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Brand Name : **AMILINE TABLETS** **Generic Name** : Amitriptyline Tablets BP 25 MG		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

AMILINE (Amitriptyline Tablets BP 25 MG)

2. Qualitative and Quantitative Composition:

Each film coated tablet contains: Amitriptyline Hydrochloride BP 25 mg

3. Pharmaceutical form:

Pink Coloured, circular, biconvex, film coated tablets.

4. Clinical particulars:

4.1 Posology and Method of Administration:

Posology

Not all dosage schemes can be achieved with all the pharmaceutical forms/strengths. The appropriate formulation/strength should be selected for the starting doses and any subsequent dose increments.

Major depressive disorder

Dosage should be initiated at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerability.

Adults

Initially 25 mg 2 times daily (50 mg daily). If necessary, the dose can be increased by 25 mg every other day up to 150 mg daily divided into two doses.

The maintenance dose is the lowest effective dose.

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Elderly patients over 65 years of age and patients with cardiovascular disease
Initially 10 mg – 25 mg daily

The daily dose may be increased up to 100 mg – 150 mg divided into two doses, depending on individual patient response and tolerability.

Doses above 100 mg should be used with caution.

The maintenance dose is the lowest effective dose.

Paediatric population

Amitriptyline should not be used in children and adolescents aged less than 18 years, as long term safety and efficacy have not been established (see section 4.4).

Duration of treatment

The antidepressant effect usually sets in after 2 - 4 weeks. Treatment with antidepressants is symptomatic and must therefore be continued for an appropriate length of time usually up to 6 months after recovery in order to prevent relapse.

Neuropathic pain, prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine prophylaxis

Patients should be individually titrated to the dose that provides adequate analgesia with tolerable adverse drug reactions. Generally, the lowest effective dose should be used for the shortest duration required to treat the symptoms.

Adults

Recommended doses are 25 mg - 75 mg daily in the evening. Doses above 100 mg should be used with caution.

The initial dose should be 10 mg - 25 mg in the evening. Doses can be increased with 10 mg - 25 mg every 3 – 7 days as tolerated.

The dose can be taken once daily, or be divided into two doses. A single dose above 75 mg is not recommended.

The analgesic effect is normally seen after 2 - 4 weeks of dosing.

Elderly patients over 65 years of age and patients with cardiovascular disease

A starting dose of 10 mg - 25 mg in the evening is recommended.

Doses above 75 mg should be used with caution.

It is generally recommended to initiate treatment in the lower dose range as recommended for adult. The dose may be increased depending on individual patient response and tolerability.

Paediatric population

Amitriptyline should not be used in children and adolescents aged less than 18 years, as safety and efficacy have not been established (see section 4.4).

Duration of treatment

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Neuropathic pain

Treatment is symptomatic and should therefore be continued for an appropriate length of time. In many patients, therapy may be needed for several years. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Prophylactic treatment of chronic tension type headache and prophylactic treatment of migraine in adults

Treatment must be continued for an appropriate length of time. Regular reassessment is recommended to confirm that continuation of the treatment remains appropriate for the patient.

Nocturnal enuresis

Paediatric population

The recommended doses for:

• children aged 6 to 10 years: 10 mg – 20 mg. A suitable dosage form should be used for this age group.

• children aged 11 years and above: 25 mg – 50 mg daily

The dose should be increased gradually.

Dose to be administered 1-1½ hours before bedtime.

An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

The maximum period of treatment course should not exceed 3 months.

If repeated courses of amitriptyline are needed, a medical review should be conducted every 3 months.

Special populations

Renal impairment

This medicinal product can be given in usual doses to patients with renal failure.

Hepatic impairment

Careful dosing and, if possible, a serum level determination is advisable.

Cytochrome P450 inhibitors of CYP2D6

Depending on individual patient response, a lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to amitriptyline treatment (see section 4.5).

Known poor metabolisers of CYP2D6 or CYP2C19

These patients may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Consider a 50% reduction of the recommended starting dose.

Method of Administration

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For oral administration.

