DESCRIPTION: Maprotiline hydrochloride, USP is a tetracyclic antidepressant, available as 25 mg, 50 mg and 75 mg tablets, for oral administration. Its chemical name is N,N-Dimethyl-N-(2,3-dihydro-5-methyl-1H-pyrazolo[3,4-c]pyridin-1-yl)propan-2-amine hydrochloride, and its structural formula is:

\[
\text{HCl} \quad \text{C}_14\text{H}_{19}\text{N}_2\text{O} \quad \text{HCl}
\]

Maprotiline hydrochloride is a fine, white to off-white, practically odorless crystalline powder. It is freely soluble in methanol and chloroform, slightly soluble in water, and practically insoluble in isopropanol. Its molecular weight is 313.87.

The tablets contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene, polyethylene oxide, pregelatinized starch (corn), sodium bisulfate, titanium dioxide, and triacetin. Additionally, the 50 mg tablet contains FD&C Blue No. 1 Aluminum Lake.

CLINICAL PHARMACOLOGY: The mechanism of action of maprotiline is not precisely known. It does not act primarily by stimulation of the central nervous system and is not a monamine oxidase inhibitor. The postulated mechanism of maprotiline is that it acts primarily by poten-
tiation of central adrenergic synapses by blocking muatate of noradrenalin at nerve ends. This pharmacologic action is thought to be responsible for the drug's antidepressant and anxiolytic effects.

The mean time to peak is 12 hours. The half-time of elimination averages 51 hours.

INDICATIONS AND USAGE: Maprotiline hydrochloride tablets are indicated for the treatment of depressive illness in patients with depression (dysthmic disorder) and manic depressive illness, depressive type (major depressive disorder). Maprotiline is also effective for the relief of anxiety associated with depression.

CONTRAINDICATIONS: Maprotiline hydrochloride tablets are contraindicated in patients hypersensitive to maprotiline and in patients with known or suspected seizure disorders. It should not be given concomitantly with monomine oxidase inhibitors. A minimum of 14 days should be allowed to elapse after discontinuation of MAO inhibitors before treatment with maprotiline hydrochloride is begun. If a patient develops seizures before this interval until optimum response is achieved. The drug is not recommended for use during the acute phased of manic episode.

WARNINGS: Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidality, including ideation of suicide and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with depression or agitation. It should be noted that maprotiline is not approved for use in treating bipolar depression.

No suicides occurred in any of the pediatric trials. There were no suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, hypomania, mania, agitation, anger, anger episodes, attacks of rage, and behavior disorder (suicidality) in children, adolescents and young adults ages (18 to 24) with depression or agitation or irritability, behavior disorder may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 2,085 short-term trials of 9 antidepressant drugs in over 4,848 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 286 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 7,700 patients. There was considerable variation in risk of suicidality among drugs, but a trend toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest risk differences (drug vs. placebo) occurring in MDD. The risk differences (drug vs. placebo) were relatively stable across doses and across indications. The trend toward an increase in risk of suicidality in children and adolescents in the pooled analyses of placebo-controlled trials in children and adolescents with MDD, OCD, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,840 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 286 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over

ADVERSE REACTIONS: The most common adverse reactions are: somnolence; weight gain; dry mouth; constipation; nausea; blurred vision; palpitations; sweating; urinary retention; decreased libido; insomnia; anorgasmia; and sexual dysfunction.

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

Maprotiline should be administered in caution with patients with history of urinary retention, or history of narrow angle glaucoma because of the drug's anticholinergic properties.

Information for Patients: Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with maprotiline and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness and Suicidal Thoughts or Actions" is available for maprotiline. The prescriber or health professional should review the Medication Guide and provide it to the patient if the patient is likely to ingest the medication. Patients should be advised to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete test of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues or asked to alert their prescriber if they arise:

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

Maprotiline should be administered with caution with patients with history of urinary retention, or history of narrow angle glaucoma because of the drug's anticholinergic properties.
Neurological: Drowsiness (16%), dizziness (8%), tremor (2%), and, rarely, numbness, tingling, motor hyperactivity, akathisia, akinesias, EOG alterations, tremors, extrapyramidal symptoms, ataxia, and dysarthria.

Anticholinergic: Dry mouth (22%), constipation (6%), and blurred vision (4%); rarely, anticholinergic symptoms, dry mouth, urinary retention, and delayed micturition.

Allergic: Rare instances of skin rash, petechiae, itching, photosensitivity, edema, and drug fever.

Gastrointestinal: Nausea (2%) and, rarely, vomiting, epigastric distress, diarrhea, bitter taste, abdominal cramps and dysphagia.

Hematological: Occurrences of increased or decreased libido, impotence, and elevation or depression of blood sugar levels.

Other: Weakness and fatigue (4%) and headache (4%); rarely, altered liver function, jaundice, weight loss or gain, excessive perspiration, flushing, urinary frequency, increased salivation, nasal congestion and alopecia.

