PRODUCT MONOGRAPH

PrTEVA-MAPROTILINE

(Maprotiline Hydrochloride)

25, 50 and 75 mg Tablets

USP

Antidepressant

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THERAPEUTIC CLASSIFICATION

Antidepressant

ACTION AND CLINICAl PHARMACOLOGY

TEVA-MAPROTILINE (maprotiline hydrochloride) has been shown to exhibit an antidepressant action. Noradrenaline in the brain and peripheral tissues is strongly inhibited by maprotiline, though it is ,notable in its lack of inhibition of serotonergic uptake. It has markedly less pronounced alpha adrenergic blocking activity than amitriptyline. In the pharmacologic profile of maprotiline, a strong antihistaminic and a weaker anticholinergic action are seen. Maprotiline also exerts a sedative effect on the anxiety component of depressive illness. It is postulated that maprotiline exerts its antidepressant action by inhibition of presynaptic uptake of catecholamines, thereby increasing their concentration at the synaptic clefts of the brain. The effect of maprotiline on the EEG in single doses revealed a rise in the alpha-wave density, a reduction of the alpha-wave frequency and an increase in the alpha-wave amplitude. However, maprotiline, as with other tricyclic antidepressants lowers the convulsive threshold. In one as

yet uncorroborated "sleep study", it appears that maprotiline increases the REM phase of sleep in depressed patients, from its initially reduced base line, whereas imipramine reduced the REM phase of sleep.

Maprotiline is completely absorbed after oral administration in man. The binding to serum proteins was found to be 88%. In man, the half-life of unchanged maprotiline is relatively long and ranged from 27.4 to 57.6 hours. Following repeated daily doses of maprotiline, a plasma steady state concentration was reached in the second week, with the majority of subjects receiving daily doses of 150 mg attaining steady state blood levels between 100 and 400 ng/mL. Whether the daily dosage is given as a single dose of 150 mg, in two fractions of 75 mg or 3 fractions of 50 mg, the same plasma levels are attained.

Maprotiline is metabolized by N-demethylation, deamination, aliphatic and aromatic hydroxylations and by formation of aromatic methoxy derivatives. The excretion of maprotiline is primarily in the urine, with about 30% via biliary. Of the amount excreted in the urine, 90% consists of metabolites, 75% in the form of glucuronides.

A comparative, two-way, single-dose bioavailability study was performed on two 10 mg maprotiline hydrochloride tablet formulations, TEVA- MAPROTILINE 10 mg tablets and Ludiomil® 10 mg tablets. The pharmacokinetic data calculated for maprotiline in the TEVA-MAPROTILINE and Ludiomil® tablet formulations are tabulated below:

<u>Pharmacokinetic Indices for Mamotiline:</u>

Geometric mean

Arithmetic mean (C.V.)

	TEVA-MAPROTILINE (5 x 10 mg)		Ludiomil® (5 x 10 mg)		Percentage of Ludiomil®
AUC_T (ng•h/mL)	589.9 661.0	(52)	614.0 678.5	(46)	97%
AUC_I (ng•h/mL)	749.9 880.9	(66)	727.8 802.8	(46)	103%
C_{max} (ng•h/mL)	11.9 12.1	(17)	12.0 12.3	(19)	99%

T_{max}* (h)	10.3	(30)	11.5	(26)	--
$T_{½}$* (h)	52.9	(71)	43.3	(48)	--

* For the T_{max} and $T_{½}$ parameters these are the arithmetic means (standard deviation).

A comparative, two-way, single-dose bioavailability study was performed on two 75 mg maprotiline hydrochloride tablet formulations, TEVA-MAPROTILINE 75 mg tablets and Ludiomil® 75 mg tablets. The pharmacokinetic data calculated for maprotiline in the TEVA-MAPROTILINE and Ludiomil® tablet formulations are tabulated below:

Geometric mean

Arithmetic mean (C.V.)

