SUMMARY OF PRODUCT CHARACTERISTICS
ZATRYP (Amitriptyline Hydrochloride Tablets BP 25 mg)

1. NAME OF THE MEDICINAL PRODUCT

ZATRYP (Amitriptyline Hydrochloride Tablets BP 25 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains amitriptyline hydrochloride BP 25 mg.

Excipients with known effect:

Contains lactose. For warnings, see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, biconvex, film-coated tablet, plain on one side and scored on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amitriptyline tablets are indicated for:

- The treatment of major depressive disorder in adults.
- The treatment of neuropathic pain in adults.
- The prophylactic treatment of chronic tension-type headache (CTTH) in adults.
- The prophylactic treatment of migraine in adults.
- The treatment of nocturnal enuresis in children aged 6 years and above when organic pathology has been excluded and no response has been achieved to all other non-drug and drug treatments (including antispasmodics and vasopressin-related products). This medicinal product should only be prescribed by a healthcare professional with expertise in the management of persistent enuresis.

4.2 Posology and method of administration

Major depressive disorder — Adults

Initially 25 mg twice daily (50 mg daily). If necessary, the dose can be increased by 25 mg every other day up to 150 mg daily in two divided doses. The maintenance dose is the lowest effective dose. The antidepressant effect usually sets in after 2–4 weeks. Treatment should be continued for at least 6 months after recovery to prevent relapse.

Elderly patients (>65 years) and patients with cardiovascular disease

Initially 10–25 mg daily. The daily dose may be increased up to 100–150 mg in two divided 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.

Neuropathic pain, CTTH prophylaxis and migraine prophylaxis — Adults

Initial dose 10–25 mg in the evening. Doses can be increased by 10–25 mg every 3–7 days as tolerated, up to 25–75 mg daily. Doses above 100 mg should be used with caution. A single dose above 75 mg is not recommended. The analgesic effect is normally seen after 2–4 weeks.

Nocturnal enuresis — Paediatric population

Children aged 6–10 years: 10–20 mg; children aged 11 years and above: 25–50 mg daily. Dose to be administered 1–1½ hours before bedtime. The dose should be increased gradually. An ECG should be performed prior to initiating therapy to exclude long QT syndrome. The maximum period of treatment should not exceed 3 months. Amitriptyline for enuresis should not be combined with an anticholinergic drug.

Paediatric population (general)

Amitriptyline should not be used in children and adolescents aged less than 18 years for depression, neuropathic pain, CTTH or migraine, as long-term safety and efficacy have not been established.

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.

CYP2D6 inhibitors and poor metabolisers

A lower dose of amitriptyline should be considered if a strong CYP2D6 inhibitor (e.g. bupropion, quinidine, fluoxetine, paroxetine) is added to treatment. In known poor metabolisers of CYP2D6 or CYP2C19, a 50% reduction of the recommended starting dose should be considered.

Method of administration

Oral. Tablets should be swallowed with water. When stopping therapy, the drug should be gradually withdrawn over 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). Treatment with amitriptyline may be instituted 14 days after discontinuation of irreversible non-selective MAOIs and minimum one day after discontinuation of reversible moclobemide. Treatment with MAOIs may be introduced 14 days after discontinuation of amitriptyline.
- Severe liver disease.
- Children under 6 years of age.

4.4 Special warnings and precautions for use

Cardiac effects

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 and arrhythmia have been reported post-marketing. Caution is advised in patients with significant bradycardia, uncompensated heart failure, or those concurrently taking QT-prolonging drugs. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) