Mania. Although it is used in the treatment of bipolar disorder, ziprasidone has been associated with reports of mania in bipolar patients, see under Uses and Administration, below.

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome (NMS— p.972) has been associated with ziprasidone;[1] however, the patient had also received lithium, a drug that has been associated with NMS.

1. Borovicka MC, *et al.* Ziprasidone- and lithium-induced neuroleptic malignant syndrome. *Ann Pharmacother* 2006; **40:** 139–42.

Pregnancy. For comments on the use of some atypical antipsychotics, including ziprasidone, during pregnancy, see under Precautions of Clozapine, p.983.

US licensed drug information states that ziprasidone demonstrated possible teratogenic effects in some *animals*; it was noted that there are no adequate and well-controlled studies in human pregnancy. Ziprasidone should only be used if the benefits to the mother outweigh the risks to the fetus.

Interactions

Use of ziprasidone with other drugs known to prolong the QT interval is contra-indicated because of the increased risk of arrhythmias. Monitoring of serum electrolytes is recommended if ziprasidone is given with diuretics.

The metabolism of ziprasidone is mediated by the cytochrome P450 isoenzyme CYP3A4. Therefore, there is the potential for interactions between ziprasidone and other drugs that induce, inhibit, or act as a substrate for this enzyme.

Ziprasidone may enhance the effects of other CNS depressants and certain antihypertensives; it may antagonise the effects of levodopa and dopaminergics.

Pharmacokinetics

Ziprasidone is well absorbed from the gastrointestinal tract with peak plasma concentrations being reached 6 to 8 hours after oral doses. The presence of food may double the absorption. Following intramuscular injection, peak plasma concentrations are reached within 1 hour. Plasma protein binding is about 99%. Ziprasidone is extensively metabolised by aldehyde oxidase (about 66% of a dose) and by the cytochrome P450 isoenzyme CYP3A4. The mean terminal elimination half-life has been reported to be about 7 hours after oral dosage and about 2 to 5 hours after intramuscular dosage. Ziprasidone is excreted mainly as metabolites in the faeces (about 66%) and urine (about 20%); less than 5% of a dose appears as unchanged drug.

◊ References.

1. Various. The pharmacokinetics of ziprasidone. *Br J Clin Pharmacol* 2000; **49** (suppl 1): 1S–76S.
2. Miceli JJ, *et al.* Pharmacokinetics, safety, and tolerability of intramuscular ziprasidone in healthy volunteers. *J Clin Pharmacol* 2005; **45:** 620–30.
3. Preskorn SH. Pharmacokinetics and therapeutics of acute intramuscular ziprasidone. *Clin Pharmacokinet* 2005; **44:** 1117–33.

Uses and Administration

Ziprasidone is an atypical antipsychotic reported to have affinity for adrenergic (α_1), histamine (H_1), and serotonin ($5\text{-}HT_2$) receptors as well as dopamine (D_2) receptors. It is used for the treatment of schizophrenia and in acute manic or mixed episodes associated with bipolar disorder. Ziprasidone is given by mouth usually as the hydrochloride; it is also given parenterally as the mesilate. Doses are expressed in terms of the base; ziprasidone hydrochloride 11.3 mg or ziprasidone mesilate 13.6 mg are each equivalent to about 10 mg of ziprasidone.

For the treatment of **schizophrenia**, ziprasidone hydrochloride is given in an initial oral dose of 20 mg twice daily with food. Doses may be increased if necessary at intervals of not less than 2 days up to 80 mg twice daily. For maintenance, doses as low as 20 mg twice daily may be effective.

For acute agitation in patients with schizophrenia, ziprasidone may be given as the mesilate by intramuscular injection. The recommended dose is 10 to 20 mg as required, up to a maximum of 40 mg daily for 3 consecutive days. Doses of 10 mg may be given every 2 hours and doses of 20 mg may be given every 4 hours. Patients should be switched to oral therapy as soon as possible.

For the treatment of **mania**, ziprasidone hydrochloride is given in an initial oral dose of 40 mg twice daily with food. The dose should be increased to 60 or 80 mg twice daily on the second day of treatment and subsequently adjusted according to tolerance.

Bipolar disorder. Ziprasidone is effective in the management of acute mania in patients with bipolar disorder[1] but it may also be associated with the induction of mania or hypomania in such patients.[2]

1. Keck PE, *et al.* Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003; **160:** 741–8.
2. Baldassano CF, *et al.* Ziprasidone-associated mania: a case series and review of the mechanism. *Bipolar Disord* 2003; **5:** 72–5.

Schizophrenia. A systematic review[1] of the effectiveness and safety of ziprasidone in patients with schizophrenia (p.955) found that from the limited data available ziprasidone was as effective as haloperidol; it was less likely to provoke extrapyramidal disorders but appeared to cause more nausea and vomiting, and pain at the site of injection. Comparisons with other atypical antipsychotics were lacking. A comparative study[2] of intramuscular ziprasidone with intramuscular haloperidol also found a favourable outcome in patients with acute psychoses.

