Zotepine *(BAN, rINN)*

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

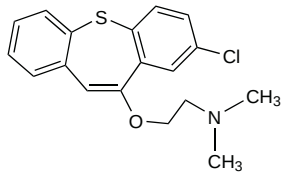
Зотепин

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

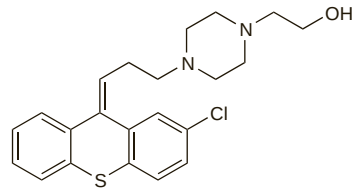
Зуклопентиксол

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