Discontinuation of treatment

When stopping therapy the drug should be gradually withdrawn during several weeks.

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Recent myocardial infarction. Any degree of heart block or disorders of cardiac rhythm and coronary artery insufficiency.

Concomitant treatment with MAOIs (monoamine oxidase inhibitors) is contra-indicated (see section 4.5). Simultaneous administration of amitriptyline and MAOIs may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia).

Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non- selective MAOIs and minimum one day after discontinuation of the reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.

Severe liver disease.

In children under 6 years of age.

4.3 Special Warnings and Precautions for Use :

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.

QT interval prolongation

Cases of QT interval prolongation and arrhythmia have been reported during the post-marketing period. Caution is advised in patients with significant bradycardia, in patients with uncompensated heart failure, or in patients concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) are known to be conditions increasing the proarrythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue this medicinal product several days before surgery; if emergency surgery is unavoidable, the anaesthetist should be informed that the patient is being so treated.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication, since cardiac arrhythmias may develop.

Elderly patients are particularly susceptible to orthostatic hypotension.

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This medical product should be used with caution in patients with convulsive disorders, urinary retention, prostatic hypertrophy, hyperthyroidism, paranoid symptomatology and advanced hepatic or cardiovascular disease, pylorus stenosis and paralytic ileus.

In patients with the rare condition of shallow anterior chamber and narrow chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Suicide/suicidal thoughts Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo- controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In manic-depressives, a shift towards the manic phase may occur; should the patient enter a manic phase amitriptyline should be discontinued.

As described for other psychotropics, amitriptyline may modify insulin and glucose responses calling for adjustment of the antidiabetic therapy in diabetic patients; in addition the depressive illness itself may affect patients' glucose balance.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic or with neuroleptic medications, especially in hot weather.

After prolonged administration, abrupt cessation of therapy may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Amitriptyline should be used with caution in patients receiving SSRIs (see sections 4.2 and 4.5).

Nocturnal enuresis

• An ECG should be performed prior to initiating therapy with amitriptyline to exclude long QT syndrome.

• Amitriptyline for enuresis should not be combined with an anticholinergic drug.

• Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression; the same precautions observed

when treating patients with depression should therefore be followed when treating patients with enuresis.

Paediatric population

Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see section 4.2).

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.4 Interaction with other medicinal products, and other forms of interaction:

Potential for amitriptyline to affect other medicinal products

Contraindicated combinations

MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) - risk of "serotonin syndrome" (see section 4.3).

Combinations that are not recommended

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.

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 quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), 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.

4.5 Pregnancy and Lactation:

Pregnancy

For amitriptyline only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity (see section 5.3).

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).

Breast-feeding

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.

Fertility

Amitriptyline reduced the pregnancy rate in rats (see section 5.3).

No data on the effects of amitriptyline on human fertility are available.

5. Pharmacological properties:

5.1 Pharmacokinetic Properties:

Pharmacotherapeutic group: Antidepressants - Non-selective monoamine reuptake inhibitor (tricyclic antidepressant)

ATC-Code: N06AA09

Mechanism of action

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.

Clinical efficacy and safety

The efficacy and safety of amitriptyline has been demonstrated in treatments of the following indications in adults:

• Major Depressive Disorder

• Neuropathic Pain

• Chronic tension type headache prophylaxis

• Migraine prophylaxis

The efficacy and safety of amitriptyline has been demonstrated for treatments of nocturnal enuresis in children aged 6 years and above (see section 4.1).

The recommended doses are provided in section 4.2. For treatment of depression, doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

The antidepressant and analgesic effects usually set in after 2-4 weeks; the sedative action is not delayed.

5.2 Pharmacokinetic properties

Absorption

Film-coated tablets

Amitriptyline 10 mg film-coated tablets, Amitriptyline 25 mg film-coated tablets

Oral administration of tablets results in maximum serum levels in about 4 hours. (t_{max}= 3.89±1.87 hours; range 1.93-7.98 hours). After peroral administration of 50 mg the mean C_{max} = 30.95±9.61 ng/ml; range 10.85-45.70 ng/ml (111.57±34.64 nmol/l; range 39.06-164.52 nmol/l). The mean absolute oral bioavailability is 53% (F_{abc} = 0.527±0.123; range 0.219-0.756).