1. Bagnall A, *et al.* Ziprasidone for schizophrenia and severe mental illness. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 20/10/05).
2. Brook S, *et al.* Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; **61:** 933–41.

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

1. Sallee FR, *et al.* Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 292–9.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Zeldox; ***Austral.:*** Zeldox; ***Austria:*** Zeldox; ***Braz.:*** Geodon; ***Chile:*** Zeldox; ***Cz.:*** Zeldox; ***Denm.:*** Zeldox; ***Fin.:*** Zeldox; ***Ger.:*** Zeldox; ***Gr.:*** Geodon; ***Hong Kong:*** Zeldox; ***Hung.:*** Zeldox; ***India:*** Zipsydon; ***Irl.:*** Geodon; ***Israel:*** Geodon; ***Malaysia:*** Zeldox; ***Mex.:*** Geodon; ***Norw.:*** Zeldox; ***NZ:*** Zeldox; ***Philipp.:*** Zeldox; ***Pol.:*** Zeldox; ***Port.:*** Zeldox; ***Rus.:*** Zeldox (Зелдокс); ***S.Afr.:*** Geodon; ***Singapore:*** Zeldox; ***Spain:*** Geodon; Zeldox; ***Swed.:*** Zeldox; ***Thai.:*** Zeldox; ***USA:*** Geodon; ***Venez.:*** Geodon.

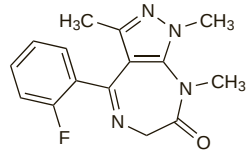
Zolazepam Hydrochloride *(BANM, USAN, rINNM)*

Cl-716; Hidrocloruro de zolazepam; Zolazépam, Chlorhydrate de; Zolazepami Hydrochloridum. 4-(*o*-Fluorophenyl)-6,8-dihydro-1,3,8-trimethylpirazole[3,4-e][1,4]diazepin-7(1*H*)-one monohydrochloride.

Золазепама Гидрохлорид

$C_{15}H_{15}FN_4O,HCl$ = 322.8.

CAS — 31352-82-6 (zolazepam); 33754-49-3 (zolazepam hydrochloride).



(zolazepam)

Pharmacopoeias. In *US* for veterinary use only.

USP 31 (Zolazepam Hydrochloride). A white to off-white crystalline powder. Freely soluble in water and in 0.1N hydrochloric acid; slightly soluble in chloroform; practically insoluble in ether; soluble in methyl alcohol. pH of a 10% solution in water is between 1.5 and 3.5. Store in airtight containers.

Profile

Zolazepam hydrochloride is a benzodiazepine with general properties similar to those of diazepam (p.992). It is used with tiletamine (p.1796) for general anaesthesia in veterinary medicine.

Zolpidem Tartrate *(BANM, USAN, rINNM)*

SL-80.0750 (zolpidem); SL-80.0750-23N; Tartrato de zolpidem; Tsolpideemitartraatti; Zolpidem Hemitartrate; Zolpidem, tartrate de; Zolpidemi tartras; Zolpidemo tartratas; Zolpidem-tartarát; Zolpidemtartrat; Zolpidemu winian. *N,N*-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-*a*]pyridin-3-yl)acetamide hemitartrate.

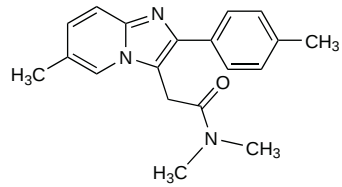
Золпидема Тартрат

$(C_{19}H_{21}N_3O)_2,C_4H_6O_6$ = 764.9.

CAS — 82626-48-0 (zolpidem); 99294-93-6 (zolpidem tartrate).

ATC — N05CF02.

ATC Vet — QN05CF02.



(zolpidem)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of zolpidem tartrate: Sleepeasy; Tic-Tacs.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zolpidem Tartrate). A white or almost white hygroscopic crystalline powder. Slightly soluble in water; practically insoluble in dichloromethane; sparingly soluble in methyl alcohol. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

Withdrawal symptoms. A 37-year-old man, who increased his dose from 10 mg to 130 mg daily over 2 months, had a generalised tonic-clonic seizure after zolpidem was abruptly stopped.[1] The patient recovered after being started on a benzodiazepine dosage tapering programme. Symptoms attributed to daytime abstinence after excessive night-time doses have been reported[2] in 2 patients and included anxiety, tremor, sweating, nausea, gastric and abdominal pain, swallowing difficulties, tachycardia, and tachypnoea. The patients had increased their doses because of the development of tolerance to the hypnotic effect but had begun to experience muscle twitches and myoclonic jerks.