	TEVA-MAPROTILINE (1 x 75 mg)		Ludiomil® (1 x 75 mg)		Percentage of Ludiomil®
AUC_T (ng•h/mL)	843.0 1089	(74)	842.2 1085(46)	(73)	100%
AUC_I (ng•h/mL)	955.3 1221(74)		952.4 1221(73)		100%
C_{max} (ng•h/mL)	16.58 17.60	(37)	15.89 16.78	(36)	104%
T_{max}* (h)	33.7	(52)	35.3	(83)	--
$T_{½}$* (h)	44.3	(44)	45.2	(46)	--

*For the Tmax and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

TEVA-MAPROTILINE (maprotiline hydrochloride) is indicated in the drug treatment of endogenous depressive illness, including the depressed phase of manic-depressive illness (bipolar depression) psychotic depression (unipolar depression) and involutional melancholia. In selected patients suffering severe depressive neurosis, maprotiline might be useful.

CONTRAINDICATIONS

TEVA-MAPROTILINE (maprotiline hydrochloride) should not be used in patients with known or suspected convulsive disorders, since it is known to lower the seizure threshold (see WARNINGS).

TEVA-MAPROTILINE is also contraindicated in patients with a history of hypersensitivity to the drug, and in those with existing severe hepatic or renal damage or a history of severe blood dyscrasias. Patients with narrow angle glaucoma should not receive TEVA-MAPROTILINE because of its anticholinergic properties. During the acute recovery phase following myocardial infarction in the presence of acute congestive heart failure, TEVA-MAPROTILINE is contraindicated.

TEVA- MAPROTILINE should not be used concomitantly with monamine oxidase inhibitors, since such use may result in an severe reaction marked by hyperpyrexia, tremors, generalized clonic convulsions, delirium and possible death. At least fourteen days should elapse between the time of discontinuing one of the interacting drugs and replacing it with the other.

TEVA-MAPROTILINE should not be employed, or should be withdrawn, in cases of acute poisoning with alcohol, hypnotics, analgesics or psychotropic drugs.

TEVA-MAPROTILINE is not recommended for use in children.

WARNINGS

Arrhythmias, sinus tachycardia and prolongation of conduction time have been reported with tricyclic and tetracyclic antidepressants, particularly in high doses. In patients with cardiovascular disorders, a few instances of unexpected death have been reported. Myocardial infarction and stroke have also been reported

with these drugs. Extreme caution should therefore be used when TEVA-MAPROTILINE (maprotiline) is given to patients with a history of cardiovascular disease, those with circulatory lability and elderly patients. Treatment, in such cases, should be initiated at low doses with progressive increases only if required and tolerated, and the patients should be under close surveillance at all dosage levels. TEVA-MAPROTILINE should be used with caution in hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity. Potentiation of the cardiovascular effects of noradrenaline and adrenaline may occur. In patients receiving guanethidine or similar antihypertensive, agents TEVA- MAPROTILINE should be used with caution since it may block the effects of these drugs.

Seizures have been reported in patients without a known history of seizures who were treated with TEVA-MAPROTILINE at therapeutic dose levels. In some of these patients other confounding factors such as concomitant medications known to lower seizure threshold were present. The risk of seizures might be reduced by initiating therapy at low dosage. Because of the long half-life of TEVA-MAPROTILINE (average 51 hours), initial dosage should be maintained for two weeks before being raised gradually in small increments (see DOSAGE AND ADMINISTRATION). Concurrent administration of electroconvulsive therapy (ECT) and maprotiline may be hazardous.

TEVA-MAPROTILINE should be used with caution in patients with increased intraocular pressure or a history of urinary retention, particularly in the presence of prostatic hypertrophy, because of its anticholinergic properties. Because of the possibility of additive effects, close supervision and careful adjustment of dosage is required when administering TEVA-MAPROTILINE with anticholingeric or sympathomimetic drugs.

An activation of psychosis has occasionally been observed in schizophrenic patients administered tricyclic antidepressant drugs and must be considered as a possibility when administering TEVA-MAPROTILINE. Similarly, hypomanic or manic episodes in patients with cyclic disorders have been known to occur during treatment of a depressed phase with a tricyclic antidepressant. A reduction in the

dosage of TEVA-MAPROTILINE discontinuation of the drug, and/or administration of an antipsychotic agent may be required should these two conditions occur.

