rINN)*

Oxazolamum; Oxazolazepam. 10-Chloro-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4]benzodiazepin-6(5*H*)-one.

Оксазолам

$C_{18}H_{17}ClN_2O_2$ = 328.8.

CAS — 24143-17-7.



Pharmacopoeias. In *Jpn.*

Profile

Oxazolam is a long-acting benzodiazepine with general properties similar to those of diazepam (p.986). It has been given by mouth for the short-term treatment of anxiety disorders.

Oxazolam has also been used as a premedicant in general anaesthesia.