1. Gilbert DL, Staats PS. Seizure after withdrawal from supratherapeutic doses of zolpidem tartrate, a selective omega I benzodiazepine receptor agonist. *J Pain Symptom Manage* 1997; **14:** 118–20.
2. Cavallaro R, *et al.* Tolerance and withdrawal with zolpidem. *Lancet* 1993; **342:** 374–5.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987.

Treatment of overdose is largely supportive. Activated charcoal may be given orally within one hour of ingestion of 100 mg zolpidem or more by adults, or more than 5 mg by children. Alternatively, gastric lavage may be considered in adults if they present within 1 hour of a potentially life-threatening overdose. Flumazenil may be considered in cases of severe CNS depression (see also Overdosage, below).

◊ Reviews.

1. Darcourt G, *et al.* The safety and tolerability of zolpidem—an update. *J Psychopharmacol* 1999; **13:** 81–93.

Abuse. Zolpidem abuse has been reported;[1,2] effects noted include a paradoxical stimulant effect when taking large doses of zolpidem. Tolerance may also develop. Intravenous abuse has also been reported.[3]

See also under Dependence and Withdrawal, above.

1. Gericke CA, Ludolph AC. Chronic abuse of zolpidem. *JAMA* 1994; **272:** 1721–2.
2. Victorri-Vigneau C, *et al.* Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol* 2007; **64:** 198–209.
3. Brunelle E, *et al.* Zolpidem: intravenous misuse in drug abusers. *Addiction* 2005; **100:** 1377–8.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving zolpidem, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

In 5 women given a 20-mg dose of zolpidem, the amount of drug excreted in breast milk after 3 hours ranged between 0.76 and

3.88 micrograms, which represented 0.004 to 0.019% of the dose.[2] No detectable (below 0.5 nanograms/mL) zolpidem was found in subsequent milk samples.

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 29/04/04)
2. Pons G, *et al.* Zolpidem excretion in breast milk. *Eur J Clin Pharmacol* 1989; **37:** 245–8.

Effects on the liver. Hepatitis developed on 2 separate occasions in a 53-year-old woman after the use of zolpidem for insomnia.[1]

1. Karsenti D, *et al.* Hepatotoxicity associated with zolpidem treatment. *BMJ* 1999; **318:** 1179.

Effects on mental function. Psychotic reactions, which may not subsequently be recalled, have been reported in patients taking therapeutic doses of zolpidem.[1-4] Somnambulism has also been reported with zolpidem.[5,6] Other complex sleep-related behaviours, such as eating or driving while asleep, have been reported with zaleplon,[7] zolpidem,[6,7] and zopiclone. Such behaviour is more likely to occur when these drugs are taken with alcohol or other CNS depressants, or when taken in doses exceeding the recommended maximum. It is not clear if there are differences in risk with individual drugs; however, as a precautionary measure, the FDA[8] had requested for labelling changes that highlight these adverse effects to be made to all hypnotics marketed in the USA.

1. Ansseau M, *et al.* Psychotic reactions to zolpidem. *Lancet* 1992; **339:** 809.
2. Iruela LM, *et al.* Zolpidem-induced macropsia in anorexic woman. *Lancet* 1993; **342:** 443–4.
3. Brodeur MR, Stirling AL. Delirium associated with zolpidem. *Ann Pharmacother* 2001; **35:** 1562–4.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Seeing things with zolpidem. *Aust Adverse Drug React Bull* 2002; **21:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0202.pdf (accessed 21/08/08)
5. Yang W, *et al.* One rare side effect of zolpidem—sleepwalking: a case report. *Arch Phys Med Rehabil* 2005; **86:** 1265–6.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Zolpidem and bizarre sleep related effects. *Aust Adverse Drug React Bull* 2007; **26:** 2–3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0702.pdf (accessed 10/03/08)
7. Southworth MR, *et al.* FDA. Nonbenzodiazepine hypnotic use and cases of "sleep driving". *Ann Intern Med* 2008; **148:** 486–7.
8. FDA. FDA news: FDA requests label change for all sleep disorder drug products (issued 14th March, 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html (accessed 07/08/08)

Hypersensitivity. Rare cases of angioedema involving the tongue, glottis, or larynx have been reported after the first or subsequent doses of hypnotics such as eszopiclone, zaleplon, zolpidem, and zopiclone; additional symptoms suggestive of anaphylaxis have also developed in some patients.

Overdosage. A retrospective analysis of 344 cases of acute overdosage with zolpidem reported to the Paris Poison Center and the manufacturers *Synthelabo* has been published.[1] The ingested dose, where known, ranged from 10 to 1400 mg, and the most common adverse effect was drowsiness (in 89 patients). Other adverse effects probably associated with the overdosage included coma in 4 patients and vomiting in 7. Recovery was usually rapid when overdosage involved only zolpidem. It was recommended that patients who had ingested more than 100 mg of zolpidem should undergo gastric lavage and should be monitored for at least 12 hours (see also above). Although it has been shown that flumazenil[2] can effectively antagonise the CNS effects of zolpidem the authors of this analysis[1] found that in general it was not required.

