PRODUCT MONOGRAPH

^{Pr}ANAFRANIL®
(Clomipramine Hydrochloride)

10 mg, 25 mg and 50 mg tablets

Antidepressant / Antiobsessional

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(clomipramine hydrochloride)
10 mg, 25 mg and 50 mg tablets

Therapeutic Classification
Antidepressant
Antiobsessional

Actions and Clinical Pharmacology

ANAFRANIL (clomipramine hydrochloride) is a tricyclic agent with both 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. Clomipramine thereby increases the concentration of transmitter monoamines at receptor sites. Clomipramine is presumed to influence depression and obsessive and compulsive behavior through its effects on serotonergic neurotransmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit serotonin reuptake is thought to be important. Clomipramine appears to have a mild sedative effect that may be helpful in alleviating the anxiety component often accompanying depression.

As with other tricyclic compounds, ANAFRANIL possesses anticholinergic properties which are responsible for certain 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 ANAFRANIL 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). Partial recovery occurs within 3 to 4 weeks as does 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.

ANAFRANIL is rapidly and completely absorbed after oral administration in humans. Peak plasma levels are usually reached two hours after dosage, but much individual variation occurs. The 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 75 mg, plasma concentrations of clomipramine ranged from 17 to 70 ng/mL , (mean = 35.7 ng/mL). The concentration of the active metabolite, desmethylclomipramine, was about twice as high. The binding of ANAFRANIL to serum proteins is very high at 96 to 97% and is practically concentration-independent within the therapeutic range. Clomipramine has a volume of distribution of approximately 12 L/kg.

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 ANAFRANIL than patients in younger age groups.

As expected, the metabolites of ANAFRANIL are quite similar to those of imipramine, all retaining the benzazepine structure. Two-thirds of ANAFRANIL is excreted as water-soluble conjugates in the urine and approximately one-third in the feces. After a 25 mg radiolabeled 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 and Clinical Use

ANAFRANIL (clomipramine hydrochloride) is indicated for the treatment of depression. ANAFRANIL also appears to have a mild sedative effect which may be helpful in alleviating the anxiety component often accompanying depression.

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

Contraindications

ANAFRANIL (clomipramine hydrochloride) is contraindicated in patients who have known or suspected hypersensitivity to the drug or its excipients, or have known or suspected hypersensitivity to tricyclic antidepressants belonging to the dibenzazepine group.

ANAFRANIL should not be given in conjunction with, or within fourteen days before or after treatment with a monoamine oxidase inhibitor **(see Drug Interactions).** The

concomitant treatment with selective, reversible MAO-A inhibitors, such as moclobemide, is also contraindicated. Hypertensive crises, hyperactivity, hyperpyrexia, spasticity, severe convulsions or coma, and death have been reported in patients receiving such combinations.

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

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

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

Warnings

Seizures

Tricyclic agents are known to lower the convulsive threshold and ANAFRANIL (clomipramine hydrochloride) 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, concomitant use of neuroleptics, alcoholism and withdrawal from alcohol, and concomitant use with other drugs that lower the seizure threshold. It appears that the occurrence of seizures is dose dependent. Therefore, the recommended total daily doses should not be exceeded **(see Dosage and Administration).**

Concurrent administration of electroconvulsive therapy and ANAFRANIL 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 ANAFRANIL 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, ANAFRANIL should be administered with extreme caution to patients with a history of cardiovascular disorders, especially those with cardiovascular insufficiency, conduction disorders (e.g., atrioventricular block grades I to III) or other arrhythmias, those with circulatory lability and elderly patients. ANAFRANIL 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 as well as in the elderly.

There may be a risk of QTc prolongation at supra-therapeutic doses or supra-therapeutic plasma concentrations of clomipramine, as occur in the case of co-medication with selective serotonin reuptake inhibitors (SSRIs) (see **Precautions).** It is established that hypokalemia is a risk-factor of QTc prolongation and Torsades de points. Therefore, hypokalemia should be treated before initiating treatment with ANAFRANIL and ANAFRANIL should be used with caution when combined with SSRIs or diuretics (see **Precautions).**

Use in Concomitant Illness

Caution should be observed in prescribing ANAFRANIL for hyperthyroid patients or for patients receiving thyroid medication. 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, ANAFRANIL should be used with caution in patients with increased intraocular pressure, narrow angle glaucoma or urinary retention, particularly in the presence of prostatic hypertrophy.

