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

♦ References

- Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. Clin Pharmacokinet 1986; 11:
- 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)

Proprietary Preparations (details are given in Part 3)

Arg.: Nervocuril; Parsimonilt; Primum; Rohypnol; Austral.: Hypnodorm;

Austria: Guttanotte; Rohypnol; Somnubene; Belg.: Rohypnol; Braz.: Rohydorm; Rohypnol; Chile: Ipnopen; Rohypnolt; Cz.: Rohypnol; Braz.: Hunipam; Rohypnol; Ronal; Fr.: Narcozep; Rohypnol; Ger.: Fluni†; Flunibeta; Flunimerck; Fluninco Rohypnol; Gr.: Hipnosedon; Ilman; Neo Nifalium; Nilium; Vulbegai; Hong Kong: Absint†; Flunita; Rohypnol; Irl.: Rohypnol; Irl.: Rohypnol; Norw.: Flunipam; Rohypnol; Pol.: Rohypnol; Port.: Rohypnol; Seder; S.Afr.: Hypnor†; Insom; Rohypnol; Spain: Rohipnol; Swed.: Flusqard: Sohypnol; Swed.: Flusqard: Sohypnol; Swed.: Flusqard: Rohypnol; Switz.: Rohypnol; Life; Rohypnol; Swed.: Fluscand; Rohypnol; Switz.: Rohypnol; Thai.: Rohypnol; UK: Ro-

Flupentixol (BAN, rINN)

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

Флупентиксол

 $C_{23}H_{25}F_3N_2OS = 434.5.$ CAS — 2709-56-0. ATC - NO5AFOI.

ATC Vet - QN05AF01.

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 - NO5AF01. 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

 $C_{23}H_{25}F_3N_2OS,2HCI = 507.4.$ CAS - 2413-38-9. ATC — NO5AF01. 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.
- 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. Turbott J, Smeeton WMI. Sudden death and flupenthixol deoate. 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, in-

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

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 schizo-

phrenia (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. 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; Austrai: Fluanxol; Austrai: Fluanxol; Deig: Fluanxol; Canda:: Fluanxol; Chile: Fluanxol; Cz.: Fluanxol; Deim: Fluanxol; Fluanx

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

Fluphenazine (BAN, rINN)

Flufenatsiini; Flufenazin; Flufenazina; Fluphenazinum. $2-\{4-[3-(2-Trifluoromethylphenothiazin-10-yl)propyl]piperazin-1-yl\}ethanol.$

Флуфеназин $C_{22}H_{26}F_3N_3OS = 437.5$. CAS - 69-23-8. ATC - N05AB02. ATC Vet - QN05AB02.

Fluphenazine Decanoate (BANM, rINNM)

Decanoato de flufenazina; Flufenatsiinidekanoaatti; Flufenazin Dekanoat; Flufenazindekanoat; Flufenazindekanoat; Flufenazindekanoat; Flufenazindekanoat; Flufenazindekanoatas; Fluphenazini, decanoate de; Fluphenazini, decanoas.

 Φ луфеназина Деканоат $C_{32}H_{44}F_3N_3O_2S=591.8.$ CAS — 5002-47-1. ATC — N05AB02. ATC Vet — QN05AB02.

Pharmacopoeias. In *Chim., Eur.* (see p.vii), *Int.*, and *US.* Ph. Eur. 6.2 (Fluphenazine Decanoate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Fluphenazine Decanoate). Store in airtight containers. Protect from light.

Fluphenazine Enantate (BANM, HNNM)

Enantato de flufenazina; Flufenatsiinienantaatti; Flufenazinenantat; Flufenazinenantat; Flufenazino enantatas; Fluphenazine, enantata de; Fluphenazine Enanthate; Fluphenazine Heptanoate; Fluphenazini enantas.

Флуфеназина Энантат $C_{29}H_{38}F_3N_3O_2S = 549.7.$ CAS — 2746-81-8. ATC — N05AB02. ATC Vet — ON05AB02.

Pharmacopoeias. In Eur. (see p.vii), Int., Jpn, and US. Ph. Eur. 6.2 (Fluphenazine Enantate). A pale yellow viscous liquid or a yellow solid. Practically insoluble in water; very soluble in dehydrated alcohol and in dichloromethane; freely soluble in methyl alcohol. Protect from light.

USP 31 (Fluphenazine Enanthate). A pale yellow to yelloworange, clear to slightly turbid, viscous liquid having a characteristic odour. Insoluble in water; soluble 1 in less than 1 of alcohol and of chloroform and 1 in 2 of ether. Stable in air at room temperature but unstable in strong light. Store in airtight containers. Protect from light.

Fluphenazine Hydrochloride (BANM, rINNM)

Flufenatsiinihydrokloridi; Flufenazin-dihydrochlorid; Flufenazin-hidroklorid; Flufenazinhydroklorid; Flufenazino hidrochloridas; Flufenazyny chlorowodorek; Fluphénazine, chlorhydrate de; Fluphenazini Dihydrochloridum; Fluphenazini hydrochloridum; Hidrocloruro de flufenazina.