1. Garnier R, *et al.* Acute zolpidem poisoning—analysis of 344 cases. *J Toxicol Clin Toxicol* 1994; **32:** 391–404.
2. Patat A, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther* 1994; **56:** 430–6.

Interactions

As for Diazepam, p.989.

Antidepressants. A 16-year-old girl who had been taking *paroxetine* 20 mg daily for 3 days began to hallucinate and became disorientated one hour after taking zolpidem 10 mg at night. The delirium cleared spontaneously 4 hours later without treatment.[1] When questioned, at least one other of the author's patients receiving this combination reported transient visual hallucinations. Other isolated cases of visual hallucinations have been reported in patients taking zolpidem with antidepressants including *bupropion, desipramine, fluoxetine, sertraline,* and *venlafaxine*.[2]

1. Katz SE. Possible paroxetine-zolpidem interaction. *Am J Psychiatry* 1995; **152:** 1689.
2. Elko CJ, *et al.* Zolpidem-associated hallucinations and serotonin reuptake inhibition: a possible interaction. *J Toxicol Clin Toxicol* 1998; **36:** 195–203.

Antiepileptics. A 47-year-old man with a history of bipolar disorder, who was receiving citalopram and zolpidem, had episodes of somnambulism after he was also given *valproic acid* for treatment of manic symptoms.[1] The episodes stopped on withdrawal of valproic acid and returned on rechallenge. An interaction between zolpidem and valproic acid was suspected (but somnambulism has also been associated with zolpidem alone, see Effects on Mental Function, above).

For the suggestion that *carbamazepine* and *phenytoin* may interact with zolpidem, see Rifampicin, below.

1. Sattar SP, *et al.* Somnambulism due to probable interaction of valproic acid and zolpidem. *Ann Pharmacother* 2003; **37:** 1429–33.

Antifungals. Use of *ketoconazole* with zolpidem has resulted in increased plasma concentrations, and an enhanced sedative effect, of zolpidem, albeit only modest.[1] The use of zolpidem with *fluconazole*[1] or *itraconazole*[1,2] has resulted in small, non-significant changes in the pharmacokinetics and sedative effects of zolpidem.

1. Greenblatt DJ, *et al.* Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole. *Clin Pharmacol Ther* 1998; **64:** 661–71.
2. Luurila H, *et al.* Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zolpidem. *Eur J Clin Pharmacol* 1998; **54:** 163–6.

Antivirals. HIV-protease inhibitors such as *ritonavir* may increase plasma concentrations of zolpidem with a risk of extreme sedation and respiratory depression; use together is possible provided the patient is carefully monitored for excessive sedative effects.

Rifampicin. Rifampicin reduced the hypnotic effect of zolpidem in a study in 8 healthy female subjects.[1] The area under the curve for zolpidem was reduced by 73% after rifampicin and the peak plasma concentration by 58%. The elimination half-life of zolpidem was reduced from 2.5 to 1.6 hours. Similar effects could be expected with other potent inducers of the cytochrome P450 isoenzyme CYP3A4 such as carbamazepine and phenytoin.

1. Villikka K, *et al.* Rifampin reduces plasma concentrations and effects of zolpidem. *Clin Pharmacol Ther* 1997; **62:** 629–34.

Pharmacokinetics

Zolpidem is rapidly absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being reached within 3 hours. Zolpidem undergoes first-pass metabolism and an absolute bioavailability of about 70% has been reported. Zolpidem has an elimination half-life of about 2.5 hours and is about 92% bound to plasma proteins. It is metabolised primarily by the cytochrome P450 isoenzyme CYP3A4; the inactive metabolites of zolpidem are excreted in the urine and faeces. Zolpidem is distributed into breast milk.

◊ References.

1. Salvà P, Costa J. Clinical pharmacokinetics and pharmacodynamics of zolpidem: therapeutic implications. *Clin Pharmacokinet* 1995; **29:** 142–53.
2. von Moltke LL, *et al.* Zolpidem metabolism in vitro: responsible cytochromes, chemical inhibitors, and vivo correlations. *Br J Clin Pharmacol* 1999; **48:** 89–97.
3. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
4. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.
5. Greenblatt DJ, *et al.* Dynamics and kinetics of a modified-release formulation of zolpidem: comparison with immediate-release standard zolpidem and placebo. *J Clin Pharmacol* 2006; **46:** 1469–80.

