Imipramine pamoate is a fine, yellow, tasteless, odorless powder. It is available as capsules for oral administration. The 75-, 100-, 125-, and 150-mg capsules contain imipramine pamoate equivalent to 75, 100, 125, and 150 mg of imipramine hydrochloride. Imipramine pamoate is (5-[3-(dimethylamino)propyl]-10,11-dihydro-5-
-methylenebis-(3-hydroxy-2-naphthoate) (2:1), and its structural formula is

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{NICH}_3\cdots\text{COOH}
\]

Imipramine pamoate is a fine, yellow, tasteless, odorless powder. It is soluble in ethanol, acetone, in ether, in chloroform, in carbon tetrachloride, and is insoluble in water. Its molecular weight is 949.21. Inactive Ingredients. D&C Red No. 28, FD&C Blue No. 1, FD&C Yellow No. 6, D&C Yellow No. 10 (100 mg and 125 mg capsules only), gelatin, magnesium stearate, parabens, silicon dioxide, sodium lauryl sulfate, starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY
The mechanism of action of imipramine is not definitely known. However, it does not act primarily by stimulation of the central nervous system. The clinical effect is hypothesized as being due to potentiation of adrenergic synapses by blocking uptake of norepinephrine at nerve endings.

INDICATIONS AND USAGE
For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states. One to three weeks of treatment may be needed before optimal therapeutic effects are evident.

CONTRAINDICATIONS
The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hypertensive crises or severe convulsive seizures may occur in patients receiving such combinations. The potential of adverse effects can be serious, or even fatal. When it is desired to substitute Tofranil®-PM in patients receiving a monoamine oxidase inhibitor, it should be discontinued at least 5 weeks prior to initiating treatment with Tofranil®-PM. (See PRECAUTIONS.)

WARNINGS
Extreme caution should be used when this drug is given to: patients with cardiovascular disease because of the possibility of conduc-}

disorder because this drug has been shown to lower the seizure threshold; patients receiving guanethidine, clonidine, or similar agents, since imipramine pamoate may block the pharmacologic effects of these drugs; patients receiving methyldopa. Since methyldopa hydrochloride may inhibit the metabolism of imipramine pamoate, downward dosage adjustment of imipramine pamoate may be required when given concomitantly with methyldopa.

Since imipramine pamoate may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly. Tofranil®-PM may enhance the CNS depressant effects of alcohol. Therefore, it should be borne in mind that the dangers inherent in a suicide attempt or accidental overdosage with the drug may be increased for those patients who use excessive amounts of alcohol. (See PRECAUTIONS.)

Usage in Children: Tofranil®-PM should not be used in children of any age because of the increased potential for acute overdosage due to the high unit potency (75 mg, 100 mg, 125 mg, and 150 mg). Each capsule contains imipramine pamoate equivalent to 75 mg, 100 mg, 125 mg, or 150 mg imipramine hydrochloride.

PRECAUTIONS
General
An ECG recording should be taken prior to the initiation of larger-than-usual doses of imipramine pamoate and at appropriate intervals thereafter until steady state is achieved. (Patients with any evidence of cardiovascular disease require cardiac surveillance at all dosage levels of the drug. See WARNINGS.) Elderly patients and patients with cardiac disease or a prior history of cardiac disease are at special risk of developing the cardiac abnormalities associated with the use of imipramine pamoate. It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with imipramine pamoate and may require hospitalization. Prescriptions should be written for the smallest amount feasible.

Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, imipramine pamoate may be resumed in lower dosage when these episodes are relieved. Administration of a tranquilizer may be useful in controlling the manic state. An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.

Concurrent administration of imipramine pamoate with electroshock therapy may increase the hazards: such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.

Patients taking imipramine pamoate should avoid excessive exposure to sunlight since there have been reports of photosensitization.

Both elevation and lowering of blood sugar levels have been reported with imipramine pamoate.

Imipramine pamoate should be used with caution in patients with significantly impaired renal or hepatic function.

Patients who develop a fever and a sore throat during therapy with imipramine pamoate should have leukocyte and differential blood counts performed.

Imipramine pamoate should be discontinued if there is evidence of pathological neutrophil depression.

Prior to elective surgery, imipramine pamoate should be discontinued for as long as the clinical situation will allow.

Drug Interactions
Drugs Metabolized by P450 2D6:

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7%-10% of Caucasians are such “poor metabolizers”); reliable estimates of the prevalence of reduced P450 2D6 activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given drugs that are metabolized by the enzyme (e.g., cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phosphonazines, and the Type 1C11 antiarrhythmics propafenone and flecainide). The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phosphonazines, and the Type 1C11 antiarrhythmics propafenone and flecainide). Tofranil®-PM may require lower doses than usual prescribed for either the tricyclic antidepressant or the other drug. Furthermore, whenever one of these other drugs is withdrawn from co-therapy, an increased dose of tricyclic antidepressant may be required. It is desirable to monitor TCA plasma levels whenever a TCA is going to be co-administered with another drug known to be an inhibitor of P450 2D6.

The plasma concentration of imipramine may increase when the drug is given concomitantly with hepatic enzyme inhibitors (e.g., cimetidine, fluoxetine) and decrease by concomitant administration with hepatic enzyme inducers (e.g., barbiturates, phenytoin), and adjustment of the dosage of imipramine may therefore be necessary. In occasional reports, patients on concurrent administration of an anticholinergic drug (including antiparkinsonism agents) in addition, the anticholinergic-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when imipramine pamoate is administered concomitantly with anticholinergic drugs.

Avoid the use of preparations, such as decongestants and local anesthetics, that contain any sympathomimetic amines (e.g., epinephrine, norepinephrine), since there has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.

Caution should be exercised when imipramine pamoate is used with agents that lower blood pressure. Imipramine pamoate may potentiate the effects of CNS depressant drugs.

Patients should be warned that imipramine pamoate may enhance the CNS depressant effects of alcohol. (See WARNINGS.)

Pregnancy
Animal reproduction studies have yielded inconclusive results. (See also ANIMAL PHARMACOLOGY & TOXICOLOGY.)

There have been no well-controlled studies conducted with pregnant women to determine the effect of imipramine on the fetus. However, there have been clinical reports of congenital malformations associated with the use of the drug. Although a causal relationship between these effects and the drug could not be established, the possibility of fetal risk from the maternal ingestion of imipramine cannot be excluded. Therefore, imipramine should be used in women who are or might become pregnant only if the clinical condition clearly justifies potential risk to the fetus.

Nursing Mothers
Limited data suggest that imipramine is likely to be excreted in human breast milk. As a general rule, a woman taking a drug should not nurse since the possibility exists that the drug may be excreted in breast milk and be harmful to the child.

Pediatric Use
See WARNINGS.

ADVERSE REACTIONS
Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine is administered.

Cardiovascular: Orthostatic hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, ECG changes indicating progression of congeugive heart failure, stroke.

Psychiatric: Confusional states (especially in the elderly) with
hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia; tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.

Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization; edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.

Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; perianal rash, stomatitis, abdominal cramps, black tongue.

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; inappropriate antidiuretic hormone (ADH) secretion syndrome.

Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia; pruriitosus to falling.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

DOSEAGE AND ADMINISTRATION

The following recommended dosages for Tofranil®-PM should be modified as necessary by the clinical response and any evidence of intolerance.

Initial Adult Dosage: Outpatients - Therapy should be initiated at 75 mg/day. Dosage may be increased to 150 mg/day which is the dose level at which optimum response is usually obtained. If necessary, dosage may be increased to 200 mg/day.

Dosage higher than 75 mg/day may also be administered on a once-a-day basis after the optimum dosage and tolerance have been determined. The daily dosage may be given at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

As with all tricyclics, the antidepressant effect of imipramine may not be evident for one to three weeks in some patients.

Hospitalized Patients - Therapy should be initiated at 100-150 mg/day and may be increased to 200 mg/day. If there is no response after two weeks, dosage should be increased to 250-300 mg/day.

Dosage higher than 150 mg/day may also be administered on a once-a-day basis after the optimum dosage and tolerance have been determined. The daily dosage may be given at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

As with all tricyclics, the antidepressant effect of imipramine may not be evident for one to three weeks in some patients.

Adult Maintenance Dosage: Following remission, maintenance medication may be continued at the lowest dose that will maintain remission after which the dosage should gradually be decreased.

The usual maintenance dosage is 75-150 mg/day. The total daily dosage can be administered on a once-a-day basis, preferably at bedtime. In some patients it may be necessary to employ a divided-dose schedule.

