PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrANAFRANIL®

Clomipramine Hydrochloride Tablets

Tablets, 10 mg, 25 mg and 50 mg, Oral1

ATC code: N06AA04

Antidepressant / Antiobsessional

Apotex Inc.
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Toronto, Ontario
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RECENT MAJOR LABEL CHANGES

N/A	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ANAFRANIL (clomipramine hydrochloride tablets) 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.
- 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.

1.1 Pediatrics

Pediatrics (<10 years): ANAFRANIL has not been studied in patients under 10 years of age and is not indicated for this age group.

Pediatrics (10-17 years): Limited information is available for the use of ANAFRANIL in children aged 10 to 17 years, therefore, ANAFRANIL is not recommended for use in this population (see 4.2 Recommended Dose and Dosage Adjustment, Children and Adolescents)

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 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.
- in conjunction with, or within fourteen days before or after treatment with a monoamine oxidase inhibitor (see 9.1 Serious Drug Interactions. Hypertensive crises, hyperactivity, hyperpyrexia, spasticity, severe convulsions or coma, and death have been reported in patients receiving such combinations.
- during the acute recovery phase following myocardial infarction and in the presence of acute congestive heart failure.
- in patients with existing liver or kidney damage, or in patients with a history of blood dyscrasias.

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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 (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Anticholinergic effects: 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 (see 7 WARNINGS AND PRECAUTIONS, General).

Endocrine and Metabolism: 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 (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Seizures: Tricyclic agents are known to lower the convulsive threshold and ANAFRANIL 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 (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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.

4.2 Recommended Dose and Dosage Adjustment

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

Limited information is available for the use of ANAFRANIL In children aged 10 to 17 years. For this age group, 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.

4.4 Administration

ANAFRANIL tablets should be swallowed whole orally. Do not break, chew or crush. Anafranil can be administered with or without food.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 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.

Signs and 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.

Signs and 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.

Signs and 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 ANAFRANIL (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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet 10 mg	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
oral	Tablet 25 mg	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
oral	Tablet 50 mg	carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

ANAFRANIL (clomipramine hydrochloride) 10 mg Tablets

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

ANAFRANIL (clomipramine hydrochloride) 25 mg Tablets

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

ANAFRANIL (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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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.

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). 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.

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.

Dental Effects

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

Dependence/Tolerance

Withdrawal Symptoms: A variety of withdrawal symptoms have been reported in association with abrupt discontinuation of ANAFRANIL, 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.

Driving and Operating Machinery

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.

Endocrine and Metabolism

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.

As with certain other psychotherapeutic drugs, ANAFRANIL 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.

Tricyclic antidepressants have been associated with porphyrinogenicity in susceptible patients.

Gastrointestinal

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.

Hematologic

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.

Hepatic/Biliary/Pancreatic

ANAFRANIL has occasionally been associated with elevations in SGOT (AST) and SGPT (ALT) 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.

Immune

In the event of an allergic skin reaction, ANAFRANIL should be withdrawn.

Neurologic

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 4.2 Recommended Dose and Dosage Adjustment).

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.

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.

Ophthalmologic

Anticholinergic effects: Because of its anticholinergic properties, ANAFRANIL should be used with caution in patients with increased intraocular pressure or narrow angle glaucoma.

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.

Psychiatric

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 ANAFRANIL 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.

Renal

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

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.

Because of its anticholinergic properties, ANAFRANIL should be used with caution in patients with urinary retention.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

  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.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of use in pregnant women has not been established. Therefore, ANAFRANIL 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.

7.1.2 Breast-feeding

Since clomipramine passes into breast milk, ANAFRANIL should be gradually withdrawn or the infant weaned if the patient is breast-feeding.

7.1.3 Pediatrics

As ANAFRANIL has not been studied in patients under 10 years of age, specific recommendations for use in this age group cannot be provided. Limited information is available for the use of ANAFRANIL in children aged 10 to 17 years, therefore, ANAFRANIL is not recommended for use in this population. The long-term effects of ANAFRANIL on childhood growth and development have not been determined.

7.1.4 Geriatrics

Evidence from clinical studies and experience suggests that use of ANAFRANIL in the geriatric population is associated with differences in safety or effectiveness.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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: Very common >10%; Common >1-10%; Rare >0.01-1%; Very rare <0.01%)

Neurological

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

Rare: epileptic seizures.

