PRESCRIBING INFORMATION

IMIPRAMINE

Imipramine Hydrochloride Tablets USP

10 mg, 25 mg, 50 mg and 75 mg

ANTIDEPRESSANT

AA PHARMA INC.
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Control #: 138726

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IMIPRAMIME
Prescribing Information

Pharmacology: The mechanism of antidepressant action of imipramine is not clear although it has been shown to block the reuptake of various neurotransmitters at the neuronal membrane. As a result, the actions of norepinephrine and serotonin may be potentiated. Imipramine has strong anticholinergic actions as well. Imipramine is not an MA0 inhibitor.

Imipramine is absorbed after oral administration with peak plasma levels occurring within 1 t o 2 hours. It is extensively metabolised by the liver and the metabolites are excreted primarily by the kidney. One metabolite, desipramine, is active. The half-life of imipramine ranges from 8 to 16 hours.

Imipramine undergoes first-pass metabolism in the liver when administered orally. Enterohepatic circulation and secretion of the drugs and their metabolites into gastric juice may occur.

Indications: IMIPRAMINE (imipramine) is indicated for the relief of symptoms of depressive illness.

Contraindications: The concomitant use of MA0 inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute imipramine in patients receiving a MA0 inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed.

Patients with a known hypersensitivity to this compound should not be given the drug.

Precautions: Exercise extreme caution when imipramine is used in patients with coronary thrombosis, angina pectoris, congestive heart failure, disorders of cardiac rate or rhythm or conduction, prostatic disorders with potential urinary retention and glaucoma, imipramine should be used cautiously in hyperactive or agitated patients and in epileptics or ambulatory, seriously depressed patients with suicidal tendencies. Elderly patients, children and those with circulatory liability or with cardiovascular disease should receive the drug in low dosage and under careful observation and only when a clear indication for the drug has been established.

The possibility of suicide in depressed patients remains during treatment and until significant remission occurs, this type of patient should not have access to large quantities of the drug.

Drug interactions: Patients should be warned that, while taking imipramine their responses to alcoholic beverages, other CNS depressants or anticholinergic agents may be exaggerated.

Since imipramine may diminish or abolish the antihypertensive effect of adrenergic neuron inhibitors, such as guanethidine, patients requiring concomitant treatment for hypertension should be given antihypertensives of a different type.

Imipramine may potentiate the cardiovascular effects of norepinephrine or epinephrine.

Methylphenidate may increase the activity and plasma concentrations of tricyclic antidepressants.

Caution should be exercised if imipramine is administered together with cimetidine since cimetidine has been shown to inhibit the metabolism of several tricyclic antidepressants and clinically significant increases in plasma levels of imipramine may occur.

Pregnancy: Imipramine should not be used during the first trimester of pregnancy.

Lactation: Use of the drug should be avoided during lactation.

Adverse Effects: 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: hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, falls. A few instances of unexpected death have occurred in patients with cardiovascular disorders.

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, dilation of the urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with desipramine.

Hematologic: bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia. 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 and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, 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.

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

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

Overdose: Deaths by deliberate or accidental overdosage have occurred with this class of drugs. Children have been reported to be more sensitive than adults to an acute overdosage of imipramine. An acute overdose in infants or young children must be considered serious and potentially fatal.

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.

Symptoms: High doses may cause temporary confusion, disturbed concentration, transient visual hallucinations, agitation, hyperactive reflexes, muscle rigidity, vomiting, or hyperpyrexia, in addition to anything listed under Adverse Effects. Based on imipramine's known pharmacologic actions, overdosage may cause drowsiness, hypothermia, tachycardia and other arrhythmic abnormalities such as bundle branch block, ECG evidence of impaired conduction and congestive heart failure. Other manifestations may be dilated pupils, convulsions, severe hypotension, stupor and coma. All patients suspected of having taken an overdose should be admitted to a hospital as soon as possible.

Treatment: Symptomatic and supportive. Cardiac arrhythmias and CNS involvement pose the greatest threat with tricyclic antidepressant overdosage and may occur suddenly even when initial symptoms appear to be mild. Therefore, patients who may have ingested an overdose of imipramine, particularly children, should be hospitalized and kept under close surveillance.

