Trifluperidol *(BAN, USAN, rINN)*

McN-JR-2498; R-2498; Triflupéridol; Trifluperidoli; Trifluperidolum. 4′-Fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone.

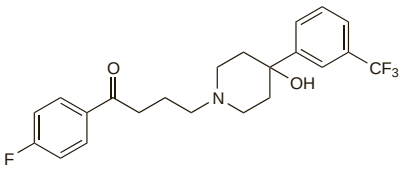
Трифлуперидол

$C_{22}H_{23}F_4NO_2$ = 409.4.

CAS — 749-13-3.

ATC — N05AD02.

ATC Vet — QN05AD02.



Trifluperidol Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trifluperidol; Triflupéridol, Chlorhydrate de; Trifluperidoli Hydrochloridum.

Трифлуперидола Гидрохлорид

$C_{22}H_{23}F_4NO_2$,HCl = 445.9.

CAS — 2062-77-3.

ATC — N05AD02.

ATC Vet — QN05AD02.

Profile

Trifluperidol is a butyrophenone with general properties similar to those of haloperidol (p.1000), and has been used as the hydrochloride in the treatment of psychoses including schizophrenia.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Triperidol.

Triflupromazine *(BAN, rINN)*

Fluopromazine; Triflupromazina; Triflupromazinum. *NN*-Dimethyl-3-(2-trifluoromethylphenothiazin-10-yl)propylamine.

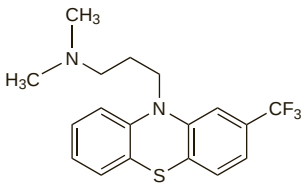
Трифлупромазин

$C_{18}H_{19}F_3N_2S$ = 352.4.

CAS — 146-54-3.

ATC — N05AA05.

ATC Vet — QN05AA05.



Pharmacopoeias. In *US*.

USP 31 (Triflupromazine). A light amber viscous oily liquid that crystallises into large irregular crystals during prolonged storage. Practically insoluble in water. Store in airtight containers. Protect from light.

Triflupromazine Hydrochloride *(BANM, rINNM)*

Fluopromazine Hydrochloride; Hidrocloruro de triflupromazina; Triflupromazine, Chlorhydrate de; Triflupromazini Hydrochloridum.

Трифлупромазина Гидрохлорид

$C_{18}H_{19}F_3N_2S$,HCl = 388.9.

CAS — 1098-60-8.

ATC — N05AA05.

ATC Vet — QN05AA05.

Pharmacopoeias. In *US*.

USP 31 (Triflupromazine Hydrochloride). A white to pale tan crystalline powder having a slight characteristic odour. Soluble 1 in less than 1 of water and of alcohol and 1 in 1.7 of chloroform; soluble in acetone; insoluble in ether. Store in glass containers. Protect from light.

Profile

Triflupromazine hydrochloride is a phenothiazine with general properties similar to those of chlorpromazine (p.969). It is used mainly in the management of psychoses (p.954) and the control of nausea and vomiting (p.1700). Triflupromazine hydrochloride is usually given by injection but in some countries oral preparations are available.

In the management of psychosis, the usual dose is 60 to 150 mg daily by intramuscular injection. For the control of nausea and vomiting 5 to 15 mg is given intramuscularly and repeated after 4 hours if necessary up to a maximum of 60 mg daily; a dose of 1 mg to a maximum total daily dose of 3 mg may be given intravenously.

A suggested intramuscular dose for children over 2 years of age is 200 to 250 micrograms/kg daily up to a maximum of 10 mg daily.

Reduced doses should be used in elderly or debilitated patients.

Preparations

USP 31: Triflupromazine Hydrochloride Injection; Triflupromazine Hydrochloride Tablets; Triflupromazine Oral Solution.

Proprietary Preparations (details are given in Part 3)
Austria: Psyquil; ***Ger.:*** Psyquil†; ***India:*** Siquil.

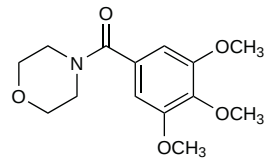
Trimetozine *(USAN, rINN)*

Abbott-22370; NSC-62939; PS-2383; Trimetozina; Trimétozine; Trimetozinum. 4-(3,4,5-Trimethoxybenzoyl)morpholine.

Триметоцин

$C_{14}H_{19}NO_5$ = 281.3.

CAS — 635-41-6.



Profile

Trimetozine has been used for its sedative properties.

Preparations

Proprietary Preparations (details are given in Part 3)
Hung.: Trioxazin.

Valnoctamide *(USAN, rINN)*

McN-X-181; NSC-32363; Valnoctamida; Valnoctamidum. 2-Ethyl-3-methylvaleramide.

