plon by adults, or 1 mg/kg by children, provided that the airway can be protected. Flumazenil may be considered in cases of severe CNS depression.

◊ References.

1. Israel AG, Kramer JA. Safety of zaleplon in the treatment of insomnia. *Ann Pharmacother* 2002; **36:** 852–9.

Abuse. In a controlled study in healthy patients with a history of drug abuse, zaleplon was shown to have a comparable abuse potential to that of the benzodiazepine, triazolam.[1]

1. Rush CR, *et al.* Zaleplon and triazolam in humans: acute behavioral effects and abuse potential. *Psychopharmacology (Berl)* 1999; **145:** 39–51.

Breast feeding. Licensed product information for zaleplon advises that it should not be given to breast-feeding mothers since, although only a small amount is excreted into breast milk, the effect on the nursing infant is not known.

Zaleplon was detected in the breast milk of 5 women who had been given a 10-mg dose.[1] The milk-to-plasma concentration ratio for zaleplon was about 0.5.

1. Darwish M, *et al.* Rapid disappearance of zaleplon from breast milk after oral administration to lactating women. *J Clin Pharmacol* 1999; **39:** 670–4.

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

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

Interactions

As for Diazepam, p.989. Zaleplon is primarily metabolised by aldehyde oxidase and use with inhibitors of this enzyme, such as cimetidine, may result in increased plasma concentrations of zaleplon (see Uses and Administration, below). Zaleplon is also partly metabolised by the cytochrome P450 isoenzyme CYP3A4 and, consequently, caution is advised when zaleplon is given with drugs that are substrates for, or potent inhibitors of, this isoenzyme. Cimetidine is also an inhibitor of CYP3A4 and thus inhibits both the primary and secondary metabolic pathways of zaleplon.

Use with rifampicin or other potent enzyme-inducing drugs may accelerate the metabolism of zaleplon and reduce its plasma concentrations.

Pharmacokinetics

Zaleplon is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in about one hour after oral dosage. A heavy meal or one with a high-fat content delays absorption and reduces peak concentrations. Bioavailability is about 30% due to significant first-pass hepatic metabolism. Zaleplon is metabolised primarily by aldehyde oxidase to form 5-oxo-zaleplon and, to a lesser extent, by the cytochrome P450 isoenzyme CYP3A4 to desethylzaleplon, which is further metabolised by aldehyde oxidase to 5-oxo-desethylzaleplon. The plasma-elimination half-life of zaleplon is about 1 hour. About 70% of a dose is excreted in the urine as these inactive metabolites or their glucuronides; less than 1% is excreted unchanged. About 17% of a dose is eliminated in the faeces, mainly as 5-oxo-zaleplon. Zaleplon is distributed into breast milk.

◊ References.

1. Greenblatt DJ, *et al.* Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. *Clin Pharmacol Ther* 1998; **64:** 553–61.
2. Drover D, *et al.* Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. *Clin Ther* 2000; **22:** 1443–61.
3. Drover DR. Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; **43:** 227–38.

Uses and Administration

Zaleplon is a pyrazolopyrimidine with similar sedative properties to the benzodiazepines (see Diazepam, p.992). It is used as a hypnotic in the short-term management of insomnia. Zaleplon has a rapid onset and short duration of action. The usual oral dose is 10 mg at bedtime although US product information notes that occasional patients may require 20 mg. Elderly or debilitated patients or those also taking cimetidine should be given 5 mg. For dosages in patients with hepatic impairment, see below.

Administration in hepatic impairment. The oral dose of zaleplon should be reduced to 5 mg at bedtime in patients with mild to moderate hepatic impairment; it should not be given to those with severe impairment.