If the patient is conscious, induced emesis followed by gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be accomplished as soon as possible.

Following lavage, activated charcoal may be administered to reduce absorption. Physical removal of tricyclic antidepressants from the gastrointestinal tract generally should be attempted and activated charcoal administered to decrease absorption, even several hours after ingestion, because the anticholinergic effects of the tricyclic antidepressants may delay gastric emptying and the drugs may also be secreted into the stomach.

An adequate airway should be established in comatose patients and assisted ventilation instituted, if necessary, but respiratory stimulants should not be used. Hyperpyrexia should be controlled by external measures, such as ice packs and cooling sponge baths. Acidosis may be treated by cautious administration of sodium bicarbonate. Adequate renal function should be maintained.

External stimulation should be minimized to reduce the tendency to convulsions. If convulsions occur, anticonvulsants (preferably i.v. diazepam) should be administered. 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. If the patient fails to respond rapidly to anticonvulsants, artificial ventillation should be instituted. 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. A patient who has ingested a toxic overdose of a tricyclic antidepressant may remain medically and psychiatrically unstable for several days due to sustained excessive drug levels. Unexpected cardiac deaths have occurred up to 6 days after overdosage with other antidepressants. The QRS interval of the electrocardiogram appears to be a reliable correlate of the severity of overdosage. If the QRS interval exceeds 100 milliseconds any time during the first 24 hours after dosage, cardiac function should be continuously monitored for 5 or 6 days.

Life-threatening cardiac arrhythmias may respond to lidocaine. Quinidine, procainamide and disopyramide generally should be avoided in the management of conduction abnormalities and cardiac arrhythmias since these agents may further depress myocardial conduction and contractility. 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 i.v. fluids, oxygen and corticosteroids. Pressor agents, such as norepinephrine (but not epinephrine), are rarely indicated and should be given only after careful consideration and under continuous monitoring.

Physostigmine i.v. has been used in the treatment of tricyclic-induced anticholinergic toxicity. Its use is controversial and should be reserved for life-threatening situations. Physostigmine is not innocuous and carries the risk of inducing seizures, bronchospasm,

hypertension and severe arrhythmias, It should not be used routinely or to reverse coma. However, it may be indicated in the treatment of seizures or combattive hallucinations. It should not be used in patients who are acidemic or who have cardiac conduction defects.

Adults: a test does of 0.5 mg i.v. is given initially. Give 1 to 2 mg slowly i.v. (over 2 minutes). If no clinical changes or cholinergic signs occur within 15 to 30 minutes, an additional 1 to 2 mg may be cautiously administered. Repeat doses of 1 to 2 mg i.v. every 30 minutes up to 2 hours.

Children: a 0.5 mg i.v. dose is given initially.

As the CNS effects of physostigmine may wear off rapidly, it is important to monitor the patient continuously.

Physostigmine is the only drug of this class that may be used. Neostigmine should not be used as it does not have any CNS effects.

If symptoms of cholinergic toxicity develop, physostigmine should be discontinued.

Peritoneal and hemodialysis are of no value because of low plasma concentrations of the drug. Most of the administered dose is distributed in tissue and not in plasma. When aggressive medical management is inadequate, hemoperfusion, but not hemodialysis, has shown some good results.

Dosage: Depression: Except in elderly patients, adolescents or children: 25 mg 3 times daily, initially, increased up to 150 mg daily, if necessary. Dosage in excess of 200 mg daily is not recommended for office patients. More severe, hospitalized cases may require up to 300 mg daily. In elderly patients and adolescents: 30 to 40 mg daily, initially, increased by 10 mg daily to a maximum of 100 mg in the elderly.

In suitable subjects, the maintenance dose may be administered in a single dose before bedtime. It does not have as much sedative effect as amitriptyline which may be used at bedtime for this effect.

Supplied: Each brown, film-coated tablet contains Imipramine HC1 10, 25, 50, or 75 mg. Imprinted 10, 25, 50, and 75, respectively.

Available in bottles of 100 or 1000 tablets.