is reported to be between 16 and 35 hours. Flunitrazepam crosses the placental barrier and is distributed into breast milk.

◊ References.

1. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
2. Pariente-Khayat A, *et al*. Pharmacokinetics and tolerance of flunitrazepam in neonates and in infants. *Clin Pharmacol Ther* 1999; **66:** 136–9.

Pregnancy. Concentrations of flunitrazepam in umbilical-vein and umbilical-artery plasma were lower than those in maternal venous plasma about 11 to 15 hours after a dose of flunitrazepam 1 mg in 14 pregnant women; concentrations in amniotic fluid were lower still.[1]

1. Kanto J, *et al*. Placental transfer and breast milk levels of flunitrazepam. *Curr Ther Res* 1979; **26:** 539–46.

Uses and Administration

Flunitrazepam is a short-acting benzodiazepine with general properties similar to those of diazepam (p.992). It is used in the short-term management of insomnia (p.957), as a premedicant in surgical procedures, and for induction of anaesthesia (p.1780).

A usual oral dose for **insomnia** is 0.5 to 1 mg at night; up to 2 mg may be given if necessary. In elderly or debilitated patients the initial dose should not exceed 0.5 mg at night; up to 1 mg may be given if necessary.

A dose of 1 to 2 mg (15 to 30 micrograms/kg) has been given intramuscularly or orally for **premedication** or by slow intravenous injection for **induction** of general anaesthesia.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Nervocuril; Parsimoni†; Primum; Rohypnol; ***Austral.:*** Hypnodorm; ***Austria:*** Guttanotte; Rohypnol; Somnubene; ***Belg.:*** Rohypnol; ***Braz.:*** Rohydorm; Rohypnol; ***Chile:*** Ipnopen; Rohypnol†; ***Cz.:*** Rohypnol†; ***Denm.:*** Flunipam; Rohypnol†; Ronal; ***Fr.:*** Narcozep; Rohypnol; ***Ger.:*** Fluni†; Flunibeta; Flunimerck†; Flunino; Rohypnol; ***Gr.:*** Hipnosedon; Ilman; Neo Nifalium; Nilium†; Vulbegal; ***Hong Kong:*** Absint†; Flunita; Rohypnol; ***Irl.:*** Rohypnol; ***Israel:*** Hypnodorm; ***Ital.:*** Darkene; Roipnol; Valsera; ***Mex.:*** Rohypnol; ***Neth.:*** Rohypnol; ***Norw.:*** Flunipam; Rohypnol†; ***Pol.:*** Rohypnol; ***Port.:*** Rohypnol; Sedex†; ***S.Afr.:*** Hypnor†; Insom; Rohypnol; ***Spain:*** Rohipnol; ***Swed.:*** Fluscand; Rohypnol†; ***Switz.:*** Rohypnol; ***Thai.:*** Rohypnol; ***UK:*** Rohypnol†.

Flupentixol *(BAN, rINN)*

Flupenthixol; Flupentiksoli; Flupentixolum; LC-44; N-7009. (*Z*)-2-{4-[3-(2-Trifluoromethylthioxanthen-9-ylidene)propyl]piperazin-1-yl}ethanol.

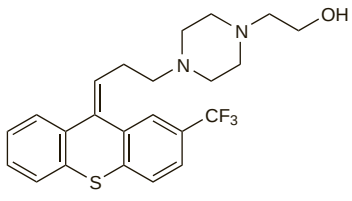
Флупентиксол

$C_{23}H_{25}F_3N_2OS$ = 434.5.

CAS — 2709-56-0.

ATC — N05AF01.

ATC Vet — QN05AF01.



cis-form

Flupentixol Decanoate *(BANM, rINNM)*

Decanoato de flupentixol; Flupenthixol Decanoate; (*Z*)-Flupenthixol Decanoate; *cis*-Flupenthixol Decanoate; Flupentiksol Dekanoat; Flupentixol, Décanoate de; Flupentixoli Decanoas.

