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

the main factor affecting dose to serum concentration ratios.[1]

1. Linnet K, Wiborg O. Influence of Cyp2D6 genetic polymorphism on ratios of steady-state serum concentration to dose of the neuroleptic zuclopenthixol. *Ther Drug Monit* 1996; **18:** 629–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clopixol; ***Austral.***: Clopixol; ***Austria***: Cisordinol; ***Belg.***: Clopixol; ***Braz.***: Clopixol; ***Canad.***: Clopixol; ***Chile***: Cisordinol; ***China***: Clopixol (高抗素); ***Cz.***: Cisordinol; ***Denm.***: Cisordinol; Clopixol; ***Fin.***: Cisordinol; ***Fr.***: Clopixol; ***Ger.***: Ciatyl-Z; ***Gr.***: Clopixol; ***Hong Kong***: Clopixol; ***Hung.***: Cisordinol; ***India***: Clopixol; ***Irl.***: Clopixol; ***Israel***: Clopixol; ***Ital.***: Clopixol; ***Malaysia***: Clopixol; ***Mex.***: Clopixol; ***Neth.***: Cisordinol; Clopixol; ***Norw.***: Cisordinol; ***NZ***: Clopixol; ***Philipp.***: Clopixol†; ***Pol.***: Clopixol; ***Port.***: Cisordinol; ***Rus.***: Clopixol (Клопиксол); ***S.Afr.***: Clopixol; Colpixol†; ***Singapore***: Clopixol; ***Spain***: Clopixol; ***Swed.***: Cisordinol; ***Switz.***: Clopixol; ***Thai.***: Clopixol; ***Turk.***: Clopixol; ***UK***: Clopixol; ***Ukr.***: Clopixol (Клопиксол).

Pharmacopoeial Preparations

BP 2014: Zuclopenthixol Acetate Injection; Zuclopenthixol Decanoate Injection; Zuclopenthixol Tablets.