Use in Pregnancy and Lactation

Safe use of TEVA-MAPROTILINE during pregnancy and lactation has not been established. Maprotiline passes into the breast milk. It should therefore not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the benefits outweigh the possible hazards to the child or fetus.

PRECAUTIONS

The possibility of suicide in seriously depressed patients is inherent in their illness and may persist until significant remission occurs. Patients must therefore be carefully supervised during all phases of treatment with TEVA-MAPROTILINE (maprotiline hydrochloride) and prescriptions should be written for the smallest amount consistent with good management. While taking TEVA-MAPROTILINE, patients' responses to alcoholic beverages or other CNS depressants may be exaggerated; the patient should therefore be warned. Patients should also be cautioned against driving an automobile, operating heavy machinery or performing potentially dangerous tasks that require mental alertness and good physical coordination.

Cardiac function should be monitored and ECG examinations performed during long-term treatment with high doses, particulariy in patients with heart diseases, as well as in elderly subjects. In patients susceptible to postural hypotension, regular measurements of the blood pressure should be conducted. Periodic blood cell counts and liver function tests are recommended with prolonged therapy.

Particularly in the elderly and in hospitalized patients, tricyclic antidepressants may give rise to paralytic ileus. Therefore, since maprotiline has similar anticholinergic properties, appropriate measures should be taken if constipation occurs.

TEVA-MAPROTILIN E should be discontinued for as long as clinically feasible prior to elective surgery, since little is known about the interaction between maprotiline and general anaesthetics.

TEVA-MAPROTILINE should be kept out of reach of children and, if possible, the drug should be dispensed in containers with child-resistant safety closures.

Drug Interactions

While taking maprotiline, patients should be warned that their responses to alcoholic beverages, barbiturates and other CNS depressants may be exaggerated.

The antihypertensive effects of adrenergic neuron blocking drugs such as guanethidine, bethanidine, reserpine, clonidine and a-methyldopa may be diminished or abolished by maprotiline. Therefore, patients requiring concomitant treatmen't for hypertension should be given antihypertensives of a different type (ie., diuretics, vasodilators, or beta-blockers which do not undergo pronounced biotransformation).

The possibility of central depressant and sedative effects with clonidine and a-methyldopa, which may aggravate an already existing depressive state, prohibit their simultaneous use with tricyclic antidepressants even in the absence of negative interactions on the vascular system.

When maprotiline is administered concomitantly with beta-blockers subject to substantial biotransformation, such as propranolol, the plasma concentrations of maprotiline may be increased. In such cases, plasma levels of maprotiline should be monitored and the dosage adapted accordingly.

The cardiovascular effects of indirect and directly acting sympathomimetic drugs such as noradrenaline, adrenaline, and methylphenidate may be potentiated by maprotiline. Maprotiline may also potentiate the effects of anticholinergic drugs

(atropine, biperiden) and levodopa. Therefore, careful adjustment of dosage and close supervision is required when administering maprotiline with anticholinergic or sympathomimetic drugs because of the possibility of additive effects.

The metabolism of maprotiline may be accelerated resulting in decreased antidepressant efficacy by drugs that activate hepatic microsomal enzymes, such as barbiturates, phenytoin, oral contraceptives and carbamazepine. If necessary, the dosage should be adapted accordingly.

Concomitant administration of maprotiline and phenytoin may increase serum phenytoin levels resulting in manifestation of maprotiline's side-effects. Adjustment of the phenytoin dosage may be necessary in such cases.

Increased plasma levels of maprotiline, a lowered convulsion threshold, and seizures may result with concomitant treatment of maprotiline and major tranquilizers.

The combination of maprotiline and benzodiazepines may cause increased sedation.