Флуфеназина Гидрохлорид $C_{22}H_{26}F_3N_3OS,2HCI=510.4.$ CAS — 146-56-5. ATC — N05AB02. ATC Vet — ON05AB02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int.*, and *US.* Ph. Eur. 6.2 (Fluphenazine Dihydrochloride). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol and in dichloromethane. A 5% solution in water has a pH of 1.9 to 2.4. Protect from light.

USP 31 (Fluphenazine Hydrochloride). A white or nearly white, odourless crystalline powder. Soluble 1 in 1.4 of water and 1 in 6.7 of alcohol; slightly soluble in acetone and in chloroform; practically insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Adverse Effects and Treatment

As for Chlorpromazine, p.969. Fluphenazine is less likely to cause sedation, hypotension, or antimuscarinic effects but is associated with a higher incidence of extrapyramidal effects.

Convulsions. For mention of fluphenazine as one of the anti-psychotics suitable for patients at risk of seizures, see p.969.

Effects on the liver. A patient developed jaundice 17 days after the first of 3 injections of a depot antipsychotic containing fluphenazine decanoate given over a 2-week period. The patient developed indicators of severe liver toxicity, with extreme hyperbilirubinaemia and raised liver enzyme values, and remained very ill for the next 4 months. The patient showed cross-sensitivity to haloperidol but not to flupentixol.

See also under Chlorpromazine, p.971.

 Kennedy P. Liver cross-sensitivity to antipsychotic drugs. Br J Psychiatry 1983; 143: 312.

Overdosage. A patient who took about 30 fluphenazine hydrochloride 2.5-mg tablets was treated with gastric lavage. Twenty hours after hospital admission he had difficulty in breathing due to spasm of the respiratory muscles; other very severe extrapyramidal adverse effects were also present. Muscle spasm was controlled by diazepam.

There were few adverse effects in a patient given intramuscular fluphenazine decanoate 50 mg every 4 hours, instead of the intended 4 weeks, to a total of 1050 mg. About 3 weeks after the period of overdosage the patient had some degree of hypothermia and tachycardia, and after a further week parkinsonian signs appeared. No specific treatment was given.

- Ladhani FM. Severe extrapyramidal manifestations following fluphenazine overdose. Med J Aust 1974; 2: 26.
- Cheung HK, Yu ECS. Effect of 1050 mg fluphenazine decanoate given intramuscularly over six days. BMJ 1983; 286: 1016–17.

Precautions

As for Chlorpromazine, p.972. Fluphenazine may exacerbate depression and therefore it is contra-indicated in severely depressed patients.

Pregnancy. A neonate delivered to a mother who had received fluphenazine hydrochloride 10 to 20 mg daily throughout pregnancy had nasal congestion with severe rhinorrhoea, respiratory distress, vomiting, and extrapyramidal symptoms. Respiratory symptoms appeared to respond to pseudoephedrine.

 Nath SP, et al. Severe rhinorrhea and respiratory distress in a neonate exposed to fluphenazine hydrochloride prenatally. Ann Pharmacother 1996; 30: 35–7.

Interactions

As for Chlorpromazine, p.973.

Pharmacokinetics

Fluphenazine hydrochloride is absorbed after oral doses, and has a reported plasma half-life of 14.7 hours after oral doses. Fluphenazine decanoate and fluphenazine enantate are very slowly absorbed from the site of subcutaneous or intramuscular injection. They both gradually release fluphenazine into the body and are therefore suitable for use as depot injections. The plasma half-life of fluphenazine decanoate has been reported to be 6 to 9 days after intramuscular injection.

 \Diamond References $^{1\text{--}4}$ to the pharmacokinetics of fluphenazine.

The plasma half-life of fluphenazine after a single dose was 14.7 hours in 1 patient given the hydrochloride orally and 14.9 and 15.3 hours in 2 patients given the hydrochloride by intramuscular injection. The half-life was 3.6 and 3.7 days in 2 patients given the enantate intramuscularly and 9.6 and 6.8 days in 2 patients given the decanoate intramuscularly. Peak plasma-fluphenazine concentrations occurred earlier in patients given fluphenazine decanoate compared with those who received the enantate. Fluphenazine sulfoxide and 7-hydroxyfluphenazine were identified in the urine and faeces.

- Curry SH, et al. Kinetics of fluphenazine after fluphenazine dihydrochloride, enanthate and decanoate administration to man. Br J Clin Pharmacol 1979; 7: 325–31.
- Wistedt B, et al. Slow decline of plasma drug and prolactin levels after discontinuation of chronic treatment with depot neuroleptics. Lancet 1981; i: 1163.
- ucs. Lancet 1981; 1: 1105.