Флупентиксола Деканоат

$C_{33}H_{43}F_3N_2O_2S$ = 588.8.

CAS — 30909-51-4.

ATC — N05AF01.

ATC Vet — QN05AF01.

Pharmacopoeias. In *Br.*
BP 2008 (Flupentixol Decanoate). A yellow viscous oil. Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform and in ether. Store at a temperature below –15° and protect from light.

Flupentixol Hydrochloride *(BANM, rINNM)*

Flupenthixol Dihydrochloride; Flupenthixol Hydrochloride; Flupentiksol Dihidroklorür; Flupentiksolidihydrokloridi; Flupentiksolio dihidrochloridas; Flupentixol, Chlorhydrate de; Flupentixol, dichlorhydrate de; Flupentixol-dihidroklorid; Flupentixol-dihydrochlorid; Flupentixoldihydroklorid; Flupentixoli dihydrochloridum; Flupentixoli Hydrochloridum; Hidrocloruro de flupentixol.

Флупентиксола Гидрохлорид

$C_{23}H_{25}F_3N_2OS,2HCl$ = 507.4.

CAS — 2413-38-9.

ATC — N05AF01.

ATC Vet — QN05AF01.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Flupentixol Dihydrochloride; Flupentixol Hydrochloride BP 2008). A white or almost white powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 3.0. Protect from light.

Stability. References.

1. Enever RP, *et al*. Flupenthixol dihydrochloride decomposition in aqueous solution. *J Pharm Sci* 1979; **68:** 169–71.
2. 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 and Treatment

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

Sudden death. There has been a report of sudden death in 3 patients given depot injections of flupentixol decanoate.[1]

1. Turbott J, Smeeton WMI. Sudden death and flupenthixol decanoate. *Aust N Z J Psychiatry* 1984; **18:** 91–4.

Precautions

As for Chlorpromazine, p.972. Flupentixol is not recommended in states of excitement or overactivity, including mania.

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

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Flupentixol is readily absorbed from the gastrointestinal tract and is probably subject to first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and faeces in the form of numerous metabolites; there is evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after estimated equivalent doses of the intramuscular depot preparation. Moreover, there is very wide intersubject variation in plasma concentrations of flupentixol, but, in practice, no simple correlation has been found between the therapeutic effect and plasma concentrations of flupentixol and its metabolites. After oral doses, peak plasma concentrations occur in about 4 hours and the biological half-life is about 35 hours. Paths of metabolism of flupentixol include sulfoxidation, side-chain *N*-dealkylation, and glucuronic acid conjugation. Flupentixol is more than 95% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier. Flupentixol crosses the placental barrier and small amounts have been detected in breast milk.

The decanoate ester of flupentixol is very slowly absorbed from the site of intramuscular injection and is therefore suitable for depot injection. It is gradually released into the bloodstream where it is rapidly hydrolysed to flupentixol.

Uses and Administration

Flupentixol is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.975). It has a piperazine side-chain. Flupentixol is used mainly in the treatment of schizophrenia (p.955) and other psychoses. Unlike chlorpromazine, an activating effect has been ascribed to flupentixol, and it is not indicated in overactive or manic patients. Flupentixol has also been used for its antidepressant properties.

Flupentixol is given orally as the hydrochloride although doses are expressed in terms of the base; flupentixol hydrochloride 3.5 mg is equivalent to about 3 mg of flupentixol. Flupentixol is also given as the longer-acting decanoate ester by deep intramuscular injection. The long-acting preparation available in the UK contains flupentixol decanoate as the *cis(Z)*-isomer (see Action, below) and doses are expressed in terms of the amount of *cis(Z)*-flupentixol decanoate.

