APO-CLOMIPRAMINE
Clomipramine Hydrochloride Tablets 25mg
Antidepressant - Antiobsessional

PHARMACOLOGY: **APO-CLOMIPRAMINE** (clomipramine hydrochloride) is a tricyclic agent with antidepressant and antiobsessional properties. Like other tricyclics, clomipramine inhibits norepinephrine and serotonin uptake into central nerve terminals, possibly by blocking the membrane-pump of neurons, thereby increasing the concentration of transmitter monoamines at receptor sites. Clomipramine is presumed to influence depression and obsessive and compulsive behaviour through its effects on serotonergic neurotransmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit serotonin reuptake is though to be important. Clomipramine appears to have a mild sedative effect which may be helpful in alleviating the anxiety component often accompanying depression.

As with other tricyclic compounds, clomipramine possesses anticholinergic properties which are responsible for some of its side effects. It also has weak antihistamine and antiserotonin properties, lowers the convulsive threshold, potentiates the effect of norepinephrine and other drugs acting on the central nervous system, has a quinidine-like effect on the heart and may impair cardiac conduction.

The action of clomipramine on the human electroencephalogram is one of desynchronization. Clomipramine causes a persistent increase in the frequency of shifts into stage I sleep and produces marked reduction or suppression of rapid eye movement sleep (REM or paradoxical sleep) with partial recovery within 3 to 4 weeks and a rebound after drug withdrawal which appears to last approximately the same time. In normal human volunteers, tricyclic antidepressants tend to produce a sedative effect accompanied by atropine-like symptoms and may produce some difficulty in concentrating and thinking.

The absorption of clomipramine is rapid and complete after oral administration in man. Plasma levels usually peak two hours after dosage but much individual variation occurs. Plasma half-life after a single oral dose is approximately 21 hours. After 28 days of oral administration to patients in a daily dosage of 75mg, plasma concentrations of clomipramine ranged from 17 to 70ng/mL (mean = 35.7ng/mL). The concentration of the active metabolite, desmethylclomipramine, was about twice as high.

The binding of clomipramine to serum proteins is very high at 96 to 97 percent and is practically concentration-independent within the therapeutic range. Clomipramine has a volume of distribution of approximately 12L/kg body weight.

Clomipramine is extensively metabolized in the body with hydroxylation, demethylation and N-oxidation being the quantitatively more important routes of metabolism.

Owing to the lower clearance of clomipramine in plasma, elderly patients require lower doses of clomipramine than patients in younger age groups.

As expected, the metabolites of clomipramine are quite similar to those of imipramine, all retaining the benzazepine structure. Two-thirds of clomipramine is excreted in the form of water soluble conjugates in the urine and approximately one-third in the feces. After a 25mg radiolabelled dose of clomipramine in 2 subjects, the urinary recoveries of clomipramine and desmethylclomipramine were about 2% and 0.5% of the total radioactivity, respectively.

INDICATIONS: **APO-CLOMIPRAMINE** (clomipramine hydrochloride) is indicated for the treatment of depression. Clomipramine also appears to have a mild sedative effect which may be helpful in alleviating the anxiety component often accompanying depression.

APO-CLOMIPRAMINE is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD). The obsessions and compulsions must cause marked distress, be time-consuming, or significantly interfere with social or occupational functioning.

The effectiveness of clomipramine for long-term use (i.e. for more than 10 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to use clomipramine for extended periods should periodically re-evaluate the long term usefulness of the drug for the individual patient.

ADVERSE EFFECTS: The most commonly observed adverse events associated with the use of clomipramine and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness and myoclonus; genitourinary complaints including changed libido, ejaculatory failure, impotence and micturition

disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes.

The tabulations that follow list adverse reactions that have also been observed with clomipramine; these are categorized by organ system and listed in order of decreasing frequency.

