Clomipramine, the 3-chloro analog of imipramine, is a dibenzazepine-derivative tricyclic antidepressant (TCA).
TCAs are structurally similar to phenothiazines. They contain a tricyclic ring system with an alkyl amine substituent on the central ring. In non-depressed individuals, clomipramine does not affect mood or arousal, but may cause sedation. In depressed individuals, clomipramine exerts a positive effect on mood. TCAs are potent inhibitors of serotonin and norepinephrine reuptake. Tertiary amine TCAs, such as clomipramine, are more potent inhibitors of serotonin reuptake than secondary amine TCAs, such as nortriptyline and desipramine. TCAs also down-regulate cerebral cortical β-adrenergic receptors and sensitize post-synaptic serotonergic receptors with chronic use. The antidepressant effects of TCAs are thought to be due to an overall increase in serotonergic neurotransmission. TCAs also block histamine-H1 receptors, α1-adrenergic receptors and muscarinic receptors, which accounts for their sedative, hypotensive and anticholinergic effects (e.g. blurred vision, dry mouth, constipation, urinary retention), respectively. See toxicity section below for a complete listing of side effects. Clomipramine may be used to treat obsessive-compulsive disorder and disorders with an obsessive-compulsive component (e.g. depression, schizophrenia, Tourette’s disorder). Unlabeled indications include panic disorder, chronic pain (e.g. central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, neuropathic pain), cataplexy and associated narcolepsy, autistic disorder, trichotillomania, onchophagia, stuttering, premature ejaculation, and premenstrual syndrome.

Clomipramine is rapidly absorbed from the gastrointestinal tract and demethylated in the liver to its primary active metabolite, desmethylclomipramine.
**Synonyms**
3-Chloroimipramine  
Chlorimipramine  
Clomipramina [INN-Spanish]  
Clomipramine HCL  
Clomipraminum [INN-Latin]  
Monochlorimipramine

**Categories**
Antidepressive Agents, Tricyclic  
Serotonin Uptake Inhibitors

**Taxonomy**

**Kingdom** : Organic

**Classes**
Dibenzazepines and Derivatives

**Substructures**
Dibenzazepines and Derivatives  
Aliphatic and Aryl Amines  
Benzene and Derivatives  
Aryl Halides  
Halobenzenes  
Heterocyclic compounds  
Aromatic compounds  
Anilines

**Pharmacology**
**Indication**: May be used to treat obsessive-compulsive disorder and disorders with an obsessive-compulsive component (e.g. depression, schizophrenia, Tourette’s disorder). Unlabeled indications include: depression, panic disorder, chronic pain (e.g. central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, neuropathic pain), cataplexy and associated narcolepsy (limited evidence), autistic disorder (limited evidence), trichotillomania (limited evidence), onchophagia (limited evidence), stuttering (limited evidence), premature ejaculation, and premenstrual syndrome.

**Pharmacodynamics**: Clomipramine, a tricyclic antidepressant, is the 3-chloro derivative of Imipramine. It was thought that tricyclic antidepressants work exclusively by inhibiting the re-uptake of the neurotransmitters norepinephrine and serotonin by nerve cells. However, this response occurs immediately, yet mood does not lift for around two weeks. It is now thought that changes occur in receptor sensitivity in the cerebral cortex and hippocampus. The hippocampus is part of the limbic system, a part of the brain involved in emotions. Presynaptic receptors are affected: α1 and β1 receptors are sensitized, α2 receptors are desensitized (leading to increased noradrenaline production). Tricyclics are also known as effective analgesics for different types of pain, especially neuropathic or neuralgic pain.

**Mechanism of action**: Clomipramine is a strong, but not completely selective serotonin reuptake inhibitor (SRI), as the active main metabolite desmethyclomipramine acts preferably as an inhibitor of noradrenaline reuptake. α1-receptor blockage and β-down-regulation have been noted and most likely play a
role in the short term effects of clomipramine. A blockade of sodium-channels and NDMA-receptors might, as with other tricyclics, account for its effect in chronic pain, in particular the neuropathic type.

