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.

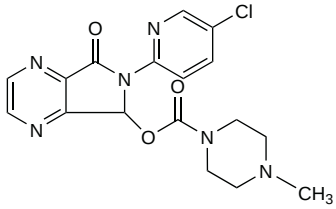
Зопиклон

$C_{17}H_{17}ClN_6O_3$ = 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his dosage of zopiclone up to 337.5 mg daily to treat insomnia without apparent adverse effects, had his zopiclone withdrawn without severe complications over 4 weeks using drug and cognitive therapy.[3] A WHO expert committee[4] considered in 2006 that the likelihood of zopiclone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†.

Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum. 2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.

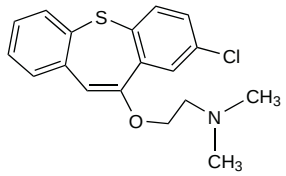
Зотепин

$C_{18}H_{18}ClNOS$ = 331.9.

CAS — 26615-21-4.

ATC — N05AX11.

ATC Vet — QN05AX11.



Adverse Effects, Treatment, and Precautions

Although zotepine 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. Common adverse effects include asthenia, headache, hypotension and, less commonly, orthostatic hypotension, tachycardia, gastrointestinal disturbances, elevated liver enzyme values, leucopenia, agitation, anxiety, dizziness, insomnia, somnolence, rhinitis, sweating, and blurred vision. Other less common adverse effects include thrombocytopenia, hyperglycaemia, hyperlipidaemia, convulsions, sexual dysfunction, and urinary incontinence. Extrapyramidal symptoms have been reported and tardive dyskinesia may occur with prolonged therapy. Neuroleptic malignant syndrome has been reported rarely. Prolactin levels may be increased and weight gain has been noted.

Zotepine can prolong the QT interval and patients with pre-existing prolongation of the QT interval should not be given the drug. It should be used with caution in patients at risk of developing arrhythmias; in such patients an ECG should be performed before starting treatment. Electrolytes should also be measured and any imbalance corrected. Monitoring of ECG and electrolytes should be continued during treatment especially at each dose increase. Zotepine may also increase the heart rate and, consequently, it should be used with care in patients with angina pectoris due to coronary artery disease. Caution is also recommended in patients with other cardiovascular disorders such as severe hypertension.

Zotepine has uricosuric properties and should not be given to patients with acute gout or a history of nephrolithiasis; it should be used with caution in patients with a history of gout or hyperuricaemia. Zotepine lowers the seizure threshold and should not be used in patients with a personal or family history of epilepsy unless the potential benefit outweighs the risk of convulsions. It has antimuscarinic actions and should be used with caution in patients with disorders such as benign prostatic hyperplasia, urinary retention, angle-closure glaucoma, and paralytic ileus. It should also be used with caution in patients with hepatic impairment; in such patients, weekly monitoring of liver function is recommended for at least the first 3 months of therapy. Zotepine may exacerbate the symptoms of Parkinson's disease. It should be used with caution in patients with tumours of the adrenal medulla such as phaeochromocytoma or neuroblastoma.

Zotepine may affect the performance of skilled tasks including driving.

Gradual withdrawal of zotepine is recommended because of the risk of withdrawal symptoms such as sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

Dementia. The FDA has issued advice against the use of atypical antipsychotics 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.

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 under Adverse Effects of Clozapine, p.981.

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

Interactions

Zotepine may enhance the effects of other CNS depressants and antimuscarinics. The risk of seizures is particularly increased when zotepine is given with high doses of other antipsychotics and the combination is not recommended. Additive hypotensive effects may theoretically occur with antihypertensives and some anaesthetic drugs; however its α-blocking actions might reduce the effects of methyldopa or clonidine.

The risk of arrhythmias with zotepine may be increased by use with other drugs that prolong the QT interval or cause hypokalaemia. Use of zotepine with fluoxetine or diazepam may lead to increased plasma concentrations of zotepine.