Although not reported for maprotiline, cimetidine has been shown to inhibit the metabolism of several tricyclic antidepressants resulting in increased plasma concentrations of the latter and an increase in unwanted effects (dryness of mouth, disturbed vision). Therefore, downward dosage adjustments may be required when given concomitantly with cimetidine, for both initiation and discontinuation of cimetidine therapy.

After the discontinuation of treatment with MAO-inhibitors, maprotiline should not be administered for a period of at least 14 days due to the potential for severe interactions (see CONTRAINDICATIONS). The same caution should also be observed when administering a MAO-inhibitor after previous treatment with maprotiline.

Maprotiline should be discontinued for as long as clinically feasible prior to elective surgery since little is known about the interaction between maprotiline and general anesthetics.

Concurrent use of parenteral ,magnesium sulfate and maprotiline may result in serious potentiation of CNS depressant effects.

ADVERSE REACTIONS

The most common adverse reactions reported with maprotiline are due to its anticholinergic, largely autonomic, effects which include: dry mouth, day sedation, vertigo, blurred vision, constipation, headache and nervousness. In the event of serious side-effects, such as those of a neurological or psychiatric nature, treatment with TEVA-MAPROTILINE should be discontinued.

The following adverse reactions have been reported either with maprotiline or other similar tricyclic antidepressant drugs.

Neurological: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy, extrapyramidal symptoms; myoclonus, seizures, (see Chronic Toxicity-dogs) alterations in EEG patterns, tinnitus.

Behavioural : confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation, insomnia and nightmares; hypomania, mania, exacerbation of psychosis, decrease in memory, feelings of unreality, weakness and fatigue, drowsiness, dizziness, urinary frequency.

Autonomic: dry mouth and rarely, associated sublingual adenitis; blurred vision, mydriasis, disturbances of accomodation; constipation; paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract, perspiration, flushing.

Cardiovascular : hypotension, hypertension, tachycardia, palpitations, arrhythmia, heartblock, syncope, atrial flutter, reversible T-wave changes, Q-T

prolongation and atypical ventricular tachycardia have been reported with maprotiline. The following have been reported with tricyclic antidepressants: quinidine-like effect and other reversible ECG changes, such as flattening or inversion of T-waves, bundle branch block, depressed S-T segments, prolonged conduction time and asystole, arrhythmias, heart block, fibrillation, myocardial infarction, stroke and unexpected death in patients with cardiovascular disorders.

Respiratory Tract: Isolated cases: allergic alveolitis with or without eosinophilia.

Hematoloaic: bone marrow depression including agranulocytosis, eosinophilia, purpura and thrombocytopenia may occur as an idiosyncratic response. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.

Gastrointestinal : nausea or vomiting, anorexia, epigastric distress, diarrhea; bitter taste, stomatitis, abdominal cramps, black tongue, dysphagia, increased salivation, altered liver function.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female, increased or decreased libido, impotence, testicular swelling, elevation or depression of blood sugar levels, weight gain or loss.

Allergic or toxic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, obstructive jaundice, nasal congestion.

Other: Occasional to frequent: sweating; rare: altered liver function, increased serum transaminase; isolated case: hepatitis with or without jaundice, flushing, urinary frequency, nasal congestion, and alopecia.

An increased incidence of dental caries has been reported in patients receiving

long-term treatment with antidepressants. Regular dental inspections are therefore advisable during long-term therapy with maprotiline.

SYMPTOMS AND TREATMENT OF 0VERDOSAGE

Svmptoms: The response of the patient to toxic overdosage of maprotiline may vary in severity. Accidental ingestion in children of any amount should be regarded as serious and potentially fatal.

Experience to date suggests that overdoses of maprotiline generally produce the same spectrum of toxicity as the tricyclic antidepressants. After 1 to 2 hours after ingestion, the first symptoms of intoxication arise and may include motor unrest, muscular twitching and rigidity, tremor, ataxia, convulsions, hyperpyrexia, vertigo, mydriasis, vomiting, cyanosis, hypotension, shock, tachycardia, cardiac arrhytimias and disturbances of consciousness up to deep coma. Initial hyperreflexia is subsequently followed by hyporeflexia.