Very rare: tinnitus, incoordination, ataxia, alterations in EEG patterns, extrapyramidal symptoms, speech disorders, weakness, hyperpyrexia.

Behavioral

Common: 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.

Very rare: aggressiveness.

Anticholinergic

Very common: dry mouth and rarely associated sublingual adenitis, disturbances of visual accommodation, hot flushes.

Common: dilation of the urinary tract.

Very rare: mydriasis, glaucoma, paralytic ileus.

Cardiovascular

Very common: 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.

Common: arrhythmia, palpitation, syncope.

Very rare: 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

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

Gastrointestinal

Common: vomiting, abdominal cramps.

Rare: diarrhea, elevated transaminases.

Very rare: bitter taste, stomatitis, epigastric distress, black tongue, dysphagia, increased salivation, hepatitis with or without jaundice.

Respiratory

Very rare: bronchospasm

Endocrine

Very rare: 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

Common: skin rash, urticaria,

Very rare: 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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- 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 2 CONTRAINDICATIONS). The same caution should also be observed when administering a MAO-inhibitor after previous treatment with ANAFRANIL.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Alcoholic beverages, other CNS depressants or Anticholinergic agents	T	↑ANAFRANIL	Patients should be warned that, while taking ANAFRANIL, their responses to alcoholic beverages, other CNS depressants (e.g., barbiturates, benzodiazepines or general anesthetics) or anticholinergic agents (e.g., atropine, antihistamines, biperiden, levodopa) may be exaggerated.
Anticholinergics or Neuroleptics	T	Hyperexcitation states, delirium glaucoma	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.
Arrhythmic agents (quinidine type)	T		Tricyclic antidepressants should not be employed in combination with anti-arrhythmic agents of the quinidine type (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).
Antihypertensives	T	↓antihypertensive effects	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).

Diuretics	T	Hypokalemia	Comedication with diuretics may lead to hypokalemia, which should be treated prior to administration of ANAFRANIL.
Noradrenaline or adrenaline, amphetamine, sympathomimetics	T	↑cardiovascular effects	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)	T	↑ANAFRANIL	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.
Cimetidine or Methylphenidate	C	↑ANAFRANIL	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.
Barbiturates, carbamazepine, phenytoin, nicotine and oral contraceptives	T	↓ANAFRANIL	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.

General anesthetics	T		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.
Phenothiazines, butyrophenones, thioridazine and diazepam	T	↑ANAFRANIL	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.
Coumarin drugs	T	↑anticoagulant effect	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.
Estrogens	T	↑clomipramine	If administered concomitantly with estrogens, the dose of clomipramine should be reduced since steroid hormones inhibit the metabolism of clomipramine.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.2 Pharmacodynamics

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-induced 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-metatyramine 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.

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.

10.3 Pharmacokinetics

Absorption

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.

Distribution

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.

Metabolism

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

Elimination

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.

Animal 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 %. 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.

Special Populations and Conditions

- **Geriatrics:** Owing to the lower clearance of clomipramine in plasma, elderly patients require lower doses of ANAFRANIL than patients in younger age groups.
- **Pregnancy and Breast-feeding**: Clomipramine passes into breast milk, ANAFRANIL should be gradually withdrawn or the infant weaned if the patient is breast-feeding.

11 STORAGE, STABILITY AND DISPOSAL

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 and sight of children.

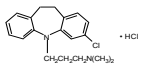
12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Clomipramine hydrochloride
Chemical name:	3 -chloro-5 -[3 -(dimethylamino)propyl]- 10,11 -dihydro-5H-dibenz[b,f]azepine monohydrochloride
Molecular formula and molecular mass:	$C_{19}H_{23}ClN_2 \bullet HCl$ and 351.3 g/mol
Structural formula:	
Physicochemical properties:	White to off-white crystalline powder freely soluble in water, methanol and methylene chloride, and insoluble in ethyl ether and hexane, with a pKa of ca. 9.5 and a melting oint of ca. 191-194°C

14 CLINICAL TRIALS

This information is not available for this drug product.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.	630
	S.C.	245
	I.V.	44
	I.P.	98
Rat	P.O.	1450
	S.C.	1000
	I.V.	26
	I.P.	102
Guinea Pig	P.O.	575
	I.V.	30
Rabbit	P.O.	700
	I.V.	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.