Uses and Administration

Zolpidem tartrate is an imidazopyridine that is reported to have similar sedative properties to the benzodiazepines (see Diazepam, p.992), but minimal anxiolytic, muscle relaxant, and anticonvulsant properties. It has a rapid onset and short duration of action, and is used as a hypnotic in the short-term management of insomnia. The usual oral dose is 10 mg taken immediately before retiring. In elderly or debilitated patients, treatment should be limited to a dose of 5 mg at night. Doses should also be reduced in patients with hepatic impairment, see below. A modified-release formulation of zolpidem tartrate is also available.

Administration in hepatic impairment. In patients with hepatic impairment, treatment with immediate-release formulations of zolpidem tartrate should be started with a dose of 5 mg at night; the dose may be increased to 10 mg, if necessary, in those under 65 years. UK licensed product information contraindicates the use of zolpidem in patients with severe impairment.

Catatonia. Anecdotal reports[1,2] suggesting that zolpidem may be a useful test in the diagnosis of catatonia.

1. Thomas P, *et al.* Test for catatonia with zolpidem. *Lancet* 1997; **349:** 702.
2. Zaw ZF, Bates GDL. Replication of zolpidem test for catatonia in an adolescent. *Lancet* 1997; **349:** 1914.

Insomnia. Zolpidem is an imidazopyridine with strong sedative actions, but only minor anxiolytic, muscle relaxant, or anticonvulsant properties. Some degree of amnesia has been reported. Zolpidem appears to act by binding to the benzodiazepine receptor component of the GABA receptor complex. It has, however, a selective affinity for the subtype of benzodiazepine receptors prevalent in the cerebellum (BZ1- or ω_1-receptors) as opposed to those more commonly found in the spinal cord (BZ2- or ω_2-receptors) or in the peripheral tissues (BZ3- or ω_3-receptors). Zolpidem has a rapid onset and short duration of hypnotic action and at usual doses decreases time to sleep onset and increases duration of sleep with little apparent effect on sleep stages (see Insomnia, p.957). Reviews agree that clinical studies have shown zolpidem to have hypnotic activity superior to placebo and generally similar to comparative benzodiazepines. Although it does not appear to produce rebound insomnia to any great extent, there appears to be little evidence that zolpidem offers any advantage over short-acting benzodiazepines in terms of residual effects the next day, or its potential to induce tolerance or withdrawal symptoms or dependence (see also under Dependence and Withdrawal, above).

References.

1. Langtry HD, Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; **40:** 291–313.
2. Lobo BL, Greene WL. Zolpidem: distinct from triazolam? *Ann Pharmacother* 1997; **31:** 625–32.
3. Nowell PD, *et al.* Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997; **278:** 2170–7.
4. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; **59:** 865–89.
5. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.
6. Harrison TS, Keating GM. Zolpidem: a review of its use in the management of insomnia. *CNS Drugs* 2005; **19:** 65–89.

Parkinsonism. Although preliminary findings[1] in 10 patients suggested that zolpidem might improve symptoms of Parkinson's disease concern has been expressed[2] over the risk of falls associated with zolpidem-induced drowsiness and the serious consequences for these patients. Benefit has also been reported[3] in the treatment of antipsychotic-induced parkinsonism in one patient with symptoms of repetitive persistent gross tremors of the hands.

1. Daniele A, *et al.* Zolpidem in Parkinson's disease. *Lancet* 1997; **349:** 1222–3.
2. Lavoisy J, Marsac J. Zolpidem in Parkinson's disease. *Lancet* 1997; **350:** 74.
3. Farver DK, Khan MH. Zolpidem for antipsychotic-induced parkinsonism. *Ann Pharmacother* 2001; **35:** 435–7.

Permanent vegetative state. Zolpidem in a single dose of 10 mg has produced temporary arousal in 3 patients thought to be in permanent vegetative state.[1] Effects lasted for about 4 hours.

1. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation* 2006; **21:** 23–8.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Balidorm†; Dormilan; Durnit; Nocte; Somit; Sumenan; Zolodorm; ***Austral.:*** Dormizol; Somidem; Stildem; Stilnox; Zolpibell; ***Austria:*** Ivadal; Mondeal; Zoldem; Zolpidohexal; ***Belg.:*** Stilnoct; ***Braz.:*** Lioram; Stilnox; ***Chile:*** Adormix; Damixan; Dormilam; Dormosol; Somnil; Somnipron; Somno; Sucedal; ***Cz.:*** Eanox; Hypnogen; Stilnoct; Stilnox; Zolpimerck; Zolpinox; Zolsana; Zonadin; ***Denm.:*** Eanox†; Nimadorm; Stilnoct; Zonoct; ***Fin.:*** Somnor; Stella; Stilnoct; ***Fr.:*** Stilnox; ***Ger.:*** Bikalm; Stilnox; Zodormdura; Zoldem; Zolpi-Lich; Zolpi-Q; Zolpinox; ***Gr.:*** Alespan; Hypnoforin; Stilnox; ***Hong Kong:*** Stilnox; Stilpidem; ***Hung.:*** Ambien; Hypnogen; Pidezol; Sanval; Stilnox; ***India:*** Ambiz; Sove; Zleep; Zoldem; ***Indon.:*** Stilnox; Zolmia; ***Irl.:*** Nytamel; Stilnoct; Zoldem; Zolnod; ***Israel:*** Stilnox; Zodorm; ***Ital.:*** Niotal; Nottem; Stilnox; ***Jpn:*** Myslee; ***Malaysia:*** Sobrium; Somidem; Stilnox; ***Mex.:*** Nocte; Stilnox; ***Neth.:*** Stilnoct; Zolpidol; ***Norw.:*** Stilnoct; ***Philipp.:*** Stilnox; Ziohex; ***Pol.:*** Hypnogen; Nasen; Polsen; Sanval; Stilnox; Xentic; Zolpic; ZolpiGen; Zolsana; Zoratio; ***Port.:*** Cymerion; Stilnox; ***Rus.:*** Hypnogen (Гипноген); Nitrest (Нитрест); Sanval (Санвал); Snovitel (Сновител); ***S.Afr.:*** Ivedal; Noxidem; Stilnox; Zolnox; Zolpihexal; ***Singapore:*** Stilnox; ***Spain:*** Dalparan; Stilnox; ***Swed.:*** Stilnoct; ***Switz.:*** Sedovalin; Stilnox; Zoldorm; Zolpi-Med; ***Thai.:*** Stilnox; ***UK:*** Stilnoct; ***USA:*** Ambien; Tovalt; ***Venez.:*** Atrimon; Stilnox; Zolpidex.

Zopiclone *(BAN, rINN)*

27267-RP; Tsopikloni; Zopiclona; Zopiclonum; Zopiklon; Zopiklonas. 6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

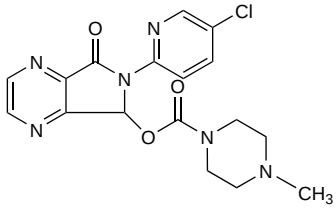
Зопиклон

$C_{17}H_{17}ClN_6O_3$ = 388.8.

CAS — 43200-80-2.

ATC — N05CF01.

ATC Vet — QN05CF01.



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

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Zopiclone). A white or slightly yellowish powder. Practically insoluble in water and in alcohol; sparingly soluble in acetone; freely soluble in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.987.

◊ There have been reports[1,2] of zopiclone dependence and associated withdrawal symptoms on dosage reduction or cessation of use. However, a 67-year-old man who increased his dosage of zopiclone up to 337.5 mg daily to treat insomnia without apparent adverse effects, had his zopiclone withdrawn without severe complications over 4 weeks using drug and cognitive therapy.[3] A WHO expert committee[4] considered in 2006 that the likelihood of zopiclone abuse was low and not great enough to warrant international control.

1. Jones IR, Sullivan G. Physical dependence on zopiclone: case reports. *BMJ* 1998; **316:** 117.
2. Sikdar S. Physical dependence on zopiclone. *BMJ* 1998; **317:** 146.
3. Kuntze MF, *et al.* Excessive use of zopiclone: a case report. *Swiss Med Wkly* 2002; **132:** 523.
4. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 06/08/08)

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. A bitter or metallic taste in the mouth has been the most frequently reported adverse effect with zopiclone.

Treatment of overdose is largely supportive. Activated charcoal may be given orally within one hour of ingestion of more than 150 mg zopiclone by adults, or 1.5 mg/kg by children. Alternatively gastric lavage may be considered in adults if they present within 1 hour of a potentially life-threatening overdose. Flumazenil has been used in cases of severe CNS depression (see also Overdosage, below).

Incidence of adverse effects. In a French postmarketing survey[1] of 20 513 patients treated with zopiclone the most commonly reported adverse events were bitter taste (3.6%), dry mouth (1.6%), difficulty arising in the morning (1.3%), sleepiness (0.5%), nausea (0.5%) and nightmares (0.5%). The UK CSM[2] had received 122 reports of adverse reactions to zopiclone over a period of about one year since the product's introduction in November 1989. A fifth of these were neuropsychiatric reactions, a proportion similar to that found with other hypnotics. Many of these reactions were potentially serious and involved hallucinations (3 auditory and 2 visual), amnesia (4 cases), and behavioural disturbances (10, including 3 cases of aggression). Most reactions started immediately or shortly after the first dose and improved rapidly on stopping the drug. Three patients had difficulty in stopping treatment, 2 because of withdrawal symptoms and one due to repeated rebound insomnia. The CSM considered that, although differing structurally from the benzodiazepines, zopiclone has the same potential for adverse psychiatric reactions, including dependence. As with the benzodiazepines it should be reserved for patients with severe sleep disturbance and its duration of use limited to 28 days; care should also be taken in the elderly, those who have a history of previous psychiatric illness, or who are prone to drug abuse.