Neurological: extrapyramidal effects such as ataxia, also headache, delirium, speech disorders, muscle weakness, muscle hypertonia, tinnitus, paresthesias of the extremities, convulsions, EEG changes, hyperpyrexia. Peripheral neuropathy has been reported with other tricyclic antidepressants.

Behavioural: drowsiness, fatigue, restlessness, confusion accompanied by disorientation (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety states, agitation, sleep disturbances, insomnia, nightmares, aggravated depression, hypomania or manic episodes, disturbed concentration, visual hallucinations, impaired memory, aggressiveness, yawning, depersonalization, activation of latent psychosis, delusions.

Autonomic: difficulty with accommodation, slurred speech, urinary retention, hot flushes, mydriasis, glaucoma, paralytic ileus.

Cardiovascular: hypotension, particularly orthostatic hypotension with associated vertigo, sinus tachycardia, palpitations, a quinidine-like effect and other reversible ECG changes in patients with normal cardiac status (such as flattening or inversion of T-waves, depressed S-T segments). Arrhythmias, hypertension, conduction disorders (e.g. widening of QRS complex, PQ changes, bundle-branch block), syncope.

Fibrillation, myocardial infarction, stroke and unexpected death in patients with cardiovascular disorders have been reported with tricyclic antidepressants.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, eosinophilia and purpura. One case of pancytopenia has been reported.

Gastrointestinal: vomiting, abdominal pain, diarrhea, taste perversion, elevated transaminases, obstructive jaundice, hepatitis with or without jaundice.

Endocrine: weight loss, breast enlargement and galactorrhea in the female, inappropriate antidiuretic hormone (ADH) secretion syndrome, gynecomastia in the male, changes in blood sugar levels, increase in prolactin levels, menstrual irregularity.

Allergic or Toxic: allergic skin reactions (skin rash, urticaria), photosensitization, pruritus, edema, drug fever.

Withdrawal Symptoms: abrupt cessation of treatment with tricyclic antidepressants after prolonged administration may occasionally produce nausea, vomiting, abdominal pain, diarrhea, insomnia, nervousness, anxiety, headache and malaise. These symptoms are not indicative of addiction.

PRECAUTIONS: Suicide: The possibility of a suicide attempt is inherent in depression with or without obsessive-compulsive disorder. These patients should be carefully supervised during treatment with APO-CLOMIPRAMINE (clomipramine hydrochloride), and hospitalization or concomitant electroconvulsive therapy may be required. To minimize the risk of an intentional overdose by a depressed patient, prescriptions for clomipramine should be written for the smallest possible quantity of the drug consistent with good patient management.

Psychosis, Mania-Hypomania, and other Neuropsychiatric Phenomena: In patients treated with tricyclic antidepressants, activation of latent schizophrenia or aggravation of existing psychotic manifestations in schizophrenic patients may occur; patients with manic depressive tendencies may experience hypomanic or manic shifts; and hyperactive or agitated patients may become overstimulated. A reduction in dose or discontinuation of clomipramine should be considered under these circumstances.

In predisposed and elderly patients, tricyclic antidepressants may, particularly at night, provoke pharmacogenic (delirious) psychoses which disappear without treatment within a few days of withdrawing the drug.

Since clomipramine may produce sedation, particularly during the initial phase of therapy, patients should be cautioned about the danger of engaging in activities requiring mental alertness, judgement and physical coordination.

Cardiovascular: Before initiating treatment, it is advisable to check the patient's blood pressure, because individuals with hypotension or a labile circulation may react to the drug with a fall in blood pressure. Regular measurements of blood pressure should be performed in susceptible patients. Postural hypotension may be controlled by reducing the dosage or administering circulatory stimulants. ECG abnormalities have been observed in patients treated with clomipramine. The most common ECG changes were premature ventricular contractions (PVCs), ST-T wave changes, and abnormalities in intraventricular conduction. These changes were rarely associated with significant clinical symptoms.