Other Chronic Toxicity Studies

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.

Carcinogenicity:

No animal studies have been performed to evaluate carcinogenic potential of ANAFRANIL.

Genotoxicity:

No animal studies have been performed to evaluate the mutagenic potential of ANAFRANIL.

Reproductive and Developmental Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrANAFRANIL

Clomipramine Hydrochloride Tablets

Read this carefully before you start taking **ANAFRANIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ANAFRANIL**

Serious Warnings and Precautions

Heart Problems: Serious, and sometimes fatal, heart problems have been reported in patients taking tricyclic antidepressants, like ANAFRANIL. ANAFRANIL can cause a rapid heartbeat, **heart rhythm problems**, **heart attack** or **stroke** that can lead to death. You should talk to your healthcare professional before you take ANAFRANIL if you have a history of heart problems, especially problems with your heart rhythm, or if you are elderly. See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Anticholinergic Effects: ANAFRANIL can have an effect on the way chemical signals are passed between cells. This can cause problems in certain areas of the body, including the eyes and urinary tract. If you have increased pressure in your eye, glaucoma, trouble passing urine or an enlarged prostate gland your healthcare professional will have to monitor you closely as ANAFRANIL can make these conditions worse.

Thyroid Problems: If you have problems with your thyroid gland (hyperthyroidism) or are taking thyroid medication your healthcare professional will need to monitor you closely. Heart rhythm problems have been seen in patients taking tricyclic antidepressants, like ANAFRANIL, together with thyroid medication.

Seizures: Tricyclic antidepressants, like ANAFRANIL, can make you more likely to have seizures or fits. This risk is higher is patients who have a history of seizures, have had brain damage, are taking other medicines, particularly antipsychotics (used to treat mental health problems) or are suffering from alcoholism or withdrawal from alcohol. Talk to your healthcare professional about your risk of having seizures while you are taking ANAFRANIL.

What is ANAFRANIL used for?

ANAFRANIL is used in adults to treat:

- depression.
- obsessions and compulsions in patients with obsessive compulsive disorder (OCD).

How does ANAFRANIL work?

ANAFRANIL belongs to a group of medicines called tricyclic antidepressants. It works by increasing the levels of two naturally occurring chemicals within the brain, noradrenaline and serotonin. This helps relieve the symptoms of depression and OCD.

What are the ingredients in ANAFRANIL?

Medicinal ingredients: Clomipramine hydrochloride

Non-medicinal ingredients: Carnauba wax, colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow (10 mg and 25mg tablets only), hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

ANAFRANIL comes in the following dosage forms:

Tablets: 10 mg, 25 mg and 50 mg

Do not use ANAFRANIL if:

- you are allergic to clomipramine or any of the non-medicinal ingredients in ANAFRANIL (see **What are the ingredients in ANAFRANIL?**)
- you are allergic to any other tricyclic antidepressants
- you are taking, or have taken within the last 14 days medicines for depression called monoamine oxidase inhibitors (MAOIs)
- you are taking medicines for depression called selective, reversible monoamine oxidase-A (MAO-A) inhibitors, such as moclobemide
- you have recently had a heart attack
- you are in heart failure
- you have any serious liver or kidney problems
- you have or have had a blood disorder
- you have glaucoma (increased eye pressure)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ANAFRANIL. Talk about any health conditions or problems you may have, including if you:

- have ever had suicidal thoughts
- suffer from epilepsy (fits) or seizures
- have suffered brain damage
- are going to have electric shock therapy (ECT)
- have heart problems
- are elderly
- have been told you have a low level of potassium in your blood (hypokalemia). Your healthcare professional will need to treat this before you start taking ANAFRANIL.
- have an overactive thyroid gland or are taking thyroid medication
- have increased pressure in your eye
- have trouble passing urine

- have an enlarged prostate gland
- have a tumour (cancer) of the adrenal gland (such as phaeochromocytoma or neuroblastoma)
- have schizophrenia or any other mental health problems
- have low blood pressure or other problems with your blood circulation
- have liver problems
- have kidney problems
- have dental problems
- wear contact lenses
- have or have had breast cancer
- are taking medicines for depression called selective-serotonin reuptake inhibitors (SSRIs)
- are taking diuretics or "water pills", used to treat high blood pressure
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption
- Because lactose is a non-medicinal ingredient in ANAFRANIL.

