nox; ***Neth.***: Stilnoct; ***Norw.***: Stilnoct; ***Philipp.***: Stilnox; Ziohex; Zoldem; Zolpid; ***Pol.***: Apo-Zolpin; Hypnogen; Nasen; Onirex; Polsen; Sanval; Stilnox; Xentic; Zolpic; ZolpiGen; Zolsana; Zoratio; ***Port.***: Cymerion; Stilnox; ***Rus.***: Hypnogen (Гипноген); Ivadal (Ивадал); Nitrest (Нитрест); Sanval (Санвал); Snovitel (Сновител); Zolsana (Зольсана); Zonadine (Зонадин); ***S.Afr.***: Ivedal; Noxidem; Stilnox; Zolnoxs; Zolpihexal; ***Singapore***: Stilnox; ***Spain***: Dalparan; Stilnox; ***Swed.***: Stilnoct; ***Switz.***: Dorlotil; Stilnox; Zoldorm; ***Thai.***: Stilnox; ***UK***: Stilnoct; ***USA***: Ambien; Edluar; Intermezzo; Tovalt†; Zolpimist; ***Venez.***: Atrimon; Stilnox; Zolpidex.

Pharmacopoeial Preparations

USP 36: Zolpidem Tartrate Extended-Release Tablets; Zolpidem Tartrate Tablets.

Zopiclone *(BAN, rINN)*

27267-RP; Tsopikloni; Zopiclon; Zopiclona; Zopiclonum; Zopiklon; Zopiklonas; Зопиклон.

6-(5-Chloro-2-pyridyl)-6,7-dihydro-7-oxo-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

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

CAS — 43200-80-2.

ATC — N05CF01.

ATC Vet — QN05CF01.

UNII — 03A5ORL08Q.

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

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

Ph. Eur. 8: (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.

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. 1063.3). 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 (below). The usual oral dose is 7.5 mg taken shortly before retiring. Treatment should start with a dose of 3.75 mg in elderly patients. Reduced doses are also recommended in patients with hepatic or renal impairment, see below.

Eszopiclone, the (+)-isomer of zopiclone, is used similarly (see p. 1072.3).

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 taken shortly before retiring. 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. 1033.2). 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, below.

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.

Dependence and Withdrawal

As for Diazepam, p. 1065.1.

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. 1065.3. A bitter or metallic taste in the mouth has been the most frequently reported adverse effect with zopiclone.

Treatment of overdose is largely supportive. The benefit of gastric decontamination is uncertain; activated charcoal may be given orally to adults or children who present within one hour of ingesting more than 1 mg/kg of zopiclone. Flumazenil (p. 1552.2) may rarely be used to reverse the effects of severe zopiclone toxicity. (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. CSM. Zopiclone (Zimovane) and neuro-psychiatric reactions. *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 20/07/09)

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 benzodiazepines, see p. 1067.1.

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, p. 1117.2.

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.

For precautions and doses recommended in licensed product information, see under Uses and Administration, above.

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, p. 1117.2.

Overdosage. Fatalities have been reported after zopiclone overdose.[1,2] Methaemoglobinaemia and renal failure have been reported in a patient who took 2.25 g of zopiclone in a suicide attempt.[3]

Flumazenil may rarely be used to reverse the effects of severe zopiclone toxicity. see Non-benzodiazepine Antagonism under Flumazenil, p. 1552.2.

1. Boniface PJ, Russell SGG. Two cases of fatal zopiclone overdose. *J Anal Toxicol* 1996; **20:** 131–3.
2. Meatherall RC. Zopiclone fatality in a hospitalized patient. *J Forensic Sci* 1997; **42:** 340–3.
3. Kung SW, *et al.* Zopiclone-associated methemoglobinemia and renal impairment. *Clin Toxicol* 2008; **46:** 1099–1100.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zopiclone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for Diazepam, p. 1068.1. 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 via the cytochrome P450 isoenzyme CYP3A4 and, to a lesser extent, CYP2C8; 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.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Foltran; Imovane; Insomnium; ***Austral.***: Imovane; Imrest; ***Austria***: Somnal; ***Belg.***: Imovane; ***Braz.***: Imovane; ***Canad.***: Imovane; Rhovane; ***Chile***: Alpaz; Imovane; Losopil; Zetix; Zometic; Zonix; ***China***: Imovane (忆梦返); Jin Meng (金盟); Qing Er Qi (青尔齐); San Chen (三辰); ***Cz.***: Zopitin; ***Denm.***: Imoclone; Imovane; Imozop; ***Fin.***: Imovane; Zopinox; Zopitin; ***Fr.***: Imovane; ***Ger.***: Optidorm; Somnosan; Ximovan; Zop†; Zopi-Puren†; ***Gr.***: Imovane; ***Hong Kong***: Dopareel; Eurovan; Imolone†; Imovane; Zolief; Zomni; ***Hung.***: Imovane; Somnol; Zopigen; ***India***: Lyzop; Zopicon; ***Irl.***: Zileze; Zimoclone; Zimovane; Zopitan; Zorclone; ***Israel***: Imovane; Nocturno; ***Ital.***: Imovane; ***Malaysia***: Imovane; Insopin; Zolon; ***Mex.***: Imovane; ***Neth.***: Imovane; ***Norw.***: Imovane; ***NZ***:

Imovane; ***Pol.***: Dobroson; Imovane; Senzop; Zopiratio; ***Rus.***: Imovane (Имован); Milovan (Милован); Piclodorm (Пиклодорм); Relaxon (Релаксон); Slipvell (Слипвэлл); Somnol (Сомнол); Torson (Торсон); Zolinox (Золинокс); ***S.Afr.***: Adco-Zopimed; Alchera; Imovane; Z-Dorm; Zopigen; Zopivane; ***Singapore***: Imovane; ***Spain***: Datolan; Limovan; Siaten; Zopicalma; ***Swed.***: Imovane; ***Switz.***: Imovane; ***Turk.***: Imovane; ***UK***: Zimovane; ***Ukr.***: Imovane (Имован); Normason (Нормасон); Piklon (Піклон); Sonnat (Соннат).

Pharmacopoeial Preparations
BP 2014: Zopiclone Tablets.

Zotepine *(BAN, rINN)*

Zotepina; Zotépine; Zotepinum; Зотепин.
2-[(8-Chlorodibenzo[*b,f*]-thiepin-10-yl)oxy]-*N,N*-dimethylethylamine.
$C_{18}H_{18}ClNOS$=331.9
CAS — 26615-21-4.
ATC — N05AX11.
ATC Vet — QN05AX11.
UNII — U29O83JAZW.

Profile

Zotepine is an atypical antipsychotic that, in addition to its antagonist action at central dopamine (D_1 and D_2) receptors, binds to serotonin ($5\text{-}HT_2$), adrenergic (α_1), and histamine (H_1) receptors and also inhibits noradrenaline reuptake. It has been given in the treatment of schizophrenia (below) in an initial oral dose of 25 mg three times daily, 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 doses above 300 mg daily. For elderly patients, a starting dose of 25 mg has been 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.

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.

Administration in hepatic or renal impairment. For patients with renal or hepatic impairment, an initial oral dose of zotepine 25 mg has been 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. 1031.3) 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. A later systematic review[2] that compared zotepine with other atypical antipsychotics found insufficient evidence 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).
2. Subramanian S, *et al.* Zotepine versus other atypical antipsychotics for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 10. Chichester: John Wiley; 2010 (accessed 03/06/13).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Nipolept†; ***Cz.***: Zoleptil; ***Ger.***: Nipolept†; ***Indon.***: Lodopin; ***Jpn***: Lodopin; Losizopilon; Majorpin; Setous; ***Port.***: Zoleptil; ***Turk.***: Zoleptil; ***UK***: Zoleptil†.

Zuclopenthixol *(BAN, rINN)*

AY-62021 (clopenthixol or clopenthixol hydrochloride); *cis*-Clopenthixol; α-Clopenthixol; *Z*-Clopenthixol; N-746 (clopenthixol or clopenthixol hydrochloride); NSC-64087 (clopenthixol); Tsuklopentiksoli; Zuclopenthixolum; Zuclopentixol; Zuklopentixol; Зуклопентиксол.
(*Z*)-2-{4-[3-(2-Chloro-10*H*-dibenzo[*b,e*]thiin-10-ylidene)propyl]piperazin-1-yl}ethanol.
$C_{22}H_{25}ClN_2OS$=401.0
CAS — 53772-83-1 (zuclopenthixol); 982-24-1 (clopenthixol).
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 47ISU063SG.

NOTE. Clopenthixol (*BAN, INN, USAN*) is a mixture of the *Z* and *E* isomers.

Zuclopenthixol Acetate *(BANM, rINNM)*

Acetato de zuclopentixol; Zuclopenthixol, Acétate de; Zuclopenthixoli Acetas; Zuclopentixol, acetato de; Zuklopentiksol Asetat; Зуклопентиксола Ацетат.
$C_{24}H_{27}ClN_2O_2S$=443.0
CAS — 85721-05-7.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 349S2ZHF05.

Pharmacopoeias. In *Br.*

BP 2014: (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 degrees. Protect from light.

Zuclopenthixol Decanoate *(BANM, rINNM)*

Decanoato de zuclopentixol; Tsuklopentiksolidekanoaatti; Zuclopenthixol, Décanoate de; Zuclopenthixoldecanoat; Zuclopenthixoli decanoas; Zuclopentixol, decanoato de; 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.
UNII — TSS9KIZ5OG.

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

Ph. Eur. 8: (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 degrees. Protect from light.

Zuclopenthixol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de zuclopentixol; Zuclopenthixol, Chlorhydrate de; Zuclopenthixol Dihydrochloride; Zuclopenthixoli Hydrochloridum; Zuclopentixol, hidrocloruro de; Zuklopentiksol Dihidroklorür; Зуклопентиксола Гидрохлорид.
$C_{22}H_{25}ClN_2OS,2HCl$=473.9
CAS — 58045-23-1.
ATC — N05AF05.
ATC Vet — QN05AF05.
UNII — 7042692VYN.

Pharmacopoeias. In *Br.*

BP 2014: (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.

Uses and Administration

Zuclopenthixol is a thioxanthene of high potency with general properties similar to the phenothiazine, chlorpromazine (p. 1045.3). It has a piperazine side-chain.

Zuclopenthixol is used for the treatment of schizophrenia (below), mania (see Bipolar Disorder, p. 397.2), and other psychoses. It may be particularly suitable for agitated or aggressive patients who may become over-excited with flupentixol. Zuclopenthixol hydrochloride is usually given orally with doses expressed in terms of the base; zuclopenthixol hydrochloride 11.8 mg is equivalent to about 10 mg of zuclopenthixol. Zuclopenthixol hydrochloride has also been given intramuscularly. Zuclopenthixol acetate and zuclopenthixol decanoate are given by deep intramuscular injection; doses are expressed in terms of the ester. The acetate ester has a rapid onset of action and a duration of action of 2 to 3 days; it is used as a 5% oily solution for the initial treatment of acute psychoses and for exacerbations of chronic psychoses. The longer-acting decanoate ester is used as a 20% oily solution for the maintenance treatment of chronic psychoses; a 50% solution is available for those requiring high doses.

- The usual initial *oral* dose of the hydrochloride for the treatment of **psychoses** is the equivalent of 20 to 30 mg of the base daily in divided doses; in severe or resistant cases up to 150 mg daily has been given. The recommended maximum single dose is 40 mg. The usual maintenance dose is 20 to 50 mg daily.
- The usual dose of zuclopenthixol acetate is 50 to 150 mg by deep *intramuscular* injection repeated, if necessary, after 2 or 3 days. Some patients may need an additional injection between 1 and 2 days after the first dose. Zuclopenthixol acetate is not intended for maintenance treatment; no more than 4 injections should be given in a maximum course of 2 weeks and the total dose should not exceed 400 mg. When maintenance treatment is required, *oral* zuclopenthixol hydrochloride may be introduced 2 to 3 days after the last injection of zuclopenthixol acetate, or *intramuscular* injections of the decanoate (see below) begun with the last injection of the acetate.
- The long-acting decanoate should be given by deep *intramuscular* injection; treatment is usually started with a test dose of 100 mg. This may be followed after at least 1 week by a dose of 200 to 500 mg or more, every 1 to 4 weeks, adjusted according to response. Injection volumes greater than 2 mL should be divided between 2 separate injection sites. The maximum recommended dose of zuclopenthixol decanoate is 600 mg weekly.

Elderly or debilitated patients should be given reduced doses of zuclopenthixol. Licensed product information states that the dose of the hydrochloride or the decanoate may need to be reduced to one-quarter or one-half of the usual initial dose; in addition, the maximum single dose of the acetate should be limited to 100 mg.

Dosage adjustment is also advised in patients with hepatic or renal impairment (see below).

Administration in hepatic or renal impairment. Licensed product information recommends that for both zuclopenthixol acetate and hydrochloride, half the usual recommended intramuscular and oral dose, respectively, should be used for patients with hepatic impairment; a dosage reduction is considered to be unnecessary in patients with renal impairment but where there is renal failure half the usual dosage is recommended.

Schizophrenia. A systematic review[1] comparing zuclopenthixol decanoate with other depot antipsychotics considered that although it may induce more adverse effects, limited data suggested it might offer advantages such as lower relapse rates and increased acceptability in the treatment of schizophrenia (p. 1031.3) and similar serious mental illnesses. Similar reviews of the use of the acetate[2] or hydrochloride[3] found, however, that evidence of additional benefit over other antipsychotics was lacking.

1. Coutinho E, *et al.* Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 14/04/05).
2. Gibson RC, *et al.* Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 14/04/05).
3. Kumar A, Strech D. Zuclopenthixol dihydrochloride for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 12/05/06).

Adverse Effects, Treatment, and Precautions

As for Chlorpromazine, p. 1047.2. Zuclopenthixol is less likely to cause sedation but extrapyramidal effects are more frequent.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies zuclopenthixol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 21/10/11)

Interactions

As for Chlorpromazine, p. 1051.3.

Pharmacokinetics

Zuclopenthixol is absorbed after oral doses and peak plasma concentrations occur 3 to 6 hours later. The biological half-life after oral doses is reported to be about 1 day. Paths of metabolism of zuclopenthixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. It is mainly excreted in the faeces as unchanged drug and its *N*-dealkylated metabolite. Zuclopenthixol is about 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Small amounts of drug or metabolites cross the placenta and are distributed into breast milk.

On intramuscular injection the acetate and decanoate esters of zuclopenthixol are hydrolysed to release zuclopenthixol. Zuclopenthixol acetate has a relatively quick onset of action after injection and a duration of action of 2 to 3 days. It is therefore useful for the control of acute psychotic symptoms while avoiding repeated injections. The decanoate has a much longer duration of action and is a suitable depot preparation for maintenance treatment.

Metabolism. Determination of metaboliser phenotype with regard to cytochrome P450 isoenzyme CYP2D6 appeared to be of limited value in patients receiving zuclopenthixol as interindividual variation appeared to be