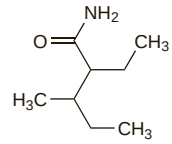
Вальноктамид

$C_8H_{17}NO$ = 143.2.

CAS — 4171-13-5.

ATC — N05CM13.

ATC Vet — QN05CM13.



Profile

Valnoctamide, an isomer of valpromide (p.508), has been given orally in the treatment of anxiety disorders.

◊ References.

1. Bialer M, *et al.* Pharmacokinetics of a valpromide isomer, valnoctamide, in healthy subjects. *Eur J Clin Pharmacol* 1990; **38:** 289–91.
2. Barel S, *et al.* Stereoselective pharmacokinetic analysis of valnoctamide in healthy subjects and in patients with epilepsy. *Clin Pharmacol Ther* 1997; **61:** 442–9.

Interactions. For a discussion of the potential interaction between carbamazepine and valnoctamide, see Antiepileptics, p.474.

Veralipride *(rINN)*

Veraliprida; Véralipride; Veralipridum. *N*-[(1-Allyl-2-pyrrolidinyl)methyl]-5-sulphamoyl-2-veratramide.

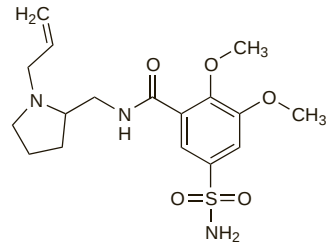
Вералиприд

$C_{17}H_{25}N_3O_5S$ = 383.5.

CAS — 66644-81-3.

ATC — N05AL06.

ATC Vet — QN05AL06.



Profile

Veralipride is a substituted benzamide antipsychotic. It has been used in the treatment of cardiovascular and psychological symptoms associated with the menopause; the usual oral dose is 100 mg daily for 20 days repeated at intervals of 7 to 10 days. Preparations of veralipride have now been withdrawn from the market in some countries because of the opinion that there is an unacceptable balance of risks and benefits; adverse effects such as anxiety, depression, and tardive dyskinesia have been associated with veralipride, both during and after treatment.

Menopausal disorders. HRT with oestrogens is the mainstay of treatment for acute symptoms associated with the menopause (see p.2077) but when it is considered to be unsuitable a variety of other drugs including veralipride have been tried.[1] It has also been tried with raloxifene in postmenopausal women.[2] However, treatment with veralipride has been associated with extrapyramidal adverse effects.[3,4]

1. Young RL, *et al.* Management of menopause when estrogen cannot be used. *Drugs* 1990; **40**: 220–30.
2. Morgante G, *et al.* Veralipride administered in combination with raloxifene decreases hot flushes and improves bone density in early postmenopausal women. *Gynecol Endocrinol* 2004; **18:** 194–8.
3. Masmoudi K, *et al.* Troubles extrapyramidaux sous véralipride (Agréal), traitement symptomatique des bouffées de chaleur: à propos de 17 cas. *Rev Med Interne* 2005; **26:** 453–7.
4. Raja M, Azzoni A. Tardive dyskinesia after long-term veralipride treatment. *J Neuropsychiatr Clin Neurosci* 2005; **17:** 252–3.

Porphyria. Veralipride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Veralipral; ***Belg.:*** Agreal†; ***Braz.:*** Agreal; ***Chile:*** Agreal; ***Fr.:*** Agreal†; ***Ital.:*** Agradil; Veralipril†; ***Mex.:*** Aclimafel; Veraligral; ***Port.:*** Agreal†; ***Spain:*** Agreal†.

Multi-ingredient: ***Arg.:*** Veralipral T.

Zaleplon *(BAN, USAN, rINN)*

CL-284846; L-846; LJC-10846; Tsaleploni; ZAL-846; Zaleplón; Zaléplone; Zaleplonum. 3′-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetanilide.

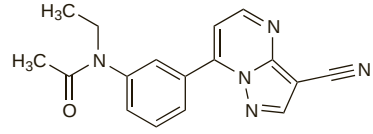
Залеплон

$C_{17}H_{15}N_5O$ = 305.3.

CAS — 151319-34-5.

ATC — N05CF03.

ATC Vet — QN05CF03.



Dependence and Withdrawal

As for Diazepam, p.987.

Adverse Effects, Treatment, and Precautions

As for Diazepam, p.987. Zaleplon should be used with caution and in reduced doses in patients with hepatic impairment, and should be avoided where this is severe.

Treatment of overdose is largely supportive. Activated charcoal may be given orally to patients who present within one hour of ingestion of more than 50 mg zale-

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.

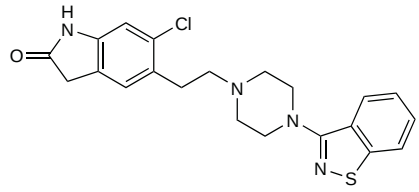
Зипрасидон

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