 Midha KK, et al. Kinetics of oral fluphenazine disposition in humans by GC-MS. Eur J Clin Pharmacol 1983; 25: 709–11.

 Marder SR, et al. Plasma levels of parent drug and metabolites
- Marder SR, et al. Plasma levels of parent drug and metabolites in patients receiving oral and depot fluphenazine. Psychopharmacol Bull 1989; 25: 479–82.

Uses and Administration

Fluphenazine is a phenothiazine with general properties similar to those of chlorpromazine (p.975). It has a piperazine side-chain. Fluphenazine is used in the treatment of psychiatric disorders including schizophrenia (p.955), mania (see Bipolar Disorder, p.372), severe anxiety (p.952), and behavioural disturbances (p.954). Fluphenazine is given as the hydrochloride by mouth or sometimes by intramuscular injection; for both routes, doses are expressed in terms of fluphenazine hydrochloride. The longer-acting decanoate or enantate esters of fluphenazine are given by intramus-

cular or sometimes subcutaneous injection; for both esters, doses are expressed in terms of the ester.

The usual initial oral dose of the hydrochloride for the treatment of schizophrenia, mania, and other psychoses is 2.5 to 10 mg daily in two or three divided doses; the dose is then increased according to response up to a usual maximum of 20 mg daily, although higher doses have occasionally been given. Dosage may subsequently be reduced to a usual maintenance dose of 1 to 5 mg daily. A lower initial dose of 1 to 2.5 mg daily, increased according to response up to a maximum of 10 mg daily, is recommended in the elderly. Treatment is sometimes started with an initial intramuscular injection of 1.25 mg of the hydrochloride adjusted thereafter according to response. The usual initial intramuscular daily dose is 2.5 to 10 mg given in divided doses every 6 to 8 hours. In general the required parenteral doses of fluphenazine hydrochloride have been found to be about one-third to one-half of those given orally. When symptoms are controlled, oral maintenance therapy may be substituted.

The long-acting decanoate or enantate esters of fluphenazine are usually given by deep intramuscular injection and are used mainly for the *maintenance* treatment of patients with schizophrenia or other chronic psychoses. The onset of action is usually within 1 to 3 days of injection and significant effects on psychosis are usually evident within 2 to 4 days. An initial dose of fluphenazine decanoate 12.5 mg (6.25 mg in the elderly) is given intramuscularly. Subsequent adjustments in the amounts and the dosage interval should be made according to the patient's response; the amounts required may range from 12.5 to 100 mg and the intervals required may range from 2 weeks to 5 or 6 weeks. Lower doses may be possible in some patients (see Schizophrenia, below). If doses greater than 50 mg are considered necessary, cautious increments should be made in steps of 12.5 mg. The enantate ester of fluphenazine has been given in a similar dose range at intervals of 1 to 3 weeks.

Fluphenazine hydrochloride has also been given *orally* in initial doses of 1 mg twice daily, increased if necessary to 2 mg twice daily, for the short-term adjunctive management of severe **anxiety** or **behavioural disturbances**.

Schizophrenia. References¹⁻³ to fluphenazine decanoate in schizophrenia (p.955) indicating that low doses (10 mg or less every 2 weeks) may be effective in some patients. Use of standard doses at greater intervals (6 weeks) has also been tried.⁴ A systematic review of the use of depot fluphenazine in schizophrenia found little advantage over oral use in terms of compliance.⁵ Another systematic review of considered that although oral fluphenazine is inexpensive and widely available, other drugs may be preferable because of its adverse effects.

- Kane JM, et al. Low-dose neuroleptic treatment of outpatient schizophrenics: I preliminary results for relapse rates. Arch Gen Psychiatry 1983; 40: 893–6.
- Marder SR, et al. Low- and conventional-dose maintenance therapy with fluphenazine decanoate: two-year outcome. Arch Gen Psychiatry 1987; 44: 581–21.
- Hogarty GE, et al. Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia: results of a two-year controlled study. Arch Gen Psychiatry 1988; 45: 797–805.
- Carpenter WT, et al. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. Am J Psychiatry 1999; 156: 412–18.
- David A, et al. Depot fluphenazine decanoate and enanthate for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/04/05).
- Matar HE, AlMerie MQ. Oral fluphenazine versus placebo for schizophrenia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 18/03/08).

Tourette's syndrome. Fluphenazine has been tried¹ as an alternative to standard dopamine antagonists such as haloperidol or pimozide in the symptomatic management of Tourette's syndrome (p.954).

 Singer HS, et al. Haloperidol, fluphenazine and clonidine in tourette syndrome: controversies in treatment. Pediatr Neurosci 1985–86; 12: 71–4.

Preparations

BP 2008: Fluphenazine Decanoate Injection; Fluphenazine Tablets; USP 31: Fluphenazine Decanoate Injection; Fluphenazine Enanthate Injection; Fluphenazine Hydrochloride Elixir; Fluphenazine Hydrochloride Injection; Fluphena