Tricyclic antidepressants may give rise to paralytic ileus, particularly in the elderly and in hospitalized patients. Therefore, appropriate measures should be taken if constipation occurs.

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

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

Use in Pregnancy

The safety of use in pregnant women has not been established. Therefore, ANAFRAN IL should not be administered to women of childbearing potential, or during pregnancy, unless, in the opinion of the physician, the expected benefit to the patient outweighs the potential risk to the fetus. Withdrawal symptoms including tremors, dyspnea, lethargy, colic, irritability, hypotonia/ hypertonia, convulsions and respiratory depression have been reported in neonates whose mothers received tricyclic antidepressants during the third trimester of pregnancy. To avoid such symptoms, ANAFRANIL should, if possible, be gradually withdrawn at least 7 weeks before the calculated date of confinement.

Use During Lactation

Since clomipramine passes into breast milk, ANAFRANIL should be gradually

withdrawn or the infant weaned if the patient is breast-feeding.

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 ANAFRANIL (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 ANAFRAN IL 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. Hyperactive or agitated patients may become over-stimulated. A reduction in dose or discontinuation of ANAFRANIL should be considered under these circumstances.

In predisposed and elderly patients, tricyclic antidepressants may, particularly at night, provoke pharmacogenic (delirious) psychoses that disappear within a few days of withdrawing the drug.

Since ANAFRANIL 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 ANAFRANIL. 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 when treating patients with heart disease, 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

ANAFRANIL has occasionally been associated with elevations in SGOT and SGPT of potential clinical significance (e.g., 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 ANAFRANIL 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, ANAFRANIL should be withdrawn.

Central Nervous System

More than 30 cases of hyperthermia have been recorded by nondomestic post-marketing surveillance systems. Most cases occurred when ANAFRANIL was used in combination with other drugs. When ANAFRANIL 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 ANAFRAN IL, 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 ANAFRANIL have not been systematically evaluated in controlled trials, they are well known with closely related tricyclic antidepressants. 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 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.

Lacrimation

Decreased lacrimation and accumulation of mucoid secretions, due to the anticholinergic properties of tricyclic antidepressants, may cause damage to the corneal epithelium in patients with contact lenses.

Endocrine Effects

As with certain other psychotherapeutic drugs, AN AFRAN IL 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 ANAFRANIL 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.

Use in Children

As ANAFRANIL 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 ANAFRANIL on childhood growth and development have not been determined.

Drug Interactions

Patients should be warned that, while taking ANAFRANIL, their responses to alcoholic beverages, other CN S depressants (e.g., barbiturates, benzodiazepines or general anesthetics) or anticholinergic agents (e.g., atropine, antihistamines, biperiden, levodopa) may be exaggerated.

When tricyclic antidepressants are given in combination 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 **(see Cardiovascular section under Warnings).**

Since ANAFRANIL may diminish or abolish the antihypertensive effects of

guanethidine, bethanidine, clonidine, reserpine, or alpha-methyldopa, patients requiring concomitant treatment for hypertension should be given antihypertensives of a different type (e.g., vasodilators, beta-blockers).

Comedication with diuretics may lead to hypokalemia, which should be treated prior to administration of ANAFRANIL.

ANAFRANIL may potentiate the cardiovascular effects of noradrenaline or adrenaline, amphetamine, as well as nasal drops and local anesthetics containing sympathomimetics (e.g., isoprenaline, ephedrine, phenylephrine).

Fluoxetine, fluvoxamine and other selective serotonin reuptake inhibitors (SSRIs) may increase the activity and plasma concentrations of tricyclic antidepressants, such as ANAFRANIL, with corresponding adverse effects. Comedication with SSRIs may lead to additive effects on the serotonergic system.

Caution should be exercised if ANAFRANIL is administered together with cimetidine or methylphenidate since these drugs have been shown to inhibit the metabolism of several tricyclic antidepressants. Clinically significant increases in plasma levels of ANAFRANIL may occur, necessitating a dosage reduction.

Substances which activate the hepatic mono-oxygenase enzyme system (e.g., barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives) may lower plasma concentrations of tricyclic antidepressants and so reduce their antidepressive effects. In addition, ANAFRANIL may increase plasma levels of phenytoin and carbamazepine, therefore, it may be necessary to adjust the dosage of these drugs.