One case of acute intoxication with 5 gm of maprotiline in a 58 year old woman has been reported, in which full recovery occurred. Other cases of recorded clinical recovery have been reported in the dose range of 1.6-2.0 g of maprotiline. However, a 22 year old woman died from cardiac arrest 5 days after ingestion of 3.0 g of the drug. Fatal outcomes have also been reported in combined intoxication with tricyclic antidepressants, sedatives or hypnotics in the maprotiline dose range of 2.0 to 10.0 g.

Treatment: There is no specific antidote and treatment is essentially symptomatic and supportive. The greatest threat is posed from cardiac arrhythmias and CNS involvement and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdosage of maprotiline, particularly children, should be hospitalized and kept under close surveillance.

The stomach should be emptied as quickly as possible by gastric lavage or, if the patient is alert, by induced emesis. It may be helpful to leave the tube in the stomach, with irrigation (with an electrolyte balanced fluid) and continual aspiration of stomach contents possibly promoting more rapid elimination of the drug from the body. If the patient is not alert, a cuffed endotracheal tube should be inserted before lavage is performed and emesis should not be induced. Since the anticholinergic effect of the drug may delay gastric emptying, these measures are recommended up to 12 hours or even more after the overdose. Administration of activated charcoal may help to reduce absorption of maprotiline. The value of dialysis is doubtful due to the extensive plasma protein binding of maprotiline.

Treatment should be designed to insure maintenance of the vital functions. An open airway should be maintained in comatose patients and assisted ventilation instituted, if necessary, but respiratory stimulants should not be used. External measures such as ice packs and cooling sponge baths should be used to control hyperpyrexia. Acidosis may be treated by cautious administration of sodium bicarbonate. Adequate renal function should be maintained.

To reduce the tendency to convulsions, external stimulation should be minimized. Anticonvulsants (preferably intravenous diazepam) should be administered if convulsions occur. Barbiturates may intensify respiratory depression, particularly in children, and aggravate hypotension and coma. Paraldehyde may be used in some children to counteract muscular hypertonus and convulsions with less likelihood of causing respiratory depression. Artificial ventilation should be instituted if the patient fails to respond rapidly to anticonvulsants. Prompt control of convulsions is essential since they aggravate hypoxia and acidosis and may thereby precipitate cardiac arrhythmias and arrest.

ECG monitoring in an intensive care unit is recommended in all patients, particularly in the presence of ECG abnormalities, and should be maintained for several days after the cardiac rhythm has returned to normal. Several days

following an apparent recovery from tricyclic antidepressant overdose, unexpected deaths attributed to cardiac arrhythmias have been reported. Correction of hypoxia and acidosis, if present, may be beneficial. Because of its effect on cardiac conduction, digitalis should be used only with caution. If rapid digitalization is required for the treatment of congestive heart failure, special care should be exercised in using the drug.

Shock should be treated with supportive measures, such as intravenous fluids oxygen and corticosteroids, as indicated. Hypotension usually responds to elevation of the foot of the bed. Pressor agents (but not epinephrine) should be given cautiously, if indicated. In the event of reduced myocardial function, consider recourse to treatment with dopamine or dobutamine by i.v. drip.

The slow intravenous administration of physostigmine salicylate has been reported to reverse the cardiovascular and CNS anticholinergic manifestations of tricylic overdosage; however, it should not be used routinely because of its short duration of action and potentially serious adverse effects. The recommended dosage in adults has been 1 to 2 mg in very slow intravenous injection. In children, the initial dosage should not exceed 0.5 mg and should be adjusted to age and response. Due to its short duration of action, administration may have to be repeated at 30 to 60 minute intervals.

Deaths by deliberate or accidental overdosage have occurred with the use of tricyclic and tetracyclic antidepressants. Since the propensity for suicide is high in depressed patients, a suicide attempt by other means may occur during the recovery phase. The possibility of simultaneous ingestion of other drugs should also be considered.

