Triptolol
Tablets

1. **Generic Name**

   Amitriptyline Hydrochloride + Propranolol Hydrochloride

2. **Qualitative and Quantitative Composition**

Amitriptyline Hydrochloride IP 10mg

Propranolol Hydrochloride IP 40mg

3. **Dosage form and strength**

Oral tablets are available in the strength of Amitriptyline 10mg, Propranolol 40mg

4. **Clinical particulars**

4.1 Therapeutic indication

Migraine with co-morbid conditions like Insomnia, Neuralgic Pain, Hypertension, Anxiety

4.2 Posology and method of administration

Recommended oral dose of Triptolol is once a day at bedtime.

4.3 Contraindication

The use of Triptolol Tablet is contraindicated in patients with:

- Known hypersensitivity to any ingredient in this product.
- On prescription of MAO inhibiting compound.
- Severe hepatic dysfunction.
- history of urinary retention – BPH
- cardiogenic Shock, sinus Bradycardia and greater than first degree block, bronchial Asthma

4.4 Special warnings and precautions for use

- Triptolol Tablet should be used with caution in patients with renal or hepatic dysfunction and cardiovascular problems.
- Caution is advised in untreated angle-closure glaucoma, phaeochromocytoma, and hyperthyroidism.
- Avoid consuming alcohol when taking the Triptolol as it may cause excessive drowsiness.

4.5 Drug interactions

- Amitriptyline

Most common (but not the only) medications used that have the potential for major drug interactions when combined with amitriptyline are duloxetine, citalopram, fluoxetine, topiramate, tramadol, sertraline, cyclobenzaprine and trazodone

Most common (but not the only) medications used that have the potential for moderate drug interactions when combined with amitriptyline are pregabalin, levothyroxine, alprazolam.

Medications that may interact with amitriptyline are:

- drugs taken for an irregular heartbeat, as well as other heart medications
- disulfiram, a medication used to help people with alcoholism avoid from drinking
- atropine, phenobarbital, and similar drugs
- blood thinners, such as Warfarin
- bromocriptine
- cimetidine, a heartburn/ulcer medication, as well as metoclopramide
- high blood pressure clonidine, as well as labetalol
- delavirdine, as well as other drugs used to treat HIV infection
- diphenoxylate, a diarrhea medication
- the chemotherapy drugs imatinib and procarbazine
- Parkinson's medications, such as levodopa
- Alzheimer's medications, such as donepezil, galantamine, and tacrine
- epilepsy and seizure medication

- some antibiotics
- thyroid hormones, such as levothyroxine
- SSRI medications
- Propranolol

Antiarrhythmics: Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.

Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with β-blockers such as propranolol.

Digitalis Glycosides: Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Calcium Channel Blockers Caution should be exercised when patients receiving a beta blocker are administered a calciumchannel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

4.6 Use in special population

- Paediatric: Not safe in children.
- Geriatric: Adults over the age of 65 may be at greater risk for the side-effects.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: US FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Triptolol is known.

4.8 Undesirable effects

Weight Gain, Dry mouth, blurred vision, increased intraocular pressure, constipation, Sedation and Drowsiness, Hypotension, syncope, tachycardia, palpitations, myocardial infarction, and arrhythmias

4.9 Overdose

There is limited experience of overdose with Triptolol Tablets. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

Amitriptyline inhibits the membrane pump mechanism responsible for uptake of serotonin in serotonergic neurons. Increased Serotonin levels decreases electrical activity in the brain. This effect is the mechanism known to be involved in the migraine prophylaxis.

Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. Membrane Stabilizing Action on cranial blood vessel contributes to migraine treatment.

The combination of Amitriptyline and propranolol in Triptolol Tablets helps to relieve migraine.

5.2 Pharmacodynamic properties

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 non-malignant pain

Propranolol, the prototype of the beta-adrenergic receptor antagonists, is a competitive, nonselective beta-blocker similar to nadolol without intrinsic sympathomimetic activity. Propanolol is a racemic compound; the l-isomer is responsible for adrenergic blocking activity.

5.3 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 6 hours after oral doses. Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and N-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form. Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours.

Propranolol is almost completely absorbed from the gastrointestinal tract, but is subject to considerable hepatic-tissue binding and first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after an oral dose. Plasma concentrations vary greatly between individuals. Propranolol has high lipid solubility. It crosses the blood-brain barrier and the placenta, and is distributed into breast milk. Propranolol is about 90% bound to plasma proteins. It is metabolised in the liver and at least one of its metabolites (4-hydroxypropranolol) is considered to be active, but the contribution of metabolites to its overall activity is uncertain. The metabolites and small amounts of unchanged drug are excreted in the urine. The plasma half-life of propranolol is about 3 to 6 hours.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

- **Amitriptyline Hydrochloride**

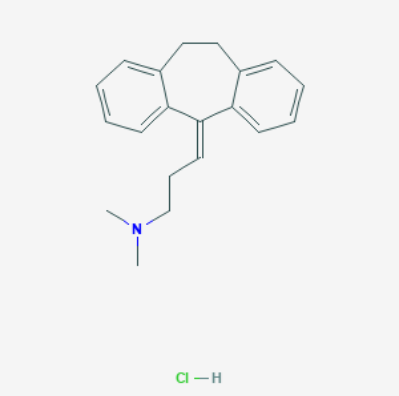
Amitriptyline Hydrochloride is the hydrochloride salt of the tricyclic dibenzocycloheptadiene amitriptyline with antidepressant and antinociceptive activities. It is an organic tricyclic compound.

Chemical Name-*N*,*N*-dimethyl-3-(2-tricyclo[9.4.0.$0^{3,8}$]pentadeca-1(15),3,5,7,11,13-hexaenylidene)propan-1-amine;hydrochloride

Molecular Weight- 313.9 g/mol

Molecular Formula- $C_{20}H_{24}ClN$

Structure-



- **Propranolol Hydrochloride**

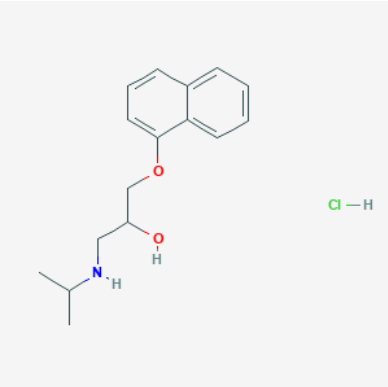
Propranolol Hydrochloride is the hydrochloride form of propranolol, a synthetic beta-adrenergic receptor blocker with antianginal, antiarrhythmic, and antihypertensive properties.

ChemicalName-1-naphthalen-1-yloxy-3-(propan-2-ylamino)propan-2-ol;hydrochloride

Molecular Weight- 295.8 g/mol

Molecular Formula- $C_{16}H_{22}ClNO_2$

Structure-



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging information

Triptolol tablets are available blister strips of 10 tablets.

8.4 Storage and handling instructions

Store protected from moisture and at temperature not exceeding 30^{o}C.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patients are advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by XENON PHARMA PVT LTD

11. Details of permission or license number with date

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12. Date of revision: January 2021