atic and the danger of an interaction between the drugs should also be borne in mind (see under Interactions, above).

1. Leucht S, *et al*. Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2004; **65:** 177–86.

Skin disorders. Some salts or derivatives of lithium (notably lithium succinate, p.1604, but also lithium gluconate) have been applied topically in preparations for seborrhoeic dermatitis.

References.

1. Dreno B, *et al*. Lithium gluconate 8% vs ketoconazole 2% in the treatment of seborrhoeic dermatitis: a multicentre, randomized study. *Br J Dermatol* 2003; **148:** 1230–6.

Preparations

BP 2008: Lithium Carbonate Tablets; Lithium Citrate Oral Solution; Prolonged-release Lithium Carbonate Tablets;
USP 31: Lithium Carbonate Capsules; Lithium Carbonate Extended-release Tablets; Lithium Carbonate Tablets; Lithium Citrate Syrup.

Proprietary Preparations (details are given in Part 3)
Arg.: Ceglution; Eskalit; Karlit; Lithiun; ***Austral.:*** Lithicarb; Quilonum; ***Austria:*** Neurolepsin; Quilonorm; ***Belg.:*** Camcolit; Maniprex; Priadel; ***Braz.:*** Carbolim; Carbolitium; Litiocar†; Neurolithium; ***Canad.:*** Carbolith; Duralith; Lithane; ***Chile:*** Cabalex†; Cade L; Carbolit; Carboron; Psicolit; ***Cz.:*** Contemnol†; ***Denm.:*** Litarex; ***Fin.:*** Lito; ***Fr.:*** Lithioderm; Neurolithium; Teralithe; ***Ger.:*** Hypnorex; leukominerase†; Li 450†; Quilonum; ***Gr.:*** Lithiofor; Milithin; ***Hong Kong:*** Camcolit; Lithicarb; Lithiofor; ***Hung.:*** Liticarb; ***India:*** Licab; Staleth; ***Indon.:*** Frimania; ***Irl.:*** Camcolit; Priadel; ***Israel:*** Licarbium; ***Ital.:*** Carbolithium; ***Jpn:*** Limas; ***Malaysia:*** Priadel†; ***Mex.:*** Carbolit; Litheum; ***Neth.:*** Camcolit; Litarex; Priadel; ***Norw.:*** Lithionit; ***NZ:*** Lithicarb; Priadel; ***Philipp.:*** Quilonium-R; ***Port.:*** Priadel; ***S.Afr.:*** Camcolit; Lentolith; Quilonum; ***Singapore:*** Camcolit; Priadel†; ***Spain:*** Plenur; ***Swed.:*** Lithionit; ***Switz.:*** Litarex; Lithiofor; Neurolithium; Priadel; Quilonorm; ***Thai.:*** Licarb; Limed; Lit-300; Phanate; ***Turk.:*** Kilonum; Lithunil; ***UK:*** Camcolit; Li-Liquid; Liskonum; Lithonate; Priadel; ***USA:*** Eskalith†; Lithobid.

Multi-ingredient: ***Austral.:*** Caprilate; ***Ger.:*** NeyDop N (Revitorgan-Dilutionen N Nr 97)†; Togal Classic; ***Spain:*** Citinoides.

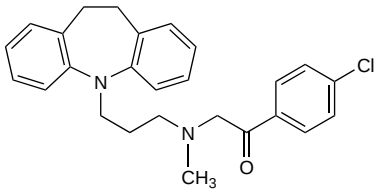
Lofepramine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de lofepramina; Leo-640; Lofépramine, Chlorhydrate de; Lofepramini Hydrochloridum; Lopramine Hydrochloride; WHR-2908A. 5-{3-[*N*-(Chlorophenacyl)-*N*-methylamino]propyl}-10,11-5*H*-dihydrodibenz[*b,f*]azepine hydrochloride.

Лофепрамина Гидрохлорид

$C_{26}H_{27}ClN_2O,HCl$ = 455.4.

CAS — 23047-25-8 (lofepramine); 26786-32-3 (lofepramine hydrochloride).
ATC — N06AA07.
ATC Vet — QN06AA07.



(lofepramine)

Pharmacopoeias. In *Br.*
BP 2008 (Lofepramine Hydrochloride). A fine, yellowish-white to green-yellow powder with a faint characteristic odour. It exhibits polymorphism. Very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376) although it has a lower incidence of antimuscarinic adverse effects. Lofepramine should be avoided in patients with severe hepatic or severe renal impairment.