DOSAGE AND ADMINISTRATION

The dosage of TEVA-MAPROTILINE (maprotiline hydrochloride) should be individualized according to the requirements of each patient. Treatment should

be initiated at the lowest recommended dose and increased gradually, noting carefully the clinical response and any evidence of intolerance. It should be kept in mind that a lag in therapeutic response usually occurs at the onset of therapy, lasting from several days to a few weeks. Increasing the dosage does not normally shorten this latent period and may increase the incidence of side effects.

Initial Dosage:

Adults:

The recommended initial dosage is 75 mg daily in two or three divided doses. Because of the long half-life of TEVA-MAPROTILINE, this dosage should usually be maintained for two weeks. It may then be increased gradually in increments of 25 mg as required and tolerated, preferably by adding to the late afternoon or bedtime dose. The maximum recommended dose in outpatients is 150 mg daily, although doses up to 200 mg may be required in some patients. A higher initial dose of 100 mg daily in two or three divided doses may be indicated in the treatment of severely depressed hospitalized patients. The usual optimal dose in these patients is 150 mg daily, but some patients may require up to 225 mg in divided doses. When these higher doses are used, it is essential to exclude a history of convulsive disorders.

Elderly and Debilitated Patients:

In general, lower dosages are recommended for these patients. Initially, 10 mg three times daily is suggested, with very gradual increments, depending on tolerance and response, up to 75 mg daily in divided doses. Usually a maintenance dose of 50 to 75 mg daily is satisfactory. Blood pressure and cardiac rhythm should be checked frequently, particularly in patients who have unstable cardiovascular function.

Maintenance Dosage:

Dosage during maintenance therapy should be kept at the lowest effective level. Medication should be continued for the expected duration of the depressive episode in order to minimize the possibility of relapse following clinical

improvement.

When a maintenance dosage has been established as described above, TEVA-MAPROTILINE may be administered in a single daily dose at bedtime, provided such a dosage regimen is well tolerated. However, if the total daily dose exceeds 150 mg, it should be administered in divided doses.

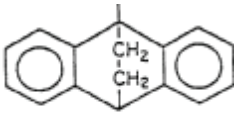
PHARMACEUTICAL INFORMATION

DRUGSUBSTANCE:

Proper Name: Maprotiline Hydrochloride

Chemical Name : N-Methyl-9,10-ethanoanthracene-9(10H)propylamine hydrochloride

Structural Formula: $CH_2CH_2CH_2$ $NHCH_3$



HCl

Molecular Formula : $C_{20}H_{23}N \cdot HCl$ Molecular Weight: 313.87

Description: It is freely soluble in methanol and in chloroform; slightly soluble in water; practically insoluble in isooctane.

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15-30°C in well-closed containers. Unit dose strips should be stored between 15-25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-MAPROTILINE (maprotiline hydrochloride) is available as:

25 mg round, orange coloured, slight bevelled edge, biconvex, film-coated tablets with white cores, engraved N on one side and plain on the reverse. 25

50 mg round, orange coloured, slight bevelled edge, biconvex, film-coated tablets with white cores, engraved N on one side and plain on the reverse. 50

75 mg round, orange-red coloured, shallow biconvex, single-scored, film-coated tablets with white cores, engraved N on one side plain on the reverse. 75

Supplied: Bottles of 100 and 500 and boxes of 100 as unit dose strips.

PHARMACOLOGY

Results of animal studies have shown that maprotiline displays many pharmacological properties in common with other tricyclic antidepressants. A dose-dependent protective effect against ptosis and catalepsy in rats treated with reserpine is exerted by maprotiline. In rats treated with tetrabenazine, maprotiline and imipramine proved to be equipotent in antagonizing cataleptic immobility. Its peripheral anticholinergic effects are roughly similar to those of imipramine, but as yet it has not been possible to demonstrate that maprotiline has any central anticholinergic effects.

