Amitriptyline

CAS Number : 50-48-6
Molecular Weight : 277.40 g/mol
Molecular Formula : C20H23N
Systematic (IUPAC) : dimethyl({3-[(2Z)-tricyclo[9.4.0.0^{3,8}]pentadeca-1(11),3(8),4,6,12,14-hexaen-2-ylidene]propyl})amine

Type : small molecule

Description : Amitriptyline hydrochloride is a dibenzocycloheptene-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, amitriptyline does not affect mood or arousal, but may cause sedation. In depressed
individuals, amitriptyline exerts a positive effect on mood. TCAs are potent inhibitors of serotonin and norepinephrine reuptake. Tertiary amine TCAs, such as amitriptyline, are more potent inhibitors of serotonin reuptake than secondary amine TCAs, such as nortriptyline. 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. Amitriptyline may be used to treat depression, chronic pain (unlabeled use), irritable bowel syndrome (unlabeled use), diabetic neuropathy (unlabeled use), post-traumatic stress disorder (unlabeled use), and for migraine prophylaxis (unlabeled use).

**Categories:**
Adrenergic Uptake Inhibitors
Analgesics, Non-Narcotic
Antidepressive Agents, Tricyclic

**Taxonomy**
**Kingdom:** Organic

**Classes:** Dibenzocycloheptenes

**Substructures**
Alkanes and Alkenes
Phenylpropenes
Benzene and Derivatives
**Pharmacology**

**Indication**: For the treatment of depression, chronic pain, irritable bowel syndrome, sleep disorders, diabetic neuropathy, agitation and insomnia, and migraine prophylaxis.

**Pharmacodynamics**: Amitriptyline, a tertiary amine tricyclic antidepressant, is structurally related to both the skeletal muscle relaxant cyclobenzaprine and the thioxanthene antipsychotics such as thiothixene. It is extremely sedating, and thus improvement of sleep patterns can be the first benefit of treatment. Amitriptyline exhibits strong anticholinergic activity, cardiovascular effects including orthostatic hypotension, changes in heart rhythm and conduction, and a lowering of the seizure threshold. As with other antidepressants, several weeks of therapy may be required in order to realize the full clinical benefit of amitriptyline. Although not a labelled indication, amitriptyline is widely used in the management of chronic nonmalignant pain (e.g., post-herpetic neuralgia, fibromyalgia).

**Mechanism of action**: Amitriptyline is metabolized to nortriptyline which inhibits the reuptake of norepinephrine and serotonin almost equally. Amitriptyline inhibits the membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Pharmacologically this action may potentiate or prolong neuronal activity since reuptake of these biogenic
amines is important physiologically in terminating transmitting activity. This interference with the reuptake of norepinephrine and/or serotonin is believed by some to underlie the antidepressant activity of amitriptyline.

**Absorption**: Rapidly and well absorbed following oral administration (bioavailability is 30-60% due to first pass metabolism). Peak plasma concentrations occur 2-12 hours following oral or intramuscular administration.

**Protein binding**: Very highly protein bound (90% or more) in plasma and tissues.

**Metabolism**: Exclusively hepatic, with first pass effect. Amitriptyline is demethylated in the liver to its primary active metabolite, nortriptyline.

**Route of elimination**: Virtually the entire dose is excreted as glucuronide or sulfate conjugate of metabolites, with little unchanged drug appearing in the urine. 25-50% of a single orally administered dose is excreted in urine as inactive metabolites within 24 hours. Small amounts are excreted in feces via biliary elimination.

**Half life**: 10 to 50 hours, with an average of 15 hours.

**Toxicity**: LD50=350 mg/kg (in mice). Symptoms of overdose include abnormally low blood pressure, confusion, convulsions, dilated pupils and other eye problems, disturbed concentration, drowsiness, hallucinations, impaired heart function, rapid or irregular heartbeat, reduced body temperature, stupor, and unresponsiveness or coma. 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

**Drug class And Mechanisms**
Amitriptyline is an antidepressant drug. Depression is an all-pervasive sense of sadness and gloom. It is believed that in some patients with depression, abnormal levels of neurotransmitters (chemicals that nerves use to communicate with each other) may relate to their depression. Amitriptyline elevates mood by raising the level of neurotransmitters in nerves of the brain. Amitriptyline was approved by the FDA in May 1983.