Other warnings you should know about:

Thoughts of suicide and worsening of your depression: Get immediate medical help if you have any thoughts of suicide or harming yourself while you are taking ANAFRANIL. Talk to your healthcare professional if you feel your depression is getting worse while you are taking ANAFRANIL.

Withdrawal symptoms: Do not stop taking ANAFRANIL without talking to your healthcare professional. You may need to lower your dose gradually and careful monitoring by your healthcare professional is required. Stopping ANAFRANIL suddenly may cause withdrawal symptoms including dizziness, nausea, vomiting, headache, malaise (general discomfort), sleep disturbance, increased body temperature, irritability and changes in behavior.

Pregnancy and Breastfeeding:

- You should not take ANAFRANIL if you are pregnant or thinking of becoming pregnant.
- Babies born to mothers that took medicines similar to ANAFRANIL while they were pregnant have experienced withdrawal symptoms after birth. Get immediate medical help for you baby if you took ANAFRANIL while you were pregnant and they have any of the following symptoms:
    - breathing problems, bluish skin
    - seizures or fits
    - body temperature changes
    - stiff or floppy muscles
    - jitteriness, irritability, lethargy
    - drowsiness
    - constant crying
- Do not breastfeeding while you are taking ANAFRANIL. ANAFRANIL passes into breastmilk.

Blood tests and monitoring: ANAFRANIL can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results. Your healthcare professional will also monitor your blood pressure and the health of your heart while you are taking ANAFRANIL.

Driving and using machines: ANAFRANIL can cause you to feel relaxed and sleepy, especially when you first start taking it. Give yourself time after taking ANAFRANIL to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

- Do **not** take ANAFRANIL if you are taking a monoamine oxidase inhibitor (MAOI), or if you have taken one in the last 14 days as this can cause serious side effects.

The following may interact with ANAFRANIL:

- Alcohol
- Medicines used to treat anxiety and help you sleep called barbiturates, and benzodiazepines, such as diazepam, alprazolam
- General anesthetics, used during surgery to put you to sleep
- Atropine, used as eye drops to dilate the pupil
- Antihistamines, used to treat allergies
- Medicines used to treat Parkinson's Disease, such as biperiden, levodopa
- Medicines used to treat heart rhythm problems, such as quinidine
- Medicines used to treat high blood pressure, such as guanethidine, bethanidine, clonidine, reserpine, alpha-methyldopa
- Diuretics or "water pills", used to treat high blood pressure
- Noradrenaline, used to treat low blood pressure
- Adrenaline, used to treat serious allergic reactions
- Nasal drops, used to relieve nasal congestion, and local anesthetics, used to numb the skin, such as isoprenaline, ephedrine, phenylephrine
- Other medicines used to treat depression called selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and fluvoxamine.
- Cimetidine, used to treat stomach ulcers or heartburn
- Medicines used to treat attention-deficit/hyperactivity disorder (ADHA), such as methylphenidate, amphetamine
- Medicines used to prevent seizures, such as carbamazepine, phenytoin
- Nicotine, this includes if you smoke or are using nicotine replacement therapy
- Medicines used to treat mental health problems, like schizophrenia, such as phenothiazines, butyrophenones
- Disulfiram, used to help you stop drinking alcohol
- Coumarin, and other similar medicines, used to thin the blood
- Medicines that contain estrogens, such as birth control pills or hormone replacement therapy

How to take ANAFRANIL:

- Always take ANAFRANIL exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Swallow ANAFRANIL tablets whole with water. Do not break, chew or crush the tablets.
- ANAFRANIL can be taken with or without food. To reduce stomach upset, take ANAFRANIL with food.
- Do not stop taking ANAFRANIL or change your dose without talking to your healthcare professional.

Usual dose:

Depression

Adults:

The recommended starting dose is 25 mg daily. Your healthcare professional may increase your dose by 25 mg increments up to 150 mg to 200 mg daily over a period of several weeks depending on your condition.