The usual initial *oral* dose for the treatment of **psychoses** is the equivalent of 3 to 9 mg of flupentixol twice daily adjusted according to response; the maximum recommended daily dose is 18 mg. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If given by *deep intramuscular* injection, an initial test dose of 20 mg of the decanoate, as 1 mL of a 2% oily solution, is used. Then after at least 7 days and according to response, this may be followed by doses of 20 to 40 mg every 2 to 4 weeks. Shorter dosage intervals or greater amounts may be required according to the patient's response. The initial dose in elderly and debilitated patients may need to be reduced to a quarter or a half of the usual starting dose. If doses greater than 40 mg (2 mL) are considered necessary they should be divided between 2 separate injection sites. Another means of reducing the volume of fluid to be injected in patients requiring high-dose therapy with flupentixol decanoate is to give an injection containing 100 or 200 mg/mL of the decanoate (10 or 20%). The usual maintenance dose is between 50 mg every 4 weeks and 300 mg every 2 weeks but doses of up to 400 mg weekly have been given in severe or resistant cases.

Flupentixol has also been given as the hydrochloride for the treatment of mild to moderate **depression**, with or without anxiety (p.373). The usual initial *oral* dose, expressed in terms of the equivalent amount of flupentixol, is 1 mg (0.5 mg in the elderly) daily, increased after 1 week to 2 mg (1 mg in the elderly) and then to a maximum of 3 mg (2 mg in the elderly) daily. Doses above 2 mg (1 mg in the elderly) should be given in 2 divided doses. The last dose of the day should be given no later than 4 p.m. and if no effect has been noted within 1 week of reaching the maximum dose, treatment should be withdrawn.

Action. Patients with acute schizophrenic illnesses taking α-flupentixol [(*Z*)-flupentixol or *cis*-flupentixol] improved more after 3 weeks than patients who were taking equal doses of β-flupentixol [(*E*)-flupentixol or *trans*-flupentixol] or a placebo.[1] The α-isomer had more effect on the positive symptoms of the disease; this difference was less apparent for the negative symptoms. The difference in activity between the isomers was attributed to the greater dopamine-receptor blocking activity of the α-isomer rather than to differences in distribution.[2]

1. Johnstone EC, *et al*. Mechanism of the antipsychotic effect in the treatment of acute schizophrenia. *Lancet* 1978; **i:** 848–51.
2. Crow TJ, Johnstone EC. Mechanism of action of neuroleptic drugs. *Lancet* 1978; **i:** 1050.

Preparations

BP 2008: Flupentixol Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Fluanxol; ***Austria:*** Fluanxol; ***Belg.:*** Fluanxol; ***Canad.:*** Fluanxol; ***Chile:*** Fluanxol; ***Cz.:*** Fluanxol; ***Denm.:*** Fluanxol; ***Fin.:*** Fluanxol; ***Fr.:*** Fluanxol; ***Ger.:*** Fluanxol; Flupendura; ***Hong Kong:*** Fluanxol; ***Hung.:*** Fluanxol; ***India:*** Fluanxol; ***Irl.:*** Depixol; Fluanxol; ***Israel:*** Fluanxol; ***Malaysia:*** Fluanxol; ***Mex.:*** Fluanxol; ***Neth.:*** Fluanxol; ***Norw.:*** Fluanxol; ***NZ:*** Fluanxol; Psytixol†; ***Philipp.:*** Fluanxol; ***Pol.:*** Fluanxol; ***Port.:*** Fluanxol; ***Rus.:*** Fluanxol (Флюанксол); ***S.Afr.:*** Fluanxol; ***Singapore:*** Fluanxol; ***Swed.:*** Fluanxol; ***Switz.:*** Fluanxol; ***Thai.:*** Fluanxol; ***Turk.:*** Fluanxol; ***UK:*** Depixol; Fluanxol.

Multi-ingredient: ***Austria:*** Deanxit; ***Belg.:*** Deanxit; ***Hong Kong:*** Anfree; Deanxit; ***Ital.:*** Deanxit†; ***Singapore:*** Deanxit; ***Spain:*** Deanxit; ***Switz.:*** Deanxit; ***Thai.:*** Deanxit.