**Absorption**: Well absorbed from the GI tract following oral administration. Bioavailability is approximately 50% orally due to extensive first-pass metabolism. Bioavailability is not affected by food. Peak plasma concentrations occur 2-6 hours following oral administration of a single 50 mg dose. Large interindividual variations in plasma concentrations occur, partly due to genetic differences in clomipramine metabolism. On average, steady state plasma concentrations are achieved in 1-2 weeks following multiple dose oral administration. Smoking appears to lower the steady-state plasma concentration of clomipramine, but not its active metabolite desmethylclomipramine.

**Volume of distribution**: Average ~ 17 L/kg (range: 9-25 L/kg)

**Protein binding**: Clomipramine is approximately 97-98% bound to plasma proteins, principally to albumin and possibly to α1-acid glycoprotein. Desmethylclomipramine is 97-99% bound to plasma proteins.

**Metabolism**: Extensively metabolized in the liver. The main active metabolite is desmethylclomipramine, which is formed by N-demethylation of clomipramine
via CYP2C19, 3A4 and 1A2. Other metabolites and their glucuronide conjugates are also produced. Other metabolites of clomipramine include 8-hydroxyclomipramine formed via 8-hydroxylation, 2-hydroxyclomipramine formed via 2-hydroxylation, and clomipramine N-oxide formed by N-oxidation. Desmethylclomipramine is further metabolized to 8-hydroxydesmethylclomipramine and didesmethylclomipramine, which are formed by 8-hydroxylation and N-demethylation, respectively. 8-Hydroxycloclomipramine and 8-hydroxydesmethylclomipramine are pharmacologically active; however, their clinical contribution remains unknown.

**Route of elimination**: Urine (51-60%) and feces via biliary elimination (24-32%)

**Half life**: Following oral administration of a single 150 mg dose of clomipramine, the average elimination half-life of clomipramine was 32 hours (range: 19-37 hours) and of desmethylclomipramine was 69 hours (range: 54-77 hours). Elimination half-life may vary substantially with different doses due to probably saturable kinetics (i.e. metabolism).

**Toxicity**: Signs and symptoms vary in severity depending upon factors such as the amount of drug absorbed, the age of the patient, and the time elapsed since drug ingestion. Critical manifestations of overdose include cardiac dysrhythmias, severe hypotension, convulsions, and CNS depression including coma. Changes in the electrocardiogram, particularly in QRS
axis or width, are clinically significant indicators of tricyclic toxicity. In U.S. clinical trials, 2 deaths occurred in 12 reported cases of acute overdosage with Anafranil either alone or in combination with other drugs. One death involved a patient suspected of ingesting a dose of 7000 mg. The second death involved a patient suspected of ingesting a dose of 5750 mg. Side effects include: sedation, hypotension, blurred vision, dry mouth, constipation, urinary retention, postural hypotension, tachycardia, hypertension, ECG changes, heart failure, impaired memory and delirium, and precipitation of hypomanic or manic episodes in bipolar depression. Withdrawal symptoms include gastrointestinal disturbances, anxiety, and insomnia.

Affected organisms: Humans and other mammals

Uses
Clomipramine is used to treat obsessive compulsive disorder (OCD). It helps decrease persistent/unwanted thoughts (obsessions), and it helps reduce the urge to perform repeated tasks (compulsions such as hand-washing, counting, checking) that interfere with daily living. This medication belongs to a class of medications called tricyclic antidepressants. It works by restoring the balance of certain natural substances (serotonin, among others) in the brain. OTHER This section contains uses of this drug that are not listed in the approved professional labeling for the drug but that may be prescribed by your health care professional. Use this drug for a condition that is listed in this section only if it has been so prescribed by your health care
professional. This medication has also been used to treat depression, panic attacks, and ongoing pain.