ANAFRANIL 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 ANAFRANIL.

ANAFRANIL should be discontinued prior to elective surgery for as long as is clinically feasible, since little is known about the interaction with general anesthetics.

Concomitant treatment with neuroleptic agents (e.g., phenothiazines and butyrophenones) may result in increased plasma concentrations of ANAFRANIL a lowered convulsion threshold and seizures. Combination with thioridazine may produce cardiac arrhythmias. No such effects are known to occur in combination with diazepam but it might be necessary to lower the dosage of ANAFRANIL if administered concomitantly with alprazolam or disulfiram.

Tricyclic antidepressants may potentiate the anticoagulant effect of coumarin drugs by inhibiting hepatic metabolism of these drugs. Careful monitoring of plasma prothrombin is therefore advised.

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

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 tricyclic compounds, ANAFRANIL 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.

Adverse Reactions

The most commonly observed adverse events associated with the use of ANAFRANIL (clomipramine hydrochloride) 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.

If severe neurological or psychiatric reactions occur, ANAFRANIL should be withdrawn.

Elderly patients are particularly susceptible to anticholinergic, psychiatric, neurological and cardiovascular effects.

The following adverse reactions have also been reported with clomipramine or other tricyclic antidepressants.

(Frequency estimates: Frequent >10%; Occasional- >1-10%; Rare- >0.01-1%; Isolated cases <0.01%)

Neurological
Occasional: headache, paresthesia (numbness, tingling sensation, symptoms suggestive of peripheral neuropathy), delirium, muscle hypertonia, muscle weakness.

Rare: epileptic seizures.
Isolated cases: tinnitus, incoordination, ataxia, alterations in EEG patterns, extrapyramidal symptoms, speech disorders, weakness, hyperpyrexia.

Behavioral
Occasional: drowsiness, insomnia, confusional states with hallucinations (particularly in geriatric patients and patients suffering from Parkinson's disease), anxiety, agitation, restlessness, sleep disturbances, nightmares, aggravated depression, hypomania, mania, decrease in memory, feeling of unreality, depersonalization, yawning, disorientation.
Rare: activation of latent psychosis.
Isolated cases: aggressiveness.

Anticholinergic
Frequent: dry mouth and rarely associated sublingual adenitis, disturbances of visual accommodation, hot flushes.
Occasional: dilation of the urinary tract.
Isolated cases: mydriasis, glaucoma, paralytic ileus.

Cardiovascular
Frequent: hypotension, particularly orthostatic hypotension with associated vertigo, sinus tachycardia, ECG changes (including flattening or inversion of T wave, depressed S-T segments) in patients of normal cardiac status.
Occasional: arrhythmia, palpitation, syncope.
Isolated cases: hypertension, congestive heart failure, myocardial infarction, heart block, asystole, stroke, peripheral vasospastic reactions, disturbances in cardiac conduction (e.g., widening of QRS complex, PQ changes, bundle-branch block, prolonged QT interval, Torsade de points in hypokalemia).

Hematologic
Isolated cases: agranulocytosis, eosinophilia, leukopenia, purpura and thrombocytopenia may occur as an idiosyncratic response. One case of pancytopenia has been reported.

Gastrointestinal
Occasional: vomiting, abdominal cramps.
Rare: diarrhea, elevated transaminases.
Isolated cases: bitter taste, stomatitis, epigastric distress, black tongue, dysphagia, increased salivation, hepatitis with or without jaundice.

Respiratory
Isolated cases: bronchospasm

Endocrine
Isolated cases: gynecomastia in the male, breast enlargement and galactorrhea in the female, testicular swelling, elevation or depression of blood sugar levels, weight loss, inappropriate antidiuretic hormone (SIADH) secretion syndrome, increase in prolactin levels, menstrual irregularity.

Allergic or Toxic
Occasional: skin rash, urticaria,
Isolated cases: petechiae, itching, photosensitization (avoid excessive exposure to sunlight), edema (general or of face and tongue), drug fever, obstructive jaundice, nasal congestion, alopecia, allergic alveolitis (pneumonia) with or without eosinophilia, systemic anaphylactic/anaphylactoid reactions including hypotension.

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.

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.

Symptoms generally appear within 4 hours of ingestion and reach maximum severity after 24 hours. Owing to delayed absorption (increased anticholinergic effect due to overdose), long half-life and enterohepatic recycling of the drug, the patient may be at risk for up to 4-6 days.