Insomnia. Zaleplon is a pyrazolopyrimidine hypnotic. Although not related structurally to the benzodiazepines it appears to act by binding selectively to the benzodiazepine type I receptor (BZ1- or ω_1-receptors) on the GABA subtype A complex. Zaleplon reduces sleep latency but has little effect on sleep duration; it is rapidly absorbed and eliminated and consequently residual effects the next day are said to be minimal. These characteristics make it best suited for the treatment of patients with insomnia (p.957) who have difficulty falling asleep; zaleplon can either be taken at bedtime or during the night if a patient has trouble falling back to sleep, provided they are assured of at least 4 hours uninterrupted sleep.

References.

1. Anonymous. Zaleplon for insomnia. *Med Lett Drugs Ther* 1999; **41:** 93–4.
2. Danjou P, *et al.* A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 h before awakening. *Br J Clin Pharmacol* 1999; **48:** 367–74.
3. Elie R, *et al.* Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry* 1999; **60:** 536–44.
4. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. *Drugs* 2000; **60:** 413–45.
5. George CFP. Pyrazolopyrimidines. *Lancet* 2001; **358:** 1623–6.
6. Terzano MG, *et al.* New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. *Drug Safety* 2003; **26:** 261–82.
7. Barbera J, Shaprio [sic] C. Benefit-risk assessment of zaleplon in the treatment of insomnia. *Drug Safety* 2005; **28:** 301–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Hegon; Hipnodem; ***Austria:*** Sonata; ***Belg.:*** Sonata; ***Braz.:*** Sonata; ***Canad.:*** Starnoc; ***Chile:*** Noctiplon†; Plenidon; Rhem†; Sedartryl; Somnipax†; ***Cz.:*** Sonata; Zerene; ***Denm.:*** Sonata; ***Fin.:*** Sonata; ***Ger.:*** Sonata; ***Gr.:*** Sonata; ***Hung.:*** Sonata; ***India:*** Zalep; Zaplon†; Zaso; ***Irl.:*** Sonata; ***Ital.:*** Sonata; Zerene; ***Mex.:*** Sonata†; ***Neth.:*** Sonata; Zerene; ***Pol.:*** Selofen; ***Port.:*** Sonata; Zerene; ***Rus.:*** Andante (Анданте); ***Spain:*** Sonata; ***Swed.:*** Sonata; ***Switz.:*** Sonata; ***UK:*** Sonata†; ***USA:*** Sonata.

Ziprasidone *(BAN, rINN)*

Ziprasidona; Ziprasidonum. 5-{2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl}-6-chloro-2-indolinone.

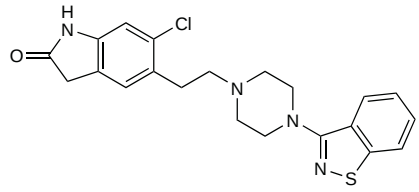
Зипрасидон

$C_{21}H_{21}ClN_4OS$ = 412.9.

CAS — 146939-27-7 (ziprasidone).

ATC — N05AE04.

ATC Vet — QN05AE04.



Ziprasidone Hydrochloride *(BANM, USAN, rINNM)*

CP-88059; CP-88059-1; Hidrocloruro de ziprasidona; Ziprasidone, chlorhydrate de; Ziprasidoni hydrochloridum.

Зипрасидона Гидрохлорид

$C_{21}H_{21}ClN_4OS,HCl,H_2O$ = 467.4.

CAS — 138982-67-9.

ATC — N05AE04.

ATC Vet — QN05AE04.

Ziprasidone Mesilate *(BANM, rINNM)*

CP-88059/27; Mesilato de ziprasidona; Ziprasidone, Mésilate de; Ziprasidone Mesylate *(USAN)*; Ziprasidoni Mesilas.

Зипрасидона Мезилат

$C_{21}H_{21}ClN_4OS,CH_4O_3S,3H_2O$ = 563.1.

CAS — 199191-69-0.

ATC — N05AE04.

ATC Vet — QN05AE04.