Effects on the liver. See under Amitriptyline, p.377.

Overdosage. Lofepramine may be less toxic in overdosage than earlier tricyclics.[1] An analysis of data from the Office of National Statistics in England and Wales has also shown that the risk of death after an overdose with lofepramine was not significantly different from that associated with the SSRIs which, as a group, are considered to be safer in overdose than the tricyclics.[2]

1. Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990; **23:** 23–27.
2. Mason J, *et al*. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50:** 366–70.

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Lofepramine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 hour of oral doses. Since lofepramine slows gastrointestinal transit time absorption can, however, be delayed, particularly in overdosage. It is extensively demethylated by first-pass metabolism in the liver to its active, primary metabolite, desipramine (p.387). Paths of metabolism also include *N*-oxidation and hydroxylation. The plasma half-life is about 5 hours. Lofepramine is mainly excreted in the urine, chiefly in the form of its metabolites. Up to 99% of lofepramine is bound to plasma proteins. Lofepramine is distributed into breast milk.

Uses and Administration

Lofepramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). One of its metabolites is desipramine (p.387). Lofepramine is one of the less sedating tricyclics.

In the treatment of depression (p.373) lofepramine is given orally as the hydrochloride although doses are expressed in terms of the base. Lofepramine hydrochloride 76.1 mg is equivalent to about 70 mg of lofepramine. The usual dose is the equivalent of 70 mg two or three times daily.

Lofepramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Administration in the elderly. UK licensed drug information suggests that some elderly patients may respond to lower than usual doses of lofepramine, but in a study[1] involving 46 elderly patients with various grades of depression lofepramine 70 mg once daily was no more effective than placebo at the end of 28 days of treatment.

1. Tan RSH, *et al*. The effect of low dose lofepramine in depressed elderly patients in general medical wards. *Br J Clin Pharmacol* 1994; **37:** 321–4.

Preparations

BP 2008: Lofepramine Tablets.

Proprietary Preparations (details are given in Part 3)
Cz.: Tymelyt†; ***Denm.:*** Tymelyt†; ***Ger.:*** Gamonil†; ***Irl.:*** Gamanil; ***Port.:*** Deprimil†; ***S.Afr.:*** Emdalen; ***Spain:*** Deftan†; ***Swed.:*** Tymelyt†; ***Switz.:*** Gamonil†; ***UK:*** Feprapax†; Gamanil†; Lomont.

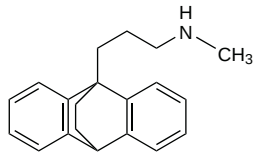
Maprotiline *(BAN, USAN, rINN)*

Maprotiliini; Maprotilin; Maprotilina; Maprotilinum. 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propyl(methyl)amine; *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propylamine.

Мапротилин

$C_{20}H_{23}N$ = 277.4.

CAS — 10262-69-8.
ATC — N06AA21.
ATC Vet — QN06AA21.



Maprotiline Hydrochloride *(BANM, rINNM)*

Ba-34276; Hidrocloruro de maprotilina; Maprotiliinihydrokloridi; Maprotilin Hidroklorür; Maprotiline, chlorhydrate de; Maprotilinhidroklorid; Maprotilin-hydrochlorid; Maprotilinhydroklorid; Maprotilini hydrochloridum; Maprotilino hidrochloridas.

Мапротилина Гидрохлорид

$C_{20}H_{23}N,HCl$ = 313.9.

CAS — 10347-81-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Maprotiline Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. Slightly soluble in water; soluble in alcohol; very slightly soluble in acetone; sparingly soluble in dichloromethane; freely soluble in methyl alcohol.
USP 31 (Maprotiline Hydrochloride). A fine white to off-white, practically odourless, crystalline powder. Slightly soluble in water; freely soluble in chloroform and in methyl alcohol; practically insoluble in isooctane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Adverse effects with maprotiline, a tetracyclic antidepressant, are broadly similar to those with tricyclic antidepressants (see Amitriptyline, p.376) but antimuscarinic effects are less frequent.

Skin rashes seem more common with maprotiline than with tricyclic antidepressants. Seizures have occurred in patients with no prior history of such disorders as well as in those with a history of epilepsy and the risk is increased if high doses of maprotiline are given. It should not be used in patients with epilepsy or a lowered seizure threshold.