**How To Use?**

Read the Medication Guide available from your pharmacist. Consult your doctor or pharmacist if you have any questions. Take this medication by mouth with or without food as directed by your doctor. To lessen side effects such as stomach upset, clomipramine may be started at a low dose, given in several doses during the day with meals, and slowly increased as your body gets used to it. After you have reached the best dose for you, the total dose can be taken once daily, usually at bedtime to prevent daytime drowsiness or as directed by your doctor. Usually, the daily dose will not be more than 250 milligrams for adults and 200 milligrams for children and teenagers. Follow your doctor's instructions carefully. Do not take more or less medication or take it more frequently than prescribed. Your condition will not improve any faster and your risk of side effects such as seizures may be increased. Dosage is based on your medical condition and response to therapy. Avoid eating grapefruit or drinking grapefruit juice while being treated with this medication unless your doctor instructs you otherwise. Grapefruit can increase the amount of certain medications in your bloodstream. Consult your doctor or pharmacist for more details. Use this medication regularly in order to get the most benefit from it. Continue to take it even if you feel well. To help you remember, use it at the same time(s) each day. Do not suddenly stop taking this medication without consulting your doctor. Some conditions may become worse when the drug is abruptly stopped. You may
experience sweating, dizziness, nausea, vomiting, headache, or irritability if you suddenly stop taking this drug. Your dose may need to be gradually decreased. It may take 2 to 3 weeks or longer before the full effects of this medication are noticed. Inform your doctor if your condition persists or if it worsens.

**Why is this medication prescribed?**
Clomipramine is used to treat people with obsessive-compulsive disorder (a condition that causes repeated unwanted thoughts and the need to perform certain behaviors over and over). Clomipramine is in a group of medications called tricyclic antidepressants. It works by increasing the amount of serotonin, a natural substance in the brain that is needed to maintain mental balance.

**How should this medicine be used?**
Clomipramine comes as a capsule to take by mouth. At the beginning of treatment, clomipramine is usually taken three times a day with meals as the body adjusts to the medication. After several weeks of treatment, clomipramine is usually taken once a day at bedtime.

Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take clomipramine exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.

Your doctor may start you on a low dose of clomipramine and gradually increase your dose. It may take several weeks or longer for you to feel the full benefit of clomipramine. Continue to take clomipramine even if you feel well. Do not stop taking clomipramine without talking to your doctor. If you
suddenly stop taking clomipramine, you may experience withdrawal symptoms such as dizziness, nausea, vomiting, headache, weakness, sleep problems, fever, and irritability. Your doctor probably will decrease your dose gradually.

**What special precautions should I follow?**

Before taking clomipramine, tell your doctor and pharmacist if you are allergic to clomipramine, other tricyclic antidepressants such as amitriptyline (Elavil), amoxapine (Asendin), desipramine (Norpramin), doxepin (Adapin, Sinequan), imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil), and trimipramine (Surmontil); any other medications, or any of the inactive ingredients in clomipramine capsules. Ask your doctor or pharmacist for a list of the inactive ingredients.

tell your doctor if you are taking a monoamine oxidase (MAO) inhibitor such as isocarboxazid (Marplan), phenelzine (Nardil), selegiline (Eldepryl, Emsam, Zelapar), and tranylcypromine (Parnate), or if you have stopped taking an MAO inhibitor within the past 14 days. Your doctor will probably tell you not to take clomipramine. If you stop taking clomipramine, you should wait at least 14 days before you start to take an MAO inhibitor.

tell your doctor and pharmacist what prescription and nonprescription medications, vitamins, nutritional supplements and herbal products you are taking or plan to take. Be sure to mention any of the following: anticoagulants (‘blood thinners’) such as warfarin (Coumadin); benztropine (Cogentin); cimetidine (Tagamet); clonidine (Catapres); dicyclomine (Bentyl);
digoxin (Lanoxin); disulfiram; flecainide (Tambocor); guanethidine (Ismelin); haloperidol (Haldol); levodopa (Sinemet, Dopar); medications for nausea, dizziness, or mental illness; methylene blue; methylphenidate (Concerta, Metadate, Ritalin); oral contraceptives; phenobarbital; phenytoin; propafenone (Rythmol); quinidine; secobarbital (Seconal); sedatives; selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (Prozac, Sarafem), sertraline (Zoloft), and paroxetine (Paxil); tranquilizers; and trihexyphenidyl (Artane); and vitamins. Your doctor may need to change the doses of your medication or monitor you more carefully for side effects. Your doctor may tell you not to take clomipramine if you have stopped taking fluoxetine during the past 5 weeks.