Nevertheless, caution is necessary in treating patients with heart diseases, as well as elderly subjects. In these patients cardiac function should be monitored and ECG examinations performed during long-term therapy. Gradual dose titration is also recommended.

Hepatic Changes: Clomipramine has occasionally been associated with elevations in AST (SGOT) and ALT (SGPT) of potential clinical significance (i.e. values greater than 3 times the upper limit of normal). In the majority of cases, these enzyme elevations were not associated with other clinical findings suggestive of hepatic injury.

Isolated cases of obstructive jaundice have been reported. Caution is indicated in treating patients with known liver disease, and periodic monitoring of hepatic function is recommended in such patients.

Hematologic Changes: Isolated cases of bone marrow depression with agranulocytosis have been reported. Leukocyte and differential blood cell counts are recommended in patients receiving treatment with clomipramine over prolonged periods, and should be performed for patients who develop fever, an influenzal infection, or sore throat. In the event of an allergic skin reaction, clomipramine should be withdrawn.

CNS: More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when clomipramine was used in combination with other drugs. When clomipramine and a neuroleptic were used concomitantly, the cases were sometimes considered to be examples of a neuroleptic malignant syndrome.

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of clomipramine, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia and irritability. In addition, such patients may experience a worsening of psychiatric status. While the withdrawal effects of clomipramine have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants, and it is recommended that the dosage be tapered gradually and the patient monitored carefully during discontinuation.

Metabolic Effects: Tricyclic antidepressants have been associated with porphyrinogenicity in susceptible patients.

Renal Function: It is also advisable to monitor renal function during long-term therapy with tricyclic antidepressants.

Dental Effects: Lengthy treatment with tricyclic antidepressants can lead to an increased incidence of dental caries.

Endocrine Effects: As with certain other psychotherapeutic drugs, clomipramine elevates prolactin levels. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of clomipramine is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence is considered too limited to be conclusive at this time.

Children: As clomipramine has not been studied in patients under 10 years of age, specific recommendations for use in this age group cannot be provided. The long-term effects of clomipramine on childhood growth and development have not been determined.

Teratology: No teratogenic effects were observed in rats and mice at doses up to 20 times the maximum daily human dose. Slight nonspecific fetotoxic effects were seen in the offspring of pregnant mice given doses 10 times the maximum daily human dose. Slight nonspecific embryotoxicity was observed in rats given doses 5 to 10 times the maximum daily human dose.

Animal Toxicology: As with other tricylic compounds, clomipramine has been associated with changes in testicular and lung tissue in long-term animal toxicology studies. In 1 and 2 year studies in rats, a dose 4 times the maximum daily human dose was associated with phospholipidosis in the lungs and changes in the testes (atrophy, aspermatogenesis, and calcification). In a 1 year toxicity study in dogs, testicular atrophy was detected in animals receiving 10 times the maximum recommended daily human dose.

WARNINGS: Seizures: Tricyclic agents are known to lower the convulsive threshold and clomipramine should, therefore, be used with extreme caution in patients with a history of convulsive disorders and other predisposing factors, e.g. brain damage of varying etiology, alcoholism, and concomitant use with other drugs that lower the seizure threshold. Total daily doses should not exceed

the recommended total daily dose (see **DOSAGE**). Concurrent administration of ECT and clomipramine may be hazardous and such treatment should be limited to patients for whom it is essential. Physicians should discuss with patients the risk of taking clomipramine while engaging in activities in which a sudden loss of consciousness could result in serious injury to the patient or others, e.g. the operation of complex machinery, driving, swimming, or climbing.

Cardiovascular: Tricyclic antidepressants, particularly in high doses, have been reported to produce sinus tachycardia, changes in conduction time and arrhythmias. A few instances of unexpected death have been reported in patients with cardiovascular disorders. Myocardial infarction and stroke have also been reported with drugs of this class. Therefore, **APO-CLOMIPRAMINE** (clomipramine hydrochloride) should be administered with extreme caution to patients with a history of cardiovascular disease, especially those who have a history of conduction disorders, those with circulatory lability and elderly patients. Clomipramine also has a hypotensive action which may be detrimental in these circumstances. In such cases, treatment 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. Monitoring of cardiac function and the ECG is indicated in such patients.