Incidence of adverse effects. By March 1985 the UK CSM[1] had received reports of the following adverse reactions associated with maprotiline from a cumulative total of 2.5 million prescriptions: convulsions (124), hepatic reactions (4), and haematological reactions (8). There had also been 454 reports of skin rashes.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the skin. In addition to many recorded instances of skin rashes with maprotiline (see Incidence of Adverse Effects, above) cutaneous vasculitis, which resolved on stopping therapy, has also been seen.[1]

1. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med* 1985; **15:** 256–7.

Epileptogenic effect. In a retrospective review of 186 psychiatric patients with no history of seizures, 5 of 32 patients taking maprotiline developed generalised tonic-clonic seizures, compared with 1 of 45 receiving a tricyclic antidepressant.[1] There were no seizures in the remaining patients who received other medications, or no drug treatment. Two of the 5 patients having seizures with maprotiline were taking doses of 75 to 150 mg daily, 2 were taking daily doses of 200 to 300 mg, and one patient had partial complex seizures with a daily dose of 150 mg and generalised tonic-clonic seizures after increasing the daily dose to 300 mg.

1. Jabbari B, *et al*. Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 1985; **42:** 480–1.

Overdosage. Apart from seizures being more common with maprotiline, features of overdosage are similar to those experienced with tricyclic antidepressant poisonings (see Adverse Effects of Amitriptyline, p.376).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

References.

1. Crome P, Newman B. Poisoning with maprotiline and mianserin. *BMJ* 1977; **2:** 260.
2. Curtis RA, *et al*. Fatal maprotiline intoxication. *Drug Intell Clin Pharm* 1984; **18:** 716–20.
3. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.
4. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.

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

Interactions

Interactions associated with maprotiline are similar to those associated with tricyclic antidepressants (see Amitriptyline, p.379).

Pharmacokinetics

Maprotiline is slowly but completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within 8 hours of an oral dose. It is widely distributed throughout the body and plasma protein binding is about 88 to 89%.

Maprotiline is extensively demethylated in the liver to its principal active metabolite, desmethylmaprotiline; paths of metabolism of both maprotiline and desmethylmaprotiline include *N*-oxidation, aliphatic and aromatic hydroxylation, and the formation of aromatic methoxy derivatives. In addition to desmethylmaprotiline, maprotiline-*N*-oxide is also reported to be pharmacologically active. The average elimination half-life of maprotiline is reported to be about 43 hours and that of its active metabolite even longer (range 60 to 90 hours). Maprotiline is excreted in the urine, mainly in the form of its metabolites, either in free or in conjugated form; appreciable amounts are also excreted in the faeces.

Maprotiline is distributed into breast milk (see Breast Feeding under Precautions of Amitriptyline, p.378).

◊ References.

1. Maguire KP, *et al*. An evaluation of maprotiline: intravenous kinetics and comparison of two oral doses. *Eur J Clin Pharmacol* 1980; **18:** 249–54.
2. Alkalay D, *et al*. Bioavailability and kinetics of maprotiline. *Clin Pharmacol Ther* 1980; **27:** 697–703.
3. Firkusny L, Gleiter H. Maprotiline metabolism appears to cosegregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994; **37:** 383–8.

Uses and Administration

Maprotiline is a tetracyclic antidepressant with actions and uses similar to those of tricyclic antidepressants (see Amitriptyline, p.381). It is one of the more sedating antidepressants but antimuscarinic effects are less marked. Like the tricyclics, maprotiline is an inhibitor of the reuptake of noradrenaline; it also has weak affinity for central adrenergic (α_1) receptors.

Maprotiline is usually given orally as the hydrochloride but it has also been given by injection as the mesilate and in oral drops as the resinate.

In the treatment of depression (p.373) maprotiline hydrochloride is given in oral doses of 25 to 75 mg daily in divided doses, gradually increased to 150 mg daily if necessary; up to 225 mg daily may be required in severely depressed patients in hospital. The dosage should be adjusted after 2 weeks according to response. Because of the prolonged half-life of maprotiline the total daily dose may also be given as a single dose. A suggested initial dose for elderly patients is 25 mg daily gradually increased according to response to 50 to 75 mg daily.

Maprotiline should be withdrawn gradually to reduce the risk of withdrawal symptoms.