tell your doctor if you have recently had a heart attack. Your doctor may tell you that you should not take clomipramine.

tell your doctor if you are being treated with electroshock therapy (procedure in which small electric shocks are administered to the brain to treat certain mental illnesses), if you drink or have ever drunk large amounts of alcohol and if you have or have ever had seizures, brain damage, problems with your urinary system or prostate (a male reproductive organ), glaucoma (an eye condition), irregular heartbeat, problems with your blood pressure, thyroid problems, or heart, kidney, or liver disease.

tell your doctor if you are pregnant, plan to become pregnant, or are breast-feeding. If you become pregnant while taking clomipramine, call your doctor.

if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking clomipramine.
you should know that this medication may make you
drowsy and may increase the risk that you will have a
seizure. Do not drive a car, operate machinery, swim, or
climb until you know how this medication affects you.
remember that alcohol can add to the drowsiness caused
by this medication.
tell your doctor if you use tobacco products. Cigarette
smoking may decrease the effectiveness of this
medication.

**What special dietary instructions should I follow?**

Unless your doctor tells you otherwise, continue your
usual diet.

**What should I do if I forget a dose?**

Take the missed dose as soon as you remember it.
However, if it is almost time for your next dose, skip the
missed dose and continue your regular dosing schedule.
Do not take a double dose to make up for a missed one.

**What side effects can this medication cause?**

Clomipramine may cause side effects. Tell your doctor if
any of these symptoms are severe or do not go away:
drowsiness
dry mouth
nausea
vomiting
diarrhea
constipation
nervousness
decreased sexual ability
decreased memory or concentration
headache
stuffy nose
change in appetite or weight
fast, irregular, or pounding heartbeat
difficulty urinating or loss of bladder control
believing things that are not true
hallucinations (seeing things or hearing voices that do not exist)
eye pain
shakiness
difficulty breathing or fast breathing
severe muscle stiffness
unusual tiredness or weakness
sore throat, fever, and other signs of infection

**What storage conditions are needed for this medicine?**

Keep this medication in the container it came in, tightly closed, and out of reach of children. Store it at room temperature and away from excess heat and moisture (not in the bathroom). Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

**Symptoms of overdose may include**

seizures
coma (loss of consciousness for a period of time)
drowsiness
restlessness
loss of coordination
sweating
stiff muscles
unusual movements
fast heartbeat
slowed breathing
blue discoloration of the skin
fever
widened pupils (dark circles in the center of the eye)
decreased urination

**What other information should I know?**

Keep all appointments with your doctor.
Do not let anyone else take your medication. Ask your pharmacist any questions you have about refilling your prescription.

It is important for you to keep a written list of all of the prescription and nonprescription (over-the-counter) medicines you are taking, as well as any products such as vitamins, minerals, or other dietary supplements. You should bring this list with you each time you visit a doctor or if you are admitted to a hospital. It is also important information to carry with you in case of emergencies.

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Clomipramine

CAS Number: 303-49-1
Molecular Weight: 314.85 g/mol
Molecular Formula: C_{19}H_{22}ClN_{2}
Systematic (IUPAC): (3-{5-chloro-2-azatricyclo[9.4.0.0^{3,8}]}pentadeca-1(11),3(8),4,6,12,14-hexaen-2-yl)propyl)dimethylamine
Clomipramine

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Molecular Weight: 314.85 g/mol
Molecular Formula: C₁₉H₂₃ClN₂
Systematic (IUPAC): (3α-[5-chloro-2-azatricyclo[9.4.0.0^3,8]]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-yl)propyl)dimethylamine