**Dosing**
Amitriptyline may be taken with or without food. The recommended adult dose is 40-150 mg daily in divided doses. The lowest effective dose should be used.

**Drug interactions**
Amitriptyline should not be used with monoamine oxidase inhibiting drugs. High fever, convulsions and even death can occur when these two drugs are used together. Epinephrine should not be used with amitriptyline, since together they can cause severe high blood pressure. Alcohol blocks the antidepressant action of amitriptyline but increases its sedative effect. Cimetidine (Tagamet) can increase blood levels of amitriptyline and its side effects.

**Why is this medication prescribed?**
Amitriptyline is used to treat symptoms of depression. Amitriptyline is in a class of medications called tricyclic antidepressants. It works by increasing the amounts of
certain natural substances in the brain that are needed to maintain mental balance.

**How should this medicine be used?**
Amitriptyline comes as a tablet to take by mouth. It is usually taken one to four times a day. Take amitriptyline at around the same time(s) every day. Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand. Take amitriptyline exactly as directed. Do not take more or less of it or take it more often than prescribed by your doctor.

Your doctor will probably start you on a low dose of amitriptyline and gradually increase your dose. It may take a few weeks or longer before you feel the full benefit of amitriptyline. Continue to take amitriptyline even if you feel well. Do not stop taking amitriptyline without talking to your doctor. If you suddenly stop taking amitriptyline, you may experience withdrawal symptoms such as nausea, headache, and lack of energy. Your doctor will probably decrease your dose gradually.

**Other uses for this medicine**
Amitriptyline is also used to treat eating disorders, post-herpetic neuralgia (the burning, stabbing pains, or aches that may last for months or years after a shingles infection), and to prevent migraine headaches. Talk to your doctor about the possible risks of using this medication for your condition.

This medication may be prescribed for other uses; ask your doctor or pharmacist for more information.

**What special precautions should I follow?**
Before taking amitriptyline, tell your doctor and pharmacist if you are allergic to amitriptyline or any other medications.
tell your doctor if you are taking cisapride (Propulsid) (not available in the U.S.) or monoamine oxidase (MAO) inhibitors such as isocarboxazid (Marplan), phenelzine (Nardil), selegiline (Eldepryl, Emsam, Zelapar), and tranylcypromine (Parnate), or if you have taken an MAO inhibitor during the past 14 days. Your doctor will probably tell you that you should not take amitriptyline.
tell your doctor and pharmacist what other prescription and nonprescription medications, vitamins, nutritional supplements, and herbal products you are taking. Be sure to mention any of the following: antihistamines, cimetidine (Tagamet); diet pills; disulfiram (Antabuse); guanethidine (Ismelin); ipratropium (Atrovent); quinidine (Quinidex); medications for irregular heartbeats such as flecainide (Tambocor) and propafenone (Rythmol); medications for anxiety, asthma, colds, irritable bowel disease, mental illness, nausea, Parkinson's disease, seizures, ulcers, or urinary problems; other antidepressants; phenobarbital (Bellatal, Solfoton); sedatives; selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa), fluoxetine (Prozac, Sarafem), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft); sleeping pills; thyroid medications; and tranquilizers. Tell your doctor or pharmacist if you have stopped taking fluoxetine (Prozac, Sarafem) in the past 5 weeks. Your doctor may need to change the doses of your medications or monitor you carefully for side effects.
tell your doctor if you have recently had a heart attack. Your doctor will probably tell you not to take amitriptyline.
tell your doctor if you drink large amounts of alcohol and if you have or have ever had glaucoma (an eye condition); an enlarged prostate (a male reproductive
gland); difficulty urinating; seizures; an overactive thyroid gland (hyperthyroidism); diabetes; schizophrenia (a mental illness that causes disturbed or unusual thinking, loss of interest in life, and strong or inappropriate emotions); or liver, kidney, or heart disease.

