1.6 Product Information

1.6.1 *Prescribing information (Summary of Product Characteristics)*

1. Name of the medicinal product

Amitrip Tablets

2. Qualitative and quantitative composition

Each coated tablets contains: Amitriptyline Hcl BP… 25mg

3. Pharmaceutical form

Tablets

4. Clinical Particulars

4.1 Therapeutic Indications

For use in the treatment of endogenous depression of the depressed phases of manic- depressive disorders as well as evolutional, climacteric, senile, arteriosclerotic and other depressions. It also may be useful in psychovegetative and neurotic depressions. For treatment of depressive reactions associated with schizophrenia it is also recommended, however long-term treatment may aggravate schizophrenic symptoms. In severe psychiatric cases it may be used as an adjunctive therapy to electro convulsions, it supplements, however does not completely substitute, electro convulsion treatment.

4.2 Posology and method of administration

Route of administration: Oral

By mouth, in a single or divided daily dose of 75mg initially, gradually increased if necessary to 150mg daily, the additional doses being given in the late afternoon or evening. Single daily doses are normally given in the evenings or bed time.

Therapy may also be initiated with a single dose of 50mg and 100mg at bed time, increased by 25 or 50mg as necessary to a total of 150mg daily. Maintenance doses are usually 50 and 100mg daily and therapy should be continued for at least 3 months before being gradually withdrawn.

Severely depressed patients may require doses up to 200mg daily and, occasionally up to 300mg daily.

Adolescents and elderly patients have reduced tolerance to amitriptyline and initial doses of 10 to 50mg daily may be adequate, given either as divided doses or as a single dose, preferably at bed time. Half the usual maintenance dose will be sufficient.

4.3 Contraindications

Contra-indicated in glaucoma and where urinary retention is present or may be expected.

It is not a monoamine oxidase inhibitor, but its concomitant administration with such drugs may lead to serious complications. It should not be given with, or for at least three weeks after discontinuing the use of, a monoamine oxidase inhibitor.

4.4 Special Warnings and Precautions for Use

The administration of AMITRIPTYLINE calls for close supervision in epileptics and aged patients; since hypomania, confusion and tremor may be produced.

Amitriptyline should be used with caution in patients with a history of epilepsy, and in those with impaired liver function or phaeochromocytoma.

Blood sugar concentrations may be altered in diabetic patients.

Cardiac arrhythmias and severe hypotension are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage.

4.5 Interaction with other medicinal products and other forms of Interaction

Sympathomimetic agents: Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants).

Adrenergic neurone blockers: Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants. There is an increased risk of hypertension on clonidine withdrawal.

Anticholinergic agents: Tricyclic antidepressants may potentiate the effects of these drugs on the eye, central nervous system, bowel and bladder; concomitant use of these should be avoided due to an increased risk of paralytic ileus, hyperpyrexia, etc.

Drugs which prolong the QT-interval including antiarrhythmics such as amiodarone (avoid concomitant use), disopyramide, procainamide, propafenone, quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, thioridazine and clozapine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants.

Use caution when using amitriptyline and methadone concomitantly due to a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects.

Caution is also advised for co-administration of amitriptyline and diuretics inducing hypokalaemia (e.g. furosemide)

Thioridazine: Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects

Tramadol: Concomitant use of tramadol (a CYP2D6 substrate) and tricyclic antidepressants (TCAs), such as amitriptyline increases the risk for seizures and serotonin syndrome. Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity.

Antifungals such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsade de pointes have occurred.

Combinations requiring precautions for use

CNS depressants: Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.

4.6 Pregnancy and Lactation

Pregnancy

For amitriptyline only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity

Amitriptyline is not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

During chronic use and after administration in the final weeks of pregnancy, neonatal withdrawal symptoms can occur. This may include irritability, hypertonia, tremor, irregular breathing, poor drinking and loud crying and possibly anticholinergic symptoms (urinary retention, constipation).

Lactation

Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from the therapy of this medicinal product taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on Ability to Drive and Use Machines

None unknown

4.8 Undesirable Effects

Amitriptyline may induce side effects similar to other tricyclic antidepressants. Some of the below mentioned side effects e.g. headache, tremor, disturbance in attention, constipation and decreased libido may also be symptoms of depression and usually attenuate when the depressive state improves.

4.9 Overdose and treatment

Overdose of amitriptyline and other tricyclic antidepressants is characterized, in part, by anticholinergic effects such as coma, respiratory depression and tachycardia, along with consequences of sodium channel blockade, including prolongation of the QRS complex and negative inotropy. Despite anticholinergic action, which can slow down gut motility, patients usually exhibit onset of coma and life-threatening cardiovascular events within a few hours of ingestion, and plasma drug concentrations usually peak within 24 hours.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: N06AA09

Amitriptyline is a tricyclic antidepressant and an analgesic. It has marked anticholinergic and sedative properties. It prevents the re-uptake, and hence the inactivation of noradrenaline and serotonin at nerve terminals. Reuptake prevention of these monoamine neurotransmitters potentiate their action in the brain. This appears to be associated with the antidepressant activity.

The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channel at both central and spinal cord level. The noradrenaline, sodium and the NMDA effects are mechanisms known to be involved in the maintenance of neuropathic pain, chronic tension type headache prophylaxis and migraine prophylaxis. The pain-reducing effect of amitriptyline is not linked to its anti-depressive properties.

Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors to varying degrees

5.2 Pharmacokinetic properties

Amitriptyline is readily absorbed from the gastrointestinal tract, peak plasma concentrations occurring within a few hours of oral administration. Since Amitriptyline slows gastro-intestinal transit time, absorption can, however be delayed particularly in over dosage.

Amitriptyline undergoes extensive, first-pass metabolism and is demethylated in the liver to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation and N-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine mainly in the form of metabolites, either free or in conjugated form. Both the drug and its active metabolites are widely distributed throughout the body and are extensively bound to plasma and tissue proteins. Amitriptyline has an estimated elimination half-life ranging from 9 to 36 hours which may be considerably extended in over dosage.

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established. Both the drug and active metabolite cross the placenta and are excreted in breast milk.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to a prescriber, which is additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1 List of Excipients

Dicalcium phosphate
White corn starch
Povidone K- 30
White corn starch (for paste)
Potassium sorbate
Sodium starch glycolate
Sodium lauryl sulfate
Purified talc
Magnesium stearate
Hydroxypropyl methylcellulose (5cps)
Titanium dioxide
Purified talc
Sunset Yellow lake colour
Polyethene glycol 6000
Isopropyl alcohol
Purified water

6.2 Incompatibilities

None.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C in a dry place.

6.5 Nature and Contents of Container

BLISTER PACKS:

Blisters of 10 x 10 tablets packed in a unit carton with a literature insert.

BULK PACKS:

1000's packed in polythene bags contained in HDPE containers with a literature insert.

6.6 Special precaution for disposal and other handling

No special requirements.

7 Marketing Authorization Holder and Manufacturing Site Addresses
Marketing Authorization Holder:

Company Name: LABORATORY & ALLIED LTD

Address: Plot No. 209/10349, Opposite Sameer Business Park, Next to Libra House, Mombasa road, P.O. Box 42875 GPO 00100, Nairobi,

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E-Mail : info@laballied.com

8 Marketing Authorization Number:
KENYA: 5913

9 Date of first Registration/ Renewal of the Registration:
KENYA: 2006

10 Date of revision of the text:
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