Pharmacokinetics

Zotepine is well absorbed from the gastrointestinal tract after oral doses with peak plasma concentrations being achieved 2 to 3 hours later. It undergoes extensive first-pass metabolism to the equipotent metabolite norzotepine and inactive metabolites. CYP1A2 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of zotepine. Plasma protein binding of zotepine and norzotepine is 97%. Zotepine is excreted mainly in the urine and faeces as inactive metabolites and has an elimination half-life of about 14 hours. It is thought to be distributed into breast milk on the basis of studies in *rats*.

Uses and Administration

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin (5-HT_2), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It is given in the treatment of schizophrenia in an initial oral dose of 25 mg three times daily; this is increased according to response, at intervals of 4 days, to a maximum of 100 mg three times daily. There is an appreciable increase in the incidence of seizures at total daily doses above the recommended maximum of 300 mg. For elderly patients, the recommended starting dose is 25 mg given twice daily, increased gradually up to a maximum of 75 mg twice daily. Doses should also be reduced in patients with hepatic or renal impairment, see below.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, the recommended initial oral dose of zotepine is 25 mg given twice daily increased gradually up to a maximum of 75 mg twice daily.

Schizophrenia. A systematic review[1] of short-term studies of zotepine for schizophrenia (p.955) concluded tentatively that it was as effective as classical antipsychotics and might be of benefit in patients with negative symptoms; in addition, it seemed less likely to provoke extrapyramidal disorders. Comparisons with atypical antipsychotics were too scanty for a meaningful comparison to be drawn.

1. DeSilva P, *et al.* Zotepine for schizophrenia. Available in The Cochrane Database of Systematic Reviews ; Issue 4. Chichester: John Wiley; 2006 (accessed 10/04/08).

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Nipolept; ***Cz.:*** Zoleptil; ***Ger.:*** Nipolept; ***Indon.:*** Lodopin; ***Jpn:*** Lodopin; ***Port.:*** Zoleptil; ***UK:*** Zoleptil.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *Z*-Clopenthixol; *cis*-Clopenthixol; α-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol. (*Z*)-2-{4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl}ethanol.

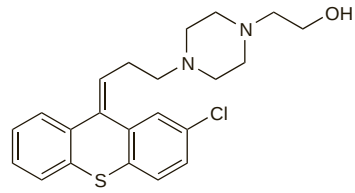
Зуклопентиксол

$C_{22}H_{25}ClN_2OS$ = 401.0.

CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).

ATC — N05AF05.

ATC Vet — QN05AF05.



NOTE. Clopenthixol (*BAN*, *INN*, *USAN*) is the racemic mixture.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuklopentiksol Asetat.

Зуклопентиксола Ацетат

$C_{24}H_{27}ClN_2O_2S$ = 443.0.

CAS — 85721-05-7.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Acetate). A yellowish, viscous oil. Very slightly soluble in water; very soluble in alcohol, in dichloromethane, and in ether. Store at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, décanoate de; Zuclopenthixoli decanoas; Zuklopenthixol-dekanoát; Zuklopentiksol Dekanoat; Zuklopentiksolio dekanoatas; Zuklopentixoldekanoat; Zuklopentyksolu dekanonian.

Зуклопентиксола Деканоат

$C_{32}H_{43}ClN_2O_2S$ = 555.2.

CAS — 64053-00-5.

ATC — N05AF05.

ATC Vet — QN05AF05.

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

Ph. Eur. 6.2 (Zuclopenthixol Decanoate). A yellow viscous oily liquid. Very slightly soluble in water; very soluble in alcohol and in dichloromethane. Store under an inert gas in airtight containers at a temperature not exceeding –20°. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuklopentiksol Dihidroklorür.

Зуклопентиксола Гидрохлорид

$C_{22}H_{25}ClN_2OS,2HCl$ = 473.9.

CAS — 58045-23-1.

ATC — N05AF05.

ATC Vet — QN05AF05.

Pharmacopoeias. In *Br.*

BP 2008 (Zuclopenthixol Hydrochloride). An off-white granular powder. Very soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; very slightly soluble in ether. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Li Wan Po A, Irwin WJ. The photochemical stability of cis- and trans-isomers of tricyclic neuroleptic drugs. *J Pharm Pharmacol* 1980; **32:** 25–9.

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p.969. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. Zuclopenthixol is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.