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 lead eventually to shock. Serious cardiovascular disturbances are frequently present, including tachycardia, cardiac arrhythmias (flutter, atriofibrillation, premature ventricular 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, QTc prolongation), 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 ANAFRAN IL (clomipramine hydrochloride) is largely protein bound, forced diuresis, peritoneal dialysis and hemodialysis are unlikely to be of value.

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. 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 thereby 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.

Since it has been reported that physostigmine may cause severe bradycardia, asystole and seizures, its use is not recommended in cases of overdosage with ANAFRANIL.

Deaths by deliberate or accidental overdosage have occurred with this class of drugs. 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 ANAFRANIL (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 ANAFRANIL should be divided and administered with meals to reduce gastrointestinal side effects.

Owing to the long elimination half-lives of ANAFRANIL 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

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

Elderly and Debilitated Patients

In general, lower dosages are recommended for these patients. Initially, 20 to 30 mg 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

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

Children and Adolescents

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

Elderly and Debilitated Patients

In general, lower dosages are recommended for these patients. Initially, 20 to 30 mg 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)

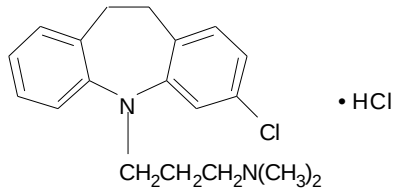
Double-blind extension phase studies of ANAFRANIL therapy in patients with Obsessive Compulsive Disorder have followed patients for up to 52 weeks. Although placebo enrollment in these studies was inadequate to permit a controlled comparison, data suggest that ANAFRANIL therapy can be continued for up 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.

Pharmaceutical Information Drug Substance

Drug Substance:



Clomipramine hydrochloride

Chemical Name:	3 -chloro-5 -[3 -(dimethylamino)propyl]- 10,11 -dihydro-5H-dibenz[b,f]azepine monohydrochloride
Molecular Formula:	$C_{19}H_{23}ClN_2 \cdot HCl$
Molecular Weight:	351.3
Description:	White to off-white crystalline powder
Solubility:	Freely soluble in water, methanol and methylene chloride; insoluble in ethyl ether and hexane
pK_a:	ca. 9.5
Melting Point:	191-194^{o}C

Composition

[Pr]ANAFRANIL (clomipramine hydrochloride) 10 mg Tablets

Each tablet contains the medicinal ingredient clomipramine hydrochloride (10 mg), and the non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

[Pr]ANAFRANIL (clomipramine hydrochloride) 25 mg Tablets

Each tablet contains the medicinal ingredient clomipramine hydrochloride (25 mg), and the non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

PrANAFRANIL (clomipramine hydrochloride) 50 mg Tablets

Each tablet contains the medicinal ingredient clomipramine hydrochloride (50 mg), and the non-medicinal ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Stability and Storage Recommendations

10 mg, 25 mg and 50 mg tablets:

Store at controlled room temperature between 15°C to 30°C in tight containers. Protect from light.

Keep out of reach of children.

Availability of Dosage Forms

PrANAFRANIL (clomipramine hydrochloride) 10 mg Tablets

Pale-yellow, triangular, biconvex, film-coated tablet. Engraved 10 on one side and CP on the other side.

PrANAFRANIL (clomipramine hydrochloride) 25 mg Tablets

Pale-yellow, round, biconvex, film-coated tablet. Engraved 25 on one side and CP on the other side.

PrANAFRANIL (clomipramine hydrochloride) 50 mg Tablets

White, round, biconvex, film-coated tablet. Engraved CP over 50 on one side, other side plain.
All strengths are available in bottles of 100 tablets.

Pharmacology

The pharmacological properties of clomipramine are similar to those of other tricyclic antidepressants, the main differences being quantitative rather than qualitative. The pharmacological profile of clomipramine includes reversal of reserpine and tetrabenazine effects, slight depressant effects on the central nervous system as manifested by behavioral, motor, electrocortical and visceral activity, anticholinergic and antihistaminic effects, and potentiation of adrenergic and serotonergic functions.