1. Allain H, *et al.* Postmarketing surveillance of zopiclone in insomnia: analysis of 20,513 cases. *Sleep* 1991; **14:** 408–13.
2. Committee on Safety of Medicines. Zopiclone (Zimovane) and neuro-psychiatric reactions. *Current Problems 30* 1990.

Abuse. For a report of zopiclone abuse see under Dependence and Withdrawal, above.

Administration. Results in 9 healthy subjects given zopiclone indicated a significant delay in onset of action when the drug was taken in the supine, as opposed to the standing, position; this was associated with a prolongation of more than 20 minutes in the lag time before absorption began.[1] In order to obtain a rapid and complete hypnotic effect from zopiclone the tablet should be swallowed in the standing position.

1. Channer KS, *et al.* The effect of posture at the time of administration on the central depressant effects of the new hypnotic zopiclone. *Br J Clin Pharmacol* 1984; **18:** 879–86.

Driving. For reference to the increased risk of road-traffic accidents for drivers taking zopiclone, see p.988.

Effects on mental function. For reports of adverse effects on mental function, such as complex sleep-related behaviours, associated with some hypnotics including zopiclone, see under Zolpidem, above.

Hepatic impairment. Zopiclone was given in a dose of 7.5 mg to 7 cirrhotic patients and 8 healthy subjects; a further 2 cirrhotic patients received 3.75 mg.[1] Mean peak plasma concentrations were similar in healthy subjects and those with hepatic impairment following equivalent doses but time to peak plasma concentration was 4 hours in the latter as compared with 2 hours in the healthy subjects. Elimination was greatly prolonged in cirrhotic patients, in whom the mean plasma half-life was 8.53 hours compared with 3.5 hours. The CNS-depressant effects of zopiclone were delayed in the cirrhotic patients in a way consistent with the pharmacokinetic changes. There was also some evidence of an increased response in these patients. The authors recommended caution when giving zopiclone to patients with severe hepatic disease; licensed product information contraindicates the use of zopiclone in such patients.

1. Parker G, Roberts CJC. Plasma concentrations and central nervous system effects of the new hypnotic agent zopiclone in patients with chronic liver disease. *Br J Clin Pharmacol* 1983; **16:** 259–65.

Hypersensitivity. For mention of anaphylactoid reactions associated with some hypnotics including zopiclone, see under Zolpidem, above.

Overdosage. Consciousness was rapidly regained after intravenous flumazenil was given to a patient who had taken an overdosage of zopiclone.[1] However, fatalities after zopiclone overdose have also been reported.[2,3]

1. Ahmad Z, *et al.* Diagnostic utility of flumazenil in coma with suspected poisoning. *BMJ* 1991; **302:** 292.
2. Boniface PJ, Russell SGG. Two cases of fatal zopiclone overdose. *J Anal Toxicol* 1996; **20:** 131–3.
3. Meatherall RC. Zopiclone fatality in a hospitalized patient. *J Forensic Sci* 1997; **42:** 340–3.

Interactions

As for Diazepam, p.989. Use with rifampicin or other potent inducers of the cytochrome P450 isoenzyme CYP3A4, such as carbamazepine or phenytoin, is likely to reduce the effects of zopiclone.

Antibacterials. In a study in healthy subjects *erythromycin* increased the rate of absorption of zopiclone and prolonged its elimination.[1] In another study[2] in 8 healthy subjects *rifampicin* was associated with an 82% reduction in the area under the curve for zopiclone. The peak plasma concentration of zopiclone was reduced from 76.9 to 22.5 nanograms/mL and the elimination half-life from 3.8 to 2.3 hours.

1. Aranko K, *et al.* The effect of erythromycin on the pharmacokinetics and pharmacodynamics of zopiclone. *Br J Clin Pharmacol* 1994; **38:** 363–7.
2. Villikka K, *et al.* Concentrations and effects of zopiclone are greatly reduced by rifampicin. *Br J Clin Pharmacol* 1997; **43:** 471–4.

Pharmacokinetics

Zopiclone is rapidly absorbed and widely distributed after oral doses. It has an elimination half-life of 3.5 to 6.5 hours and is reported to be about 45 to 80% bound to plasma proteins. Zopiclone is extensively metabolised in the liver; the 2 major metabolites, the less active zopiclone *N*-oxide and the inactive *N*-desmethylzopiclone, are excreted mainly in the urine. About 50% of a dose is converted by decarboxylation to inactive metabolites, which are partly eliminated via the lungs as carbon dioxide. Only about 5% of a dose appears unchanged in the urine and about 16% appears in the faeces. Excretion of zopiclone in the saliva may explain reports of a bitter taste. It is also distributed into breast milk.