Note: Although there have been only isolated reports of the following adverse reactions with maprotiline, its pharmacologic similarity to tricyclic antidepressants requires that each reaction be considered when administering maprotiline.

— Bone marrow depression, including agranulocytosis, eosinophilia, purpura, and thrombocytopenia, myocardial infarction, stroke, peripheral neuropathy, sublingual adenitis, black tongue, stomatitis, paralytic ileus, gynecomastia in the male, breast enlargement and galactorrhea in the female, and labial swelling.

Postinjection Reactions: Voluntary reports of adverse events temporarily associated with maprotiline that have been received since market introduction and that may have no causal relationship with the drug include the following: interstitial pneumonitis which were in some cases associated with eosinophilia and increased liver enzymes, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

OVERDOSAGE: Deaths may occur from overdose with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after overdose. Therefore, hospital monitoring is required as soon as possible.

Animal Oral LD50: The oral LD50 of maprotiline hydrochloride is 600 to 2750 mg/kg in mice, 760 to 900 mg/kg in rats, > 1000 mg/kg in rabbits, > 300 mg/kg in cats, and > 30 mg/kg in dogs.

Manifestations: Data dealing with overdosage in humans are limited with only a few cases on record. Signs and symptoms of maprotiline hydrochloride overdose are similar to those seen with tricyclic overdoses. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS axis or width are clinically significant indicators of toxicity. Other clinical manifestations include drowsiness, tachycardia, ataxia, vomiting, cyanosis, shock, restlessness, agitation, hypoglycemia, muscle rigidity, atelectasis, and mydriasis. Since concomitant heart failure has been seen with overdoses of tricyclic antidepressants, it should be considered with maprotiline hydrochloride overdose.

Management: Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination. A minimum of 6 hours of observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. There are case reports of patients succumbing to fatal dysrhythmias late after tricyclic overdose. These patients had clinical evidence of significant poisoning prior to death and most received inadequate gastric decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination: All patients suspected of overdose should receive gastric decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular: A maximal limb lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.4 to 7.5. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a PaCO2 > 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy may respond to lidocaine, bretylium, or phenytoin. Types 1A and 1C antarrhythmic agents are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

In rare instances, hemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, hemodialysis, peritoneal dialysis, or change transfusions, and forced diuresis generally have been reported as ineffective.

CNS: In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control center.

Psychiatric Follow-up: Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Pediatric Management: The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

DOSEAGE AND ADMINISTRATION: A single daily dose is an alternative to divided daily doses. Therapeutic effects are sometimes seen within 3 to 7 days, although as long as 2 to 3 weeks are usually necessary.

Initial Adult Dosage: An initial dosage of 75 mg daily is suggested for outpatients with mild to moderate depression. However, in some patients, particularly the elderly, an initial dosage of 25 mg daily may be used. Because of the long half-life of maprotiline, the initial dosage should be maintained for 2 weeks. The dosage may then be increased gradually in 25 mg increments as required and tolerated. In most outpatients a maximum dose of 150 mg daily will result in therapeutic efficacy. It is recommended that this dose not be exceeded except in the most severely depressed patients. In such patients, dosage may be gradually increased to a maximum of 225 mg.

More severely depressed, hospitalized patients should be given an initial daily dose of 100 to 150 mg which may be gradually increased as required and tolerated. Most hospitalized patients with moderate to severe depression respond to a daily dose of 150 mg although dosages as high as 225 mg may be required in some cases. Daily dosage of 225 mg should not be exceeded.

Elderly Patients: In general, lower dosages are recommended for patients over 60 years of age. Dosages of 50 mg to 75 mg daily are usually satisfactory as maintenance therapy for elderly patients who do not tolerate higher amounts.

Maintenance: Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Dosage may be reduced to levels of 75 mg to 150 mg daily during such periods, with subsequent adjustment depending on therapeutic response.

How Supplied: Maprotiline Hydrochloride, USP is available as tablets containing 25 mg, 50 mg, or 75 mg of maprotiline hydrochloride.

The 25 mg tablets are white film-coated, round, scored tablets debossed with 6 to the left of the score and 2 to the right of the score on one side of the tablet and M on the other side. They are available as follows:

NDC 0378-0060-01 bottles of 100 tablets

The 50 mg tablets are light blue film-coated, round, scored, tablets debossed with 6 to the left of the score and 7 to the right of the score on one side and M on the other side. They are available as follows:

NDC 0378-0067-01 bottles of 100 tablets

The 75 mg tablets are white film-coated, round, scored tablets debossed with 9 to the left of the score and 2 to the right of the score on one side and M on the other side. They are available as follows:

NDC 0378-0062-01 bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP for Controlled Room Temperature.]

Protect from light.

Dispense a Medication Guide with each prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

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What else do I need to know about antidepressant medicines?

Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

Visual problems: Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member. Keep a list of all medicines to show the healthcare provider, not just the use of antidepressants.

Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Call a list of all medicines to show the healthcare provider.

Antidepressant medicines prescribed for children are FDA approved for use in children. Talk to your child’s healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

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