Clomipramine has a weak anticholinergic action demonstrated in laboratory animals by attenuation of the effect of acetylcholine on blood pressure and electrical stimulation of the vagus, and slight counteraction of pilocarpine-induced salivation. The ED_{50} for inhibition of tremorine-induced tremor in the mouse was 3.3 mg/kg. At 50 mg/kg, there was only incomplete inhibition of cholinergic intoxication due to tremorine (25 mg/kg I.P.). Clomipramine also has an antihistaminic effect demonstrated by inhibition of the fall in blood pressure following histamine injection in the cat.

As with other tricyclic agents, clomipramine produces a depression of spontaneous motor activity in laboratory animals (ED_{50} approximately 40 mg/kg I.P.). Clomipramine can also produce irritability and aggressiveness. Clomipramine was considerably less effective than amitriptyline in depressing locomotor activity and similar in effectiveness to imipramine. However, on the rotating cylinder and wire traction tests, clomipramine was almost inactive, while imipramine and amitriptyline were active at relatively high doses. As with imipramine, clomipramine demonstrated only slight cataleptic activity and potentiated slightly bulbocapnine catalepsy at 50 mg/kg. However, unlike imipramine and amitriptyline, it exhibited no anticataleptic activity in chlorpromazine-induced catalepsy at the same dosage. Clomipramine also exhibited antiserotonin action, but was about 2½ times less effective than chlorpromazine in protecting against serotonin contraction of the guinea pig ileum.

Clomipramine has a depressant effect on behavioral and electrocortical arousal. Unlike the neuroleptic agents, this effect is more pronounced on electrocortical activity than on behavior. Clomipramine is as active as amitriptyline in producing slow waves of high voltage in the EEG of rabbits and in blocking the reaction induced by stimulation of the mesencephalic reticular formation. In low doses (1.25 mg/kg), clomipramine increased the duration and amplitude of after-discharges evoked by stimulation of the amygdala and had no effect on the recruiting response induced by stimulation of the anteromedian thalamic nucleus. In cats, clomipramine was found to suppress 'fast sleep' with progressive recovery. Performance on several conditioned tests was not affected significantly by clomipramine, imipramine or amitriptyline at doses up to 20 mg/kg. At doses of 10 mg/kg, clomipramine and imipramine pressed responding during the acquisition period of a conditioned avoidance test. Clomipramine is significantly less effective in inhibiting aggressive behavior in fighting mice (ED_{50} 28 mg/kg) than imipramine (ED_{50} 10 mg/kg) or amitriptyline (ED_{50} 8 mg/kg). Clomipramine exerts a partial protective action against electroshock and pentylenetetrazol-induced tonic seizures in the rat with no effect in doses up to 50 mg/kg against strychnine convulsions in the mouse. The drug appears to be devoid of analgesic activity and produced only a slight depression of respiration in the non-anesthetized rabbit.

Antiarrhythmic effects of clomipramine in the dog were similar, but of shorter duration than those resulting from the quinidine-like action also observed with imipramine. As with imipramine, low doses (below 3 mg/kg I.V.), caused myocardial stimulation; cardiac depression occurred at higher doses. Clomipramine and amitriptyline were more active than imipramine in increasing the duration of barbiturate sleep. Clomipramine also

demonstrated anti-emetic activity in dogs at doses of 10 mg/kg S.C.

Clomipramine occupies an intermediate position in reversing reserpine and tetrabenazine-induced catalepsy and ptosis. The anticholinergic effect of the drug combined with the potentiation of catecholamines may account for counteraction of ptosis. As with other tricyclics, it potentiates sympathetic functions. Clomipramine was found to potentiate amphetamine hyperthermia at 10 mg/kg S.C. and to block amphetamine toxicity in crowded mice at 75 mg/kg. It also potentiates the effect of adrenaline and noradrenaline on the blood pressure and the nictitating membrane of the anesthetized cat and inhibits the pressure effect of tyramine.

In histochemical and biochemical studies, clomipramine appeared more potent than imipramine in blocking serotonin uptake and in preventing 4-methyl-µ-ethyl-meta-tyramine induced depletion of serotonin in rat brain. Clomipramine was also more effective than amphetamine hyperthermia at 10 mg/kg S.C. and to block amphetamine toxicity in crowded mice at 75 mg/kg. It also potentiates the effect of adrenaline and noradrenaline on the blood pressure and the nicitating membrane of the anesthesized cat and inhibits the pressure effect of tyramine.