◊ Reviews.

1. Fernandez C, *et al.* Clinical pharmacokinetics of zopiclone. *Clin Pharmacokinet* 1995; **29:** 431–41.
2. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Distribution into breast milk. Zopiclone was distributed into breast milk in 12 women in concentrations about half those in plasma.[1] The calculated dose that would be received by a neonate was 1.5 micrograms/kg, corresponding to 1.2% of the maternal dose.

1. Matheson I, *et al.* The excretion of zopiclone into breast milk. *Br J Clin Pharmacol* 1990; **30:** 267–71.

Uses and Administration

Zopiclone is a cyclopyrrolone with similar sedative, anxiolytic, muscle relaxant, amnestic, and anticonvulsant properties to those of the benzodiazepines (see Diazepam, p.992). Like diazepam, its actions are mediated by enhancement of the activity of gamma-aminobutyric acid (GABA) in the brain. Zopiclone is reported to bind to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. It has a short duration of action.

Zopiclone is used as a hypnotic in the short-term management of insomnia. The usual oral dose is 7.5 mg before bed. In elderly patients, treatment should start with a dose of 3.75 mg before bed. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Eszopiclone, the (+)-isomer of zopiclone, is used similarly (see p.995).

Administration in hepatic or renal impairment. In those with renal impairment or mild to moderate hepatic impairment, treatment with zopiclone should start with an oral dose of 3.75 mg before bed. It should not be given to patients with severe hepatic impairment.

Insomnia. Zopiclone has a similar pharmacological and pharmacokinetic profile to the short-acting benzodiazepines. It is claimed to initiate sleep rapidly, without reduction of total rapid-eye-movement (REM) sleep, and then sustain it with preservation of normal slow-wave sleep (see Insomnia, p.957). It is generally considered to be as effective as a hypnotic as the benzodiazepines. Rebound insomnia has occurred but does not appear to be common. Residual effects the next day may be less pronounced after zopiclone than after short-acting benzodiazepines but there appears to be little evidence that zopiclone offers any clinical advantage in terms of its potential to induce tolerance, withdrawal symptoms, or dependence. For recommendations of the UK CSM concerning its use as a hypnotic, see Incidence of Adverse Effects, above.

References.

1. Noble S, *et al.* Zopiclone: an update of its pharmacology, clinical efficacy and tolerability in the treatment of insomnia. *Drugs* 1998; **55:** 277–302.
2. Hajak G. A comparative assessment of the risks and benefits of zopiclone: a review of 15 years' clinical experience. *Drug Safety* 1999; **21:** 457–69.
3. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Foltran; Imovane; Insomnium; ***Austral.:*** Imovane; Imrest; ***Austria:*** Sedolox; Somnal; ***Belg.:*** Imovane; ***Braz.:*** Imovane; Neurolil†; ***Canad.:*** Imovane; Rhovane; ***Chile:*** Alpaz; Imovane; Losopil; Nuctane†; Zedax†; Zetix; Zometic; Zonix; ***Cz.:*** Imovane†; Zopitin; ***Denm.:*** Imoclone; Imovane; Imozop; ***Fin.:*** Imovane; Zopinox; ***Fr.:*** Imovane; ***Ger.:*** espa-dorm†; Optidorm; Somnosan; Ximovan; Zodurat; Zop; Zopi-Puren; Zopicalm; Zopiclodura; ***Gr.:*** Imovane; ***Hong Kong:*** Amvey; Dopareel; Eurovan; Imovane; Zolief; Zomni; ***Hung.:*** Imovane; Somnol; Zopigen; ***India:*** Zonap†; Zopicon; ***Irl.:*** Zileze; Zimoclone; Zimovane; Zopitan; Zorclone; ***Israel:*** Imovane; Nocturno; ***Ital.:*** Imovane; Nenia†; ***Malaysia:*** Imovane; ***Mex.:*** Imovane; ***Neth.:*** Imovane; ***Norw.:*** Imovane; ***NZ:*** Imovane; ***Pol.:*** Dobroson; Imovane; Zopiratio; ***Rus.:*** Imovane (Имован); Piclodorm (Пиклодорм); Relaxon (Релаксон)†; Somnol (Сомнол); ***S.Afr.:*** Alchera; Imovane; Z-Dorm; Zopigen; Zopimed; Zopivane; ***Singapore:*** Imovane; ***Spain:*** Datolan; Limovan; Siaten; Zopicalma; ***Swed.:*** Imovane; ***Switz.:*** Imovane; ***Turk.:*** Imovane; ***UK:*** Zileze†; Zimovane; ***Venez.:*** Imovane†.