Maprotiline has only a slight effect on blood pressure, heart rate and ECG tracings in the non-anesthetized dog. In rats with induced renal hypertension, maprotiline does not exert any antihypertensive effect. Maprotiline was found to enhance the action of noradrenaline when tested on appropriate isolated organs. In further animal studies, maprotiline had an affinity for the nervous system, in particular the hippocampus. High concentrations were also seen in the mouse in lungs, adrenals, thyroid and bile as well as in the kidneys and liver.

TOXICOLOGY

Acute Toxicity

SPECIES	SEX	ROUTE	NUMBER	LD_{50} mg/kg
Mouse	M	I.V.	75	32
	M	S.C.	56	290
	M	P.O.	48	660
Rat	M	I.V.	50	52
	M	S.C.	24	225
	M	P.O.	24	760
Rabbit	M	I.V.	7	LD_{90-100} 20
	F	P.O.	2	1000

Single sub-lethal doses produced non-characteristic symptoms, mainly of excitation or paralysis.

Chronic Toxicity:

Rats:

A daily oral dose of 10, 30 or 60 mg/kg of maprotiline was administered to three groups of rats over a period of 78 weeks. There were no mortalities in the lower dosage group. Nineteen of 60 and 36 of 60 rats died respectively, in the intermediate and high dosage level groups. Deaths were not attributed to a consistent cause though a generally lowered resistance to infection seemed to prevail. In rats receiving 30 and 60 mg/kg, increased deposition of fat in the liver was observed, but was not observed in the livers of any of the rats sacrificed after a withdrawal period of 4 weeks; similar findings were also recorded in several control animals. In rats receiving the 10 and 30 mg doses, an increased incidence of absence of corpora lutea of the ovaries was shown.

Dogs:

Maprotiline was administered orally to four groups of dogs each over a period of one year. Each group received 1, 10, 20 or 30 mg/kg of maprotiline once per day, six days per week. The group receiving the highest dosage level was dosed for 21 weeks only since ten of the 14 dogs had died during the first 20 weeks. The

four survivors were then observed for 9 weeks before being sacrificed. Convulsive episodes were observed in all dogs receiving 30 mg/kg/day during the 21 week dosing period. Abnormal quietness, aggressive and disturbed behaviour and vomiting on the first day were also observed. Convulsive episodes were observed in 6 of the 14 dogs receiving 20 mg/kg/day, three of which died after the episodes. Other clinical signs were similar to those observed in the higher dosage group. In dogs receiving the high dosage level but not in those receiving the intermediate and lower levels, adverse effects on body weight gain, food and water consumption were observed. For dogs receiving 30 mg/kg/day, there was an increase in the values relating to red blood cells (PCV, HG and RBC). No abnormalities, macroscopically, microscopically or ophthalmoscopically were detected in the tested animals.

Reproduction and Teratology:

Reproduction studies revealed no signs of teratogenic or embryotoxic effects at oral dosage levels of 1, 10 and 30 mg/kg/day in rats and mice or at 1 , 3 and 6 mg/kg/day in rabbits. The rats and mice were treated from the 6th to 15th day of pregnancy and the rabbits from the 6th to 18th day. No signs of intolerance were observed in rats and mice even following the highest dosage level, or in the rabbits following the dosage levels of 1 and 3 mg/kg/day. However, maprotiline had a marked toxic effect on pregnant rabbits when administered in a daily dose of 6 mg/kg oral doses during the last trimester of pregnancy. It was well tolerated by the dams and no significant untoward effects were observed in either the mothers or their offspring.

Carcinogenicity:

In a 78 week study in Charles River CD rats there were subcutaneous (presumably mammary) growth noted in 5 of 23, 7 of 23, 7 of 16 and 1 of 10 females at 0, 10, 30 and 60 mg/kg/day, respectively with histopathologically classifiable mammary tumors (adenoma or carcinoma) observed at necropsy in 3 of 20, 1 of 2, 3 of 10 and 4 of 30 females in these groups, respectively. Histological incidence of mammary hyperplasia was also noted in one male and four female controls, two males at 30 mg/kg and five females at 60 mg/kg.

Mutagenicity:

A dominant lethal study in mice did not reveal any mutagenic activity.

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