Elderly:

Lower doses are recommended for elderly patients. The recommended starting dose is 20 mg to 30 mg daily in divided doses.

Obsessive Compulsive Disorder

Adults:

The recommended starting dose is 25 mg daily. Your healthcare professional may increase your dose by 25 mg increments up to 100 mg to 200 mg daily by the end of 2 weeks depending on your condition.

Children and Adolescents (10 – 17 years of age):

The recommended starting dose is 25 mg daily. The dose may be increased by 25 mg increments, up to 100 mg to 150 mg per day or 3 mg/kg of their body weight, whichever is lower.

Elderly:

Lower doses are recommended for elderly patients. The recommended starting dose is 20 mg to 30 mg daily in divided doses.

Overdose:

You may have the following symptoms if you take more ANAFRANIL than you should: drowsiness, stupor (when you are unable to move but still conscious), irregular muscle contractions, vomiting, blue skin, restlessness, agitation, enhanced reflexes, muscle stiffness, twisting and writhing movements of the hands and feet, convulsions (fits).

Other signs include fever, abnormally dilated pupil, a decrease or absence of urine production, constipation, shortness of breath, changes in blood pressure, rapid or irregular heartbeat, changes in ECG, heart attack and coma.

If you think you, or a person you are caring for, have taken too much ANAFRANIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take ANAFRANIL, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Do not take two doses at the same time to make up for a missed dose.

What are possible side effects from using ANAFRANIL?

These are not all the possible side effects you may have when taking ANAFRANIL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache
- dry mouth
- constipation
- diarrhea
- nausea, vomiting
- indigestion
- stomach pain, stomach cramps
- change in appetite
- weight gain
- sleepiness, fatigue
- trouble sleeping, nightmares
- shaking
- muscle spasms, muscle weakness
- dizziness
- nervousness
- sweating
- hot flashes
- increased sensitivity of the skin to sunlight
- yawning
- vision changes, blurred vision
- change in libido
- inability to have or maintain an erection
- inability to ejaculate or delay in ejaculation
- hair loss

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Low blood pressure: dizziness, fainting, lightheadedness. May occur with you go from lying down or sitting to standing up.	✓		
COMMON			
Peripheral neuropathy: numbness or tingling sensation in the hands or feet		✓	
Changes in feelings and behaviors: confusion, hallucinations (seeing or hearing things that are not there), anxiety, agitation, restlessness, worsening of depression, thoughts of suicide, extremely elevated and excitable mood memory problems, feeling of unreality, changes in your perception of reality, disorientation, thoughts or speech that do not make sense			✓
Heart rhythm problems: irregular heartbeat, fast heartbeat, palpitations, shortness of breath, fainting, loss of consciousness			✓
RARE			
Seizures or fits: uncontrollable shaking with or without loss of consciousness			✓
VERY RARE			
Movement disorders: continuous muscle spasms and contractions, rigid muscles, restlessness, slowness of movement, tremor, jerky or irregular movements			✓
Heart attack: chest pain or discomfort, lightheadedness, shortness of breath, pain in the jaw, neck or back, pain in the arm or shoulder, cold sweat, nausea, vomiting			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Stroke: sudden numbness or weakness in the face, arm or leg, especially on one side of the body, confusion, trouble speaking, vision problems, weakness, dizziness, loss of coordination			✓
Liver problems: abdominal pain, nausea, vomiting, loss of appetite, yellowing of skin and eyes, dark urine, pale stool		✓	
Bronchospasm: coughing, tightness in the chest, wheezing, shortness of breath, difficulty breathing			✓
Hormonal changes: breast enlargement in men, breast enlargement and abnormal milk production in women, testicular swelling, irregular menstrual periods		✓	
Allergic reaction: rash, hives, tiny purple, red, or brown spots on the skin, itching, swelling of the face, lips and tongue, trouble swallowing or breathing, fever			✓
Withdrawal symptoms: nausea, vomiting, abdominal pain, diarrhea, sleeplessness, nervousness, anxiety, headache, generally feeling unwell, increased body temperature, irritability, behavioural changes		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature between 15°C to 30°C in a tight container.

Protect from light.

Keep out of reach and sight of children.

If you want more information about ANAFRANIL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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