1.6.1.1 Name of the medicinal Product

Amitriptyline Tablets BP 25 mg

1.6.1.1.1 strength

25 mg/tablet

1.6.1.1.2 Pharmaceutical Form

Oral tablet

1.6.1.2 Qualitative and Quantitative Composition

1.6.1.2.1 Qualitative declaration

Amitriptyline HCl BP

1.6.1.2.2 Quantitative declaration

Sr. No.	Ingredients Chemical Name	Specification	Standard Quantity/Tablet (mg)	Reason for Inclusion
DRY MIXING				
01	Amitriptyline Hydrochloride	BP	25.00	Antidepressant
02	Purified Talc	BP	3.000	Glidant
03	Colloidal Anhydrous silica (Aerosil)	BP	0.700	Glidant
04	Microcrystalline cellulose (PH 102)	BP	94.80	Diluent
05	Croscarmellose Sodium	USP-NF	5.000	Disintegrate
LUBRICATION				
06.	Magnesium stearate	BP	1.500	Lubricant
Theoretical Avg. Weight (Core): 130.00 mg				
COATING				
07	Colour Brilliant Blue (SP)	IHS	3.250	Coloring Agent
08	Purified water	BP	Q.S	Solvant
Theoretical Average Weight (Coated): 133.25 mg				

1.6.1.3 Pharmaceutical Form

Oral, Tablet

Blue coloured round shaped biconvex,film coated table plain on both sides

1.6.1.4 Clinical Particulars

1.6.1.4.1 Therapeutic Indications

Symptoms of depression (especially where sedation is required).

Nocturnal enuresis where organic pathology is excluded.

1.6.1.4.2 Posology and Method of Administration

Therapy should be started with a low dosage and increased gradually, according to the clinical response and any evidence of intolerance.

Adults:

Initial dose: Usually 75 mg daily in divided doses(or a single dose at night). This may be increased if necessary to a total of l 50mg a day, with the additional doses being given in the late afternoon and/or bedtime. The sedative effect is usually rapidly apparent while antidepressant activity may be seen within 3 or 4 days or may take up to 30 days to develop adequately.

Maintenance Dose: The usual maintenance dosage is 50-100 mg daily. The total dosage may be given in a single dose preferably in the evening or at bedtime. When satisfactory improvement has been reached, dosage should be reduced to the lowest amount that will maintain relief of symptoms. Maintenance therapy should be continued for 3 months or longer to lessen chances of relapse.

Elderly: An initial dosage of 10-25 mg three times daily is recommended, which should be increased slowly. A daily dosage of 50 mg may be satisfactory in elderly patients who may not tolerate higher doses. The required dosage may be administered either as divided doses or as a single dose preferably in the evening or at bedtime.

Pediatrics:

Depression: Amitriptyline is not recommended for treatment of depression in children, under 16 years of age.

Enuresis: Children from 11-16 years may need 25 mg-50mg a day.

Treatment should not exceed three months.

1.6.1.4.3 Contraindications

Hypersensitivity to amitriptyline or any component of the formulation.

Amitriptyline hydrochloride tablets should not be given concurrently with Cisapride due to the potential for increased QT interval and increased risk for arrhythmia.

It is not recommended for use during the acute recovery phase following myocardial infarction.

1.6.1.4.4 Special Warnings and Special Precautions for Use

Amitriptyline should be used with caution in patients with a history of epilepsy, and those with impaired liver function. Due to its atropine-like action, it should be used with caution in patients with a history of urinary retention, prostatic hypertrophy, narrow-angle glaucoma, or increased intra-ocular pressure.

Patients with cardiovascular disorders, hyperthyroid patients and those receiving thyroid medication or anticholinergic drugs should be used with caution and the dosage of all medications carefully adjusted.

When used for the depressive component of schizophrenia, amitriptyline may aggravate psychotic symptoms. In manic depressives, a shift towards the manic phase may occur. Paranoid delusions, with or without associated hostility, may be aggravated.

The risk of suicide remains during treatment of depressed patients and until significant remission occurs such patients require careful supervision.

Concurrent administration with Electroconvulsive Therapy may increase the hazards of treatment, and should be limited to patients for whom it is deemed essential.

Amitriptyline should be discontinued several days before surgery. If emergency surgery is unavoidable, the anesthetist should be informed that the patient is being treated with amitriptyline, since anesthesia may increase the risk of hypotension and arrhythmias. Hyponatremia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant.

Hepatic impairment: Use with caution in patients with hepatic impairment.

Pregnancy: Category C: Amitriptyline crosses the placenta. Amitriptyline should be used only during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation: Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, it is not recommended during lactation.

1.6.1.4.5 Interaction with other medicinal products and other forms of interaction

Not Applicable

1.6.1.4.6 Fertility, Pregnancy and Lactation

Pregnancy: Category C: Amitriptyline crosses the placenta. Amitriptyline should be used only during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation: Amitriptyline is detectable in breast milk. Because of the potential for serious adverse reactions in infants from amitriptyline, it is not recommended during lactation.