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Amitriptyline 50 mg film-coated tablets

After oral administration amitriptyline is absorbed slowly but completely. Due to the often delayed gastrointestinal tract passage maximum plasma concentrations are reached after 1 to 5 (-8) hours.

The systemic bioavailability is about 50% of the intravenous injection.

Distribution

The apparent volume of distribution $(V_d)_\beta$ estimated after intravenous administration is 1221 L±280 L; range 769-1702 L (16±3 L/kg).

The plasma protein binding is about 95%.

Amitriptyline and the main metabolite nortriptyline pass across the placental barrier.

In nursing mothers amitriptyline and nortriptyline are excreted in small amounts with the breast milk. The ratio milk concentration/plasma concentration in women is around 1:1. The estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight related doses of amitriptyline (in mg/kg) (see section 4.6).

Biotransformation

In vitro the metabolism of amitriptyline proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. Other isozymes involved are CYP1A2 and CYP2C9. The metabolism is subject to genetic polymorphism. The main active metabolite is the secondary amine, nortriptyline.

Nortriptyline is a more potent inhibitor of noradrenaline than of serotonin uptake, while amitriptyline inhibits the uptake of noradrenaline and serotonin equally well. Other metabolites such as cis- and trans-10-hydroxyamitriptyline and cis- and trans-10-hydroxynortriptyline have the same profile as nortriptyline but is considerably weaker. Demethylnortriptyline and amitriptyline N oxide are only present in plasma in minute amounts; the latter is almost inactive. All the metabolites are less anticholinergic than amitriptyline and nortriptyline. In plasma the amount of total 10-hydroxynortriptyline dominates but most of the metabolites are conjugated.

Elimination

The elimination half-life $(t_{½}\,\beta)$ amitriptyline after peroral administration is about 25 hours (24.65±6.31 hours; range 16.49-40.36 hours). The mean systemic clearance (Cl_s) is 39.24±10.18 L/h, range 24.53-53.73 L/h.

The excretion proceeds mainly with urine. The renal elimination of unchanged amitriptyline is insignificant (about 2%).

Steady state plasma levels of amitriptyline + nortriptyline are reached within a week for most patients, and in steady state the plasma level comprises approximately equal parts of amitriptyline and nortriptyline around the clock following treatment with conventional tablets 3 times a day.

Elderly

Longer half-lives and decreased oral (Cl_o) clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Hepatic impairment

Hepatic impairment may reduce hepatic extraction resulting in higher plasma levels and caution should be exercised when dosing these patients (see section 4.2).

Renal impairment

Renal failure has no influence on the kinetics.

Polymorphism

The metabolism is subject to genetic polymorphism (CYP2D6 and CYP2C19) (see section 4.2).

Pharmacokinetic/pharmacodynamic relationship

Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

The therapeutic plasma concentration in major depression is around 80 – 200 ng/ml (≈ 280 – 700 nmol/l) (for amitriptyline + nortriptyline). Levels above 300-400 ng/ml are associated with increased risk of disturbance in cardiac conduction in terms of prolonged QRS-complex or AV block.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose	BP
Microcrystalline cellulose	BP
Maize starch	BP
Polyvinyl pyrrolidone K-30 (Povidone)	BP
Iso propyl Alcohol	BP
Purified talc	BP
Magnesium stearate	BP
Sodium starch Glycolate	BP
Colloidal silicon dioxide	BP
Methylene Dichloride	BP
Colour instacoate sole pink	INH

6.2 Incompatibilities:

None Reported

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Store in a cool, dry and dark place. Protect from light.

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6.5 Nature and Contents of Container:
Jar pack of 1000 tablets, 10x10 blister pack.

6.6 Special precautions for disposal:
None reported.

7. Registrant:
AGOG PHARMA LTD.
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Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

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9. Date of revision of the text :