In cases of relapse due to premature withdrawal of the drug, the effective dosage of imipramine should be reinstituted.

OVERDOSAGE

Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic 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 tricyclic overdose. Therefore, hospital monitoring is required as soon as possible.

Children have been reported to be more sensitive than adults to an acute overdosage of imipramine pamoate. An acute overdose of any amount in infants or young children, especially, must be considered serious and potentially fatal.

Manifestations

These may vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the interval between drug ingestion and the start of treatment. 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 tricyclic toxicity.

Other CNS manifestations may include drowsiness, stupor, ataxia, restlessness, agitation, hyperactive reflexes, muscle rigidity, atetosis and choreiform movements.

Cardiac abnormalities may include tachycardia, and signs of congestive failure. Respiratory depression, cyanosis, shock, vomiting, hypopryxia, mydriasis, and diaphoresis may also be present.

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 is recommended. Carnitine or renin for signs of myonephrosis, 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 overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate gastrointestinal decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal: If vomiting or retching or reingestion of vomitus occurs, gastric lavage should be considered. If the patient is severely depressed, gastric lavage should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emergent intubation may be necessary.

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 7.45 to 7.55. If the pH response is inadequate, intravenous hypertentation may also be used. Concomitant use of hypertentation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH >7.60 or a Pco2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hypertentation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

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

CNS: In patients with CNS depression, early intubation is advised for the potential of abrupt deterioration. Seizures should be controlled with benzodiazepines, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Phystostigmine 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.

HOW SUPPLIED

Capsules 75 mg - coral (imprinted black Geyki 20) equivalent to 75 mg imipramine hydrochloride

Bottles of 30 .................................................NDC 0406-9923-03

Bottles of 100 ..................................................NDC 0406-9923-01

Capsules 100 mg - dark yellow/coral (imprinted black Geyki 40) equivalent to 100 mg imipramine hydrochloride

Bottles of 30 .................................................NDC 0406-9924-03

Bottles of 100 ..................................................NDC 0406-9924-01

Capsules 125 mg - dark yellow/coral (imprinted black Geyki 45) equivalent to 125 mg imipramine hydrochloride

Bottles of 30 ..................................................NDC 0406-9925-03

Bottles of 100 ..........................................................NDC 0406-9925-01

Capsules 150 mg - coral (imprinted black Geyki 32) equivalent to 150 mg imipramine hydrochloride

Bottles of 30 ..................................................NDC 0406-9926-03

Bottles of 100 ..........................................................NDC 0406-9926-01

Do not store above 30°C (86°F). Dispense in tight container (USP).

ANIMAL PHARMACOLOGY & TOXICOLOGY

A. Acute: Oral LD50:

Mouse 2185 mg/kg

Rat (F) 1142 mg/kg

(M) 1987 mg/kg

Rabbit 1016 mg/kg

Dog 693 mg/kg (Emesis ED50)

B. Subacute:

Two three-month studies in dogs gave evidence of an adverse drug effect on the testes, but only at the highest dose level employed, i.e., 90 mg/kg (10 times the maximum human dose). Depending on the histological section of the testes examined, the findings consisted of a range of degenerative changes up to and including complete atrophy of the seminiferous tubules, with spermatogenesis usually arrested. Human studies show no definitive effect on sperm count, sperm motility, sperm morphology or volume of ejaculate.

Rat:

One three-month study was done in rats at dosage levels comparable to those of the dog studies. No adverse drug effect on the testes was noted in this study, as confirmed by histological examination.

C. Reproduction/Teratogenic:

Oral: Imipramine pamoate was fed to male and female albino rats for 28 weeks through two breeding cycles at dose levels of 15 mg/kg/day and 40 mg/kg/day (equivalent to 21/2 and 7 times the maximum human dose). No abnormalities which could be related to drug administration were noted in gross inspection. Autopsies performed on pups from the second breeding likewise revealed no pathological changes in organs or tissues; however, a decrease in mean litter size from both matings was noted in gross inspection. Autopsies performed on pups from the second breeding likewise revealed no pathological changes in organs or tissues; however, a decrease in mean litter size from both matings was significant in the second litter of the high-level group.

Printed in U.S.A. Rev 041701

Manufactured by
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Manufactured for
Mallinckrodt Inc.
St. Louis, MO 63134