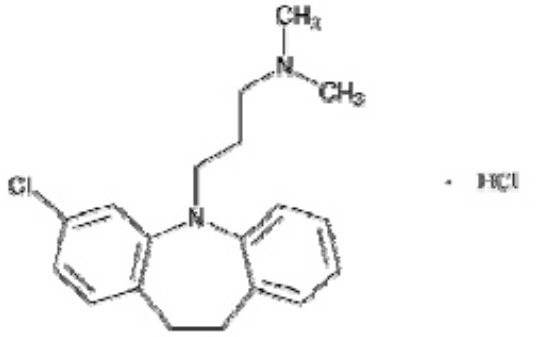
Taj Pharmaceuticals Ltd.

Clomipramine Hcl

CAS No. : 17321-77-6

Synonym:
Anafranil hydrochloride,3-Chloro-10,11-dihydro-N,N-dimethyl-5H-dibenz[b,f]azepine-5-propanamine hydrochloride
CAS Number: 17321-77-6
Linear Formula: C19H23ClN2 HCl
Molecular Weight: 351.31
EC Number: 241-344-3
MDL number: MFCD00069234



$C_{19}H_{23}ClN_2 \bullet HCl$ MW = 351.31

Description
Biochem/physiol Actions Tricyclic antidepressant; inhibits serotonin and norepinephrine transporters.

Properties
Assay: 98% (HPLC)
Form: Powder
Color: White to off-white
Solubility: H2O: soluble25 mg/mL 0.1 M HCl: soluble
Gene Information: Research your gene in Your Favorite Gene powered by Ingenuity human ... HTR1A(3350), HTR1B(3351), HTR1D(3352), HTR1E(3354), HTR1F(3355), HTR2A(3356), HTR2B(3357), HTR2C(3358), HTR3A(3359), HTR3B(9177), HTR3C(170572), HTR3D(200909), HTR3E(285242), HTR4(3360), HTR5A(3361), HTR5B(645694), HTR6(3362), HTR7(3363)

DOSAGE
Initial doses are usually 25 mg 2 or 3 times daily or 75 mg once daily in slow released form. The dose may be increased in regular intervals (the usual dose per day is 100 to 225 mg). Doses up to 300 mg may be used, but these are associated with an increased risk of seizures. This medication may be taken with food to prevent stomach upset.

In hospitalized patients initial intramuscular injections and very slow intravenous infusions can be used, but the risk of hypotension and seizures may be increased with parenteral drug use. The advantage is that the onset of action may be faster.

Usually, clomipramine needs some weeks to reach its maximum effects and needs to be given as longterm treatment, sometimes for life (narcolepsy). Sometimes, in patients with narcolepsy the full effect of clomipramine is not sufficient. In these cases treatment with clomipramine should be terminated gradually and a commonly used central stimulant (e.g. modafinil, methylphenidate or methamphetamine) tried instead.

Clomipramine is not able to elevate the mood of non-depressive persons and any unindicated use may be dangerous.

Dosage should be individualized according to the requirements of each patient. Treatment should be initiated at the lowest recommended dose and increased gradually, noting carefully the clinical response and any evidence of intolerance. During the initial dose titration phase, the total daily dose of clomipramine should be divided and served with meals to reduce gastrointestinal side-effects.

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

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

Withdrawal Symptoms:
Abrupt cessation of treatment with tricyclic antidepressants after prolonged administration may occasionally

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

INTERACTION
Tricyclic antidepressants, such as clomipramine, may interact with many other drugs. Patients should inform their physicians about all other drugs they are taking before starting treatment.

Clomipramine may intensify the effects of other drugs that act on serotonin levels, possibly producing serotonin syndrome, a rare but dangerous condition with fever, sweating, tremors, and changes in mental state. Drugs that may interact this way include other antidepressants, especially selective serotonin re-uptake inhibitor (SSRI) drugs and monoamine oxidase (MAO) inhibitors. These drugs should not be taken within two weeks of taking clomipramine. Other drugs to avoid include lithium, alprazolam(Xanax), fenfluramine (Pondimin), amphetamine, dextromethorphan (used in cough suppressants), meperidine (Demerol), and tramadol (Ultram).

Tricyclic drugs may intensify the effects of other drugs causing sedation, including alcohol, barbiturates, narcotic pain medications, minor tranquilizers, and antihistamines. Tricyclics may cause excessive reductions of blood pressure in patients taking blood pressure medicine, especially on arising or standing up. Conversely, these drugs may interfere with the pressure-reducing effects of certain other blood pressure medicines and may necessitate an adjustment in dosage. Tricyclics may interact with thyroid medications to produce abnormalities of heart rhythm. Concurrent use of tricyclic antidepressants with other psychiatric medicines may result in intensification of certain side effects.

Certain drugs may interfere with the elimination of tricyclic antidepressants from the body, causing higher blood levels and increased side effects. This effect may occur with cimetidine (Tagamet), other antidepressants, methylphenidate(Ritalin, Concerta), and some antipsychotic medications.

PHARMALOGY
Clomipramine is the 3-chloro derivative of imipramine. Clomipramine is a strong, but not completely selective serotonin reuptake inhibitor (SSRI), as the primary active metabolite desmethylclomipramine acts preferably as norepinephrine reuptake inhibitor. Other hydroxy-metabolites are also active. a1 receptor blockage and β receptor downregulation as well as postsynaptic antagonism on histamine H1 receptors and dopamine receptors have been noted.

As with other tricyclics, downregulation of NMDA receptors may also account for its effects.

Clomipramine has the disadvantage of a higher incidence of seizures than seen with other tricyclic antidepressants (up to a dose of 250 mg daily in 0,5 %, more than 300 mg in 2 %).

Clomipramine 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, thereby increasing the concentration of transmitter monoamines at receptor sites. Clomipramine is presumed to influence depression and obsessive and compulsive behaviour through its effects on serotonergic neurotransmission.

The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit serotonin reuptake is thought to be important. Clomipramine appears to have a mild sedative effect which may be helpful in alleviating the anxiety component often accompanying depression.

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

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

Absorption is rapid and complete after oral administration in man. Plasma levels usually peak 2 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.

Binding to serum proteins at 96 to 97% is very high and is practically concentration-independent within the therapeutic range. Clomipramine has a volume of distribution of approximately 12 L/kg bodyweight.

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

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

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

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