1.6.1.4.7 Effects on ability To Drive and use Machines

Not Applicable

1.6.1.4.8 Undesirable Effects

Cardiovascular: Orthostatic hypotension, syncope, postural hypotension, hypertension, palpitations, tachycardia, myocardial infarction, heart block stroke and non-specific ECG changes.

CNS and Neuromuscular: Disturbed concentration, disorientation, confusion, coordination impaired, insomnia, nightmares, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, peripheral neuropathy, numbness, tingling and paraesthesia of the extremities, ataxia, tremors, coma, convulsions, extra-pyramidal symptoms including abnormal involuntary movements and tinnitus.

Anticholinergic: Blurred vision, accommodation disturbance, increased intra-ocular pressure, mydriasis, constipation, paralyticileus, urinary retention, urinary tract dilation, hyperpyrexia and dry mouth.

Allergic: Skin rash, urticarial, photosensitivity, alopecia.

Hematological: Bone marrow depression including agranulocytosis, eosinophilia and purpura.

Gastro-intestinal: Nausea, vomiting, diarrhea, weight gain, epigastric distress, anorexia, dyspepsia, stomatitis, unpleasant taste, parotid swelling, black tongue.

Endocrine : Gynecomastia, breast enlargement, galactorrhea, testicular swelling, changes in libido, impotence, interference with sexual function, elevation or lowering of blood sugar levels, syndrome of inappropriate ADH secretion.

Other reactions: Dizziness, weakness, fatigue, headache, urinary frequency and drowsiness. Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise.

1.6.1.4.9 Overdose

Symptoms: Overdose effects are mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain. Commonly include peripheral symptoms sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils and urinary retention. The most important ECG feature of toxicity is prolongation of the QRS interval, which indicates a high risk of ventricular tachycardia. In very severe poisoning the ECG may be bizarre. Common central symptoms include ataxia, nystagmus and drowsiness, which may lead to deep coma and respiratory depression. Increased tone and hyperreflexia may be present with extensor plantar reflexes.

Treatment: An ECG should be taken and in particular the QRS interval should be assessed since prolongation signifies an increased risk of arrhythmia and convulsions. Give activated charcoal by mouth or naso-gastric tube if more than 4 mg/kg has been ingested within one hour, provided the airway can be protected. Tachyarrhythmias arc treated by correction of hypoxia and acidosis. Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances.

1.6.1.5 Pharmacological Properties

1.6.1.5.1 Pharmacodynamics Properties

Amitriptyline is a tricyclic antidepressant with marked anticholinergic and sedative properties. Its mode of action in depression is not fully understood, though it is thought to increase the synaptic concentration of norepinephrine and serotonin in the CNS by inhibiting their re-uptake by the pre-synaptic neuronal membrane.

Pharmacokinetic:

1.6.1.5.2 Pharmacokinetic Properties

Absorption: Amitriptyline is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring within about 6 hours of oral administration.

Distribution: Amitriptyline and active metabolite nortriptyline are widely distributed throughout the body and are very highly bound to plasma and tissue protein. It will cross the placental barrier and is excreted in breast milk.

Metabolism: Amitriptyline is extensively demethylated in the liver lo its primary active metabolite, nortriptyline. The metabolism pathway includes N-oxidation and conjugation with glucuronic acid.

Elimination: It is excreted in urine in the form of metabolites. The estimated half- life of amitriptyline is 9-25 hours.

1.6.1.5.3 Preclinical Safety Data

Not Applicable.

1.6.1.6 Pharmaceutical Particulars

1.6.1.6.1 List of Excipients

Purified Talc BP

Colloidal Anhydrous silica (Aerosil)BP

Microcrystalline Cellulose (PH102)BP

Croscarmellose Sodium USP-NF

Magnesium Stearate BP

Colour Brilliant Blue(SP) IH

Purified Water BP

1.6.1.6.2 Incompatibilities

Not applicable.

1.6.1.6.3 Shelf Life

36 months

1.6.1.6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light.

1.6.1.6.5 Nature and Contents of Container

10 Tablets are packed in Alu-PVC Blister Pack. Such 10 Blisters are packed in printed Carton with Packing Insert.

1.6.1.6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

1.6.1.7 Marketing Authorization Holder And Manufacturing Site Addresses

1.6.1.7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.6.1.7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

1.6.1.8 Marketing Authorization Number

To be included after obtaining first registration.

1.6.1.9 Date of First <Registration> / Renewal of The <Registration>

It will be applicable after registration of this product.

1.6.1.10 **Date of Revision of the Text**

1.6.1.11 Dosimetry (If Applicable)

Not Applicable

1.6.1.12 Instructions for preparation of radiopharmaceuticals (if Applicable)

Not Applicable