Use in Concomitant Illness: Caution should be observed in prescribing clomipramine in hyperthyroid patients or in patients receiving thyroid medication conjointly. Transient cardiac arrhythmias have occurred in rare instances in patients who have been receiving other tricyclic compounds concomitantly with thyroid medication.

Because of its anticholinergic properties, clomipramine should be used with caution in patients with increased intraocular pressure or a history of urinary retention, particularly in the presence of prostatic hypertrophy.

Particularly in the elderly and in hospitalized patients the tricyclic antidepressants may give rise to paralytic ileus and, therefore, appropriate measures should be taken if constipation occurs.

Caution is called for when employing clomipramine in patients with tumors of the adrenal medulla (e.g. pheochromocytoma, neuroblastoma) in whom the drug may provoke hypertensive crisis.

Clomipramine should be kept in a safe place, well out of the reach of children.

Use in Pregnancy and Lactation: Safe use in pregnant women has not been established. Withdrawal symptoms including tremors, convulsions and respiratory depression have been reported in neonates whose mothers received tricyclic antidepressants during the third trimester of pregnancy. Therefore, clomipramine should not be administered to women of child-bearing potential or during pregnancy, unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the fetus.

Since clomipramine passes into breast milk, nursing mothers receiving **APO-CLOMIPRAMINE** should not breast feed their infants.

Suicidality in Children and Adolescents:

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- The indication(s) approved in paediatric for the particular drug should be clearly stated / included.

CONTRAINDICATIONS: **APO-CLOMIPRAMINE** (clomipramine hydrochloride) is contraindicated in patients who have known hypersensitivity to the drug or have known hypersensitivity to tricyclic antidepressants belonging to the dibenzazepine group.

Clomipramine should not be given in conjunction with or within fourteen days of treatment with a monoamine oxidase inhibitor. Hypertensive crises, hyperactivity, hyperpyrexia, spasticity, severe convulsions or coma, and death have been reported in patients receiving such combinations.

Clomipramine is contraindicated during the acute recovery phase following myocardial infarction and in the presence of acute congestive heart failure.

Clomipramine is contraindicated in patients with existing liver or kidney damage and should not be administered to patients with a history of blood dyscrasias.

Clomipramine is contraindicated in patients with glaucoma, as the condition may be aggravated due to the atropine-like effects of the drug.

DRUG INTERACTIONS: Patients should be warned that, while taking clomipramine, their responses to alcoholic beverages, other CNS depressants (e.g. barbiturates, benzodiazepines or general anesthetics) or anticholinergic agents (e.g. atropine, biperiden, levodopa) may be exaggerated. When tricyclic antidepressants are given in combinations with anticholinergics or neuroleptics with an anticholinergic action, hyperexcitation states or delirium may occur, as well as attacks of glaucoma. Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type.

Since clomipramine may diminish or abolish the antihypertensive effects of guanethidine, clonidine, reserpine, methyldopa, patients requiring concomitant treatment for hypertension should be given antihypertensives of a different type (e.g. diuretics, beta-blockers).

Clomipramine may potentiate the cardiovascular effects of noradrenaline or adrenaline, amphetamine, as well as nasal drops and local anesthetics containing sympathomimetics.

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

Caution should be exercised if clomipramine 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 clomipramine may occur.

Substances which activate the hepatic mono-oxygenase enzyme system (e.g. barbiturates, phenytoin, nicotine) may lower plasma concentrations of tricyclic antidepressants and so reduce their antidepressive effects.

Clomipramine should not be administered for a period of at least 14 days after the discontinuation of treatment with MAO-inhibitors 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 clomipramine.

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

Concomitant administration of clomipramine and phenytoin may lead to elevated serum phenytoin concentration. If necessary, the phenytoin dosage should be adjusted accordingly.

Neuroleptic agents (e.g. phenothiazines and butyrophenones) may increase the plasma concentration of clomipramine. No such effects are known to occur in combination with diazepam but it might be necessary to lower the dosage of clomipramine if administered concomitantly with alprazolam or disulfiram.

If administered concomitantly with estrogens, the dose of clomipramine should be reduced since steroid hormones inhibit the metabolism of clomipramine.

Because clomipramine is highly bound to serum proteins, the administration of clomipramine to patients taking other drugs that are highly bound to protein (i.e. warfarin, digoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse reactions may result from the displacement of protein bound clomipramine by other highly bound drugs.

DOSAGE: The dosage of **APO-CLOMIPRAMINE** (clomipramine 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. During the initial dose titration phase, the total daily dose of clomipramine should be divided and served with meals to reduce gastrointestinal side-effects.

Owing to the long elimination half-lives of clomipramine and its active metabolite, desmethylclomipramine, steady-state plasma levels may not be achieved until 2 to 3 weeks after a dosage adjustment. It may thus be advisable to wait 2 to 3 weeks after the initial dose titration phase, before attempting further dosage adjustments. 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.

Depression: Initial Dosage: Adults: **APO-CLOMIPRAMINE** therapy should be initiated at daily doses of 25mg. Dosage may be increased by 25mg increments, as tolerated, at 3 to 4 day intervals up to a total daily dose of 150mg by the end of 2 weeks. Thereafter, the dose may be gradually increased over a period of several weeks to 200mg. Doses in excess of 200mg daily are not recommended for outpatients. Occasionally, in more severely depressed hospitalized patients, dosages up to 300mg daily may be required.

Elderly and Debilitated Patients: In general, lower dosages are recommended for these patients. Initially, 20 to 30mg daily in divided doses is suggested, with very gradual increments, depending on

tolerance and response. 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. To minimize daytime sedation during maintenance treatment, the total daily dosage may be given as a single dose at bedtime. Medication should be continued for the expected duration of the depressive episode in order to minimize the possibility of relapse following clinical improvement.

Obsessive Compulsive Disorders: Initial Dosage: Adults: **APO-CLOMIPRAMINE** therapy in adult obsessive compulsive patients should be initiated at daily doses of 25mg. Dosage may be increased by 25mg increments, as tolerated, at 3 to 4 day intervals up to a total daily dose of 100 or 150mg by the end of 2 weeks. Thereafter, the dose may be gradually increased over a period of several weeks to 200mg. Doses in excess of 200mg/day are not generally recommended for outpatients. However, in the treatment of severe cases of Obsessive Compulsive Disorder, daily doses of up to 250mg may be required.

Children and Adolescents: In children aged 10 to 17 years, an initial dose of 25mg/day is recommended. Dosage may be increased by 25mg increments, as tolerated, at 3 to 4 day intervals. By the end of 2 weeks, patients may be titrated up to 100 to 150mg/day or 3mg/kg, whichever is lower. Thereafter, the dose may be gradually increased to 200mg or 3mg/kg, whichever is lower. A total daily dose above 200mg should not be used in children or adolescents.

Elderly and Debilitated Patients: In general, lower dosages are recommended for these patients. Initially, 20 to 30mg daily in divided doses is suggested, with very gradual increments, depending on tolerance and response. Blood pressure and cardiac rhythm should be checked frequently, particularly in patients who have unstable cardiovascular function.

Maintenance Dosage (Adults, Children and Adolescents): Double blind extension phase studies of clomipramine therapy in patients with Obsessive Compulsive Disorder have followed patients for up to 52 weeks. Although placebo enrollment in these studies was inadequate to permit a controlled comparison, data do suggest that clomipramine therapy can be continued for up to a year without loss of efficacy.