Adverse Effects, Treatment, and Precautions

Although ziprasidone 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. Frequent adverse effects with ziprasidone include somnolence, rash or urticaria, gastrointestinal disturbances, dizziness, flu-like symptoms, hypertension, headache, agitation, confusion, and dyspnoea. Orthostatic hypotension may be a problem, particularly when starting treatment. Ziprasidone may increase prolactin levels and weight gain has also been noted. Sexual dysfunction has been reported infrequently. Extrapyramidal symptoms may occur, and tardive dyskinesia may develop with prolonged use. There have also been infrequent or rare cases of cholestatic jaundice, hepatitis, seizures, blood dyscrasias including leucopenia and thrombocytopenia, and hyperlipidaemia. Hyperglycaemia occurs uncommonly with ziprasidone. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with, or at risk of, developing diabetes.

Ziprasidone has been associated with dose-related prolongation of the QT interval. Because of this and the consequent danger of life-threatening arrhythmias such as torsade de pointes and sudden death, its use is contra-indicated in patients with a history of QT prolongation or cardiac arrhythmias, with recent acute myocardial infarction, or with decompensated heart failure. Certain medications may also increase the risk (see Interactions, below). Baseline serum potassium and magnesium screening should be performed in patients who are at risk of significant electrolyte disturbances and hypokalaemia or hypomagnesaemia should be corrected before starting ziprasidone therapy. Serum electrolytes should be monitored in patients who start diuretic therapy during ziprasidone treatment. Patients receiving ziprasidone who have symptoms that might indicate torsade de pointes (e.g. dizziness, palpitations, or syncope) should be further evaluated.

Ziprasidone should be used with caution in patients with a history of seizures or in conditions that lower the seizure threshold, cardiovascular or cerebrovascular disease, or conditions which predispose to hypotension. Since intramuscular injections are formulated with cyclodextrin, which is cleared by renal filtration, the manufacturer recommends caution in patients with renal impairment.

Ziprasidone may affect the performance of skilled tasks including driving.

Dementia. The FDA[1] has issued advice against the use of atypical antipsychotics, including ziprasidone, in the treatment of behavioural problems in elderly patients with dementia after analysis of placebo-controlled studies showed an increased risk of mortality with certain drugs of this class. See under Risperidone, p.1024.

1. Food and Drug Administration. FDA issues public health advisory for antipsychotic drugs used for treatment of behavioral disorders in elderly patients (issued 11/04/05). Available at: http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01350.html (accessed 30/05/05)

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

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.

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.

Extrapyramidal disorders. There have been reports[1-3] of tardive dyskinesia associated with ziprasidone therapy; onset ranged from 2 to 34 months after starting the drug. Acute dystonia has also been reported[4,5] with ziprasidone. However, the incidence of extrapyramidal adverse effects (p.971) is generally lower with atypical than classical antipsychotics.

1. Rosenquist KJ, *et al.* Tardive dyskinesia and ziprasidone. *Am J Psychiatry* 2002; **159:** 1436.
2. Keck ME, *et al.* Ziprasidone-related tardive dyskinesia. *Am J Psychiatry* 2004; **161:** 175–6.
3. Ananth J, *et al.* Tardive dyskinesia in 2 patients treated with ziprasidone. *J Psychiatry Neurosci* 2004; **29:** 467–9.
4. Ziegenbein M, *et al.* Ziprasidone-induced Pisa syndrome after clozapine treatment. *J Neuropsychiatr Clin Neurosci* 2003; **15:** 458–9.
5. Mason MN, *et al.* Ziprasidone-induced acute dystonia. *Am J Psychiatry* 2005; **162:** 625–6.

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.

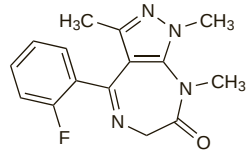
Zolazepam Hydrochloride *(BANM, USAN, rINNM)*

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.

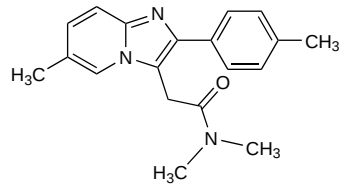
Золпидема Тартрат

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