tell your doctor if you are pregnant or plan to become pregnant. If you become pregnant while taking amitriptyline, call your doctor. Do not breast-feed while you are taking amitriptyline.
talk to your doctor about the risks and benefits of taking this medication if you are 65 years of age or older. Older adults should not usually take amitriptyline because it is not as safe or effective as other medication(s) that can be used to treat the same condition.

if you are having surgery, including dental surgery, tell the doctor or dentist that you are taking amitriptyline.
you should know that amitriptyline may make you drowsy. Do not drive a car or operate machinery until you know how this medication affects you.
remember that alcohol can add to the drowsiness caused by this medication.

What special dietary instructions should I follow?
Unless your doctor tells you otherwise, continue your normal 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 the 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?
Amitriptyline may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away:

- nausea
- vomiting
- drowsiness
- weakness or tiredness
- nightmares
- headaches
- dry mouth
- constipation
- difficulty urinating
- blurred vision
- pain, burning, or tingling in the hands or feet
- changes in sex drive or ability
- excessive sweating
- changes in appetite or weight
- confusion
- unsteadiness
- dizziness or faintness
- weakness or numbness of an arm or a leg
- crushing chest pain
- rapid, pounding, or irregular heartbeat
- severe skin rash or hives
- swelling of the face and tongue
- yellowing of the skin or eyes
- jaw, neck, and back muscle spasms
- uncontrollable shaking of a part of the body
- fainting
- unusual bleeding or bruising
- seizures
- hallucinating (seeing things or hearing voices that do not exist)
Amitriptyline may cause other side effects. Call your doctor if you have any unusual problems while taking this medication.

**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**
- irregular heartbeat
- seizures
- coma (loss of consciousness for a period of time)
- confusion
- problems concentrating
- hallucinating (seeing things or hearing voices that do not exist)
- agitation
- drowsiness
- rigid muscles
- vomiting
- fever
- cold body temperature

**What other information should I know?**
Keep all appointments with your doctor and the laboratory. Your doctor may order certain lab tests to check your body's response to amitriptyline. 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.

apollo | asia Division

APOLLO Pharmaceuticals
API Manufacturers INDIA [P] Ltd.|asia Division

Mr.Vipin Saxena|CEO
Cellular:+91-98-21050033
Cellular:+91-98-20150033
Direct :+91-22-65785588
FAX :+91-22-42950001

Wireline Purchase HELPDESK:
+91-22-65050001
+91-22-65650001

Wireline Sales HELPDESK:
+91-22-65500009
+91-22-65050009

Wireless 24x7 HELPDESK:
+9191-46-951951
+9191-46-950950
Blackberry Pin :
32E6500D | 32E65010 | 28415C58

Email:
apollo@Hotmail.Co.in
Sales@apollopharma.in
Export@apollopharma.in
purchase@apollopharma.in

www.apolloworld.in
www.apollopharma.in
www.apollopharmaceuticals.Net

Chat:
MSN Hotmail:VipinrSaxena
Skype NAME:VipinrSaxena
Rocketmail:VipinrSaxena
Google mail:VipinrSaxena
BlackBerry:28415C58

Regd. Office :-
1104, Maker Chamber V,
Nariman Point
Mumbai, INDIA
Pin:400021

Industrial Office
D-62, OIC India
Oshiwara Industrial Centre,
New Link Road,
Goregoan West,
Mumbai, INDIA
Pin:400104

Manufacturing Unit Address:
Plot No. 117A,
Village: Chamble
Near MonaTona Limited.Wada,
Maharashtra,
PIN : 421312 | INDIA

Email:
apollo@Hotmail.Co.in
Sales@apolropharma.in
Export@apolropharma.in
purchase@apolropharma.in

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