In histochemical and biochemical studies, clomipramine appeared more potent than imipramine in blocking serotonin uptake and in preventing 4-methyl-µ-ethyl-meta-tyramine induced depletion of serotonin in rat brain. Clomipramine was also more effective than imipramine in potentiating the effects of serotonin, tryptophan and nialamide on the extensor hind limb reflex in rats. Its effect on noradrenergic neurons was less pronounced.

Pharmacokinetics

Clomipramine is rapidly absorbed after oral administration to rabbits and rats and distributes to several organs, particularly liver and lungs, without exceeding blood plasma concentrations of 0.1 mg%. While clomipramine and imipramine follow similar distribution patterns in the rat after oral administration, clomipramine remains in various organs of the rabbit longer than imipramine. In the rabbit, the pattern of the breakdown products of clomipramine differs from imipramine, clomipramine giving rise to fewer conjugated metabolites. Clomipramine and imipramine are both catabolized via demethylation, hydroxylation of the ring structure, N-oxidation and removal of the side chain. In rabbit urine, only about 2% of the amount administered was found (by chromatography) unchanged.

Toxicology

Acute Toxicity

The acute toxicity of clomipramine administered by oral, subcutaneous, intravenous and intraperitoneal routes has been studied in the mouse, rat, guinea pig, rabbit, and dog. Equal numbers of male and female animals were used and, in the case of mouse and rat, the number of animals per dose was ten. Clomipramine was given orally in a gum arabic suspension and, by the other routes, in aqueous solution. The animals were observed for a period of 8 days. The LD_{50} for each route of administration was determined by the method of Litchfield-Wilcoxon. Toxic manifestations included drowsiness, ventrolateral position, respiratory disturbances, ataxia and tonic-clonic convulsions.

Acute LD_{50} Values for Clomipramine

Species	Route	LD_{50} mg/kg
Mouse	P.O. S.C. I.V. I.P.	630 245 44 98
Rat	P.O. S.C. I.V. I.P.	1450 1000 26 102
Guinea Pig	P.O. I.V.	575 30
Rabbit	P.O. I.V.	700 17
Dog	I.V.	40

Chronic Toxicity

One-year toxicity studies were performed on rats and dogs.

Rat

Doses of 0, 12.5, 25, 50 and 100 mg/kg of clomipramine were administered daily to Sprague Dawley rats (thirty-five males and thirty-five females per group). There was an increase in spontaneous mortality in animals in the highest dosage group only. No clinical or pathological alterations were noticed, except that histological examination revealed disturbance of spermatogenesis in male rats at higher dosages.

Dog

Doses of 0, 12.5, 50 and 100 mg/kg of clomipramine were administered daily to pedigree Pembrokeshire Corgi dogs (four males and four females per group). Spontaneous death occurred only in the highest dosage group. Clinical and pathological studies, autopsy findings and measurement of organ weight gave no indication of a toxic effect of clomipramine, except that testicular damage was again apparent at higher doses.

One dog in the high dose group (100 mg/kg/day) showed no evidence of any mature spermatozoa. Spermatogenesis in this animal did not appear to extend beyond the secondary spermatocyte or spermatid stage. The histological picture did not suggest immaturity. In 2 of the intermediate dose level animals (50 mg/kg/day) there was evidence of bilateral inhibition of spermatogenesis associated with atrophy of some of the cells of the seminiferous tubules. In one dog (50 mg/kg/day), there is a possibility of some reduction in cellularity of some of the seminiferous tubules, although mature cell forms were present in this animal. The testes of low dose (12.5 mg/kg/day) and control animals were within normal limits and active spermatogenesis with mature cell forms was seen.

A 29-day intramuscular toxicity study was also performed in Beagle dogs. The dogs received doses of 0, 1 or 2 mg/kg clomipramine (two males and two females per group). No significant clinical or pathological changes were observed.

Teratogenicity

Tests of the teratogenic effect of clomipramine were performed on Swiss White Mice, Wistar Rats, and a strain of New Zealand White Rabbits, known to be susceptible to the teratogenic effect of thalidomide.

At doses of 0, 15, 30 and 60 mg/kg/day in rabbits and 0, 12.5, 25, 50 and 100 mg/kg/day in rats and mice, there was no evidence to suggest that clomipramine produced fetal abnormality. Doses of 12 and 24 mg/kg/day administered to male rats for two months and to female rats for 2 weeks before mating caused only a reduction of male activity.

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