Dosage adjustments may be made during maintenance therapy with the objective of maintaining the patient at the lowest effective dose. To minimize daytime sedation during maintenance treatment, the total daily dosage may be given as a single dose at bedtime. If symptoms recur, the dosage should be increased until the symptoms are controlled. Patients should be reassessed periodically to determine the need for continued treatment. To avoid withdrawal symptoms upon discontinuation of therapy, a gradual decrease in dosage and careful patient monitoring are recommended.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Since children may be more sensitive than adults to acute overdosage with tricyclic antidepressants, and since fatalities in children have been reported, effort should be made to avoid potential overdose particularly in this age group.

Symptoms of Overdosage: These may vary in severity depending on various factors such as the amount of drug absorbed, the interval between drug ingestion and start of treatment, and the age of the patient. Accidental ingestion in children should be regarded as serious and potentially fatal.

The first signs and symptoms of overdosage with tricyclic antidepressants generally take the form of severe anticholinergic reactions which set in about 1/2 to 2 hours after the drug has been taken.

Symptoms may include drowsiness, stupor, ataxia, vomiting, cyanosis, restlessness, agitation, delirium, severe perspiration, hyperactive reflexes, muscle rigidity, athetoid and choreiform movements, and convulsions. Hyperpyrexia, mydriasis, bowel and bladder paralysis, and respiratory depression may occur.

Hypotension and initial hypertension may occur. However, the usual finding is increasing hypotension which may eventually lead to shock. Serious cardiovascular disturbances are frequently present, including tachycardia, cardiac arrhythmias (flutter, atriofibrillation, ventricular premature beats and ventricular tachycardia) as well as impaired myocardial conduction, atrioventricular and intraventricular block, ECG abnormalities (such as widened QRS complexes and marked S-T shifts and signs of congestive heart failure) and cardiac arrest. Coma may ensue.

Treatment of Overdosage: Patients in whom overdosage is suspected should be admitted to hospital without delay. No specific antidote is available and treatment is essentially symptomatic and supportive. Gastric lavage or aspiration should be performed promptly and is recommended up to 12 hours or even more after the overdose, since the anticholinergic effect of the drug may delay gastric emptying. Administration of activated charcoal may help to reduce absorption of the drug. As clomipramine is largely protein bound, forced diuresis, peritoneal dialysis and hemodialysis are unlikely to be of value.

Treatment should be designed to insure maintenance of vital functions. An open airway should be maintained 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.
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.
Unexpected deaths attributed to cardiac arrhythmias have been reported several days following an apparent recovery from tricyclic antidepressant overdose. Correction of hypoxia and acidosis, if present, may be beneficial. Correction of metabolic acidosis and low potassium concentrations by means of bicarbonate i.v. and potassium substitution may also be effective for treatment of arrhythmias. If bradyarrhythmia or AV-block occur, consider temporary insertion of a cardiac pacemaker. 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.
External stimulation should be minimized to reduce the tendency to convulsions. If convulsions occur, anticonvulsants (preferably intravenous 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 ventilation should be instituted. Prompt control of convulsions is essential since they aggravate hypoxia and acidosis and may therapy precipitate cardiac arrhythmias and arrest.
Shock should be treated with supportive measures, such as intravenous fluids, plasma expanders and oxygen. The use of corticosteroids in shock is controversial and may be contraindicated in tricyclic antidepressant overdose. 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.

AVAILABILITY OF DOSAGE FORMS:
APO-CLOMIPRAMINE is available in 25mg tablet.
25mg tablet: Each round, pale-yellow, film-coated, biconvex tablets, engraved "25" on one side, plain on the other side, contains 25mg of clomipramine hydrochloride.
Available in HDPE bottles of 100 tablets.

Storage Conditions: Store below 30°C. Protect from heat and moisture.

Manufacturer: Apotex Inc, 150 Signet Drive, Weston (Toronto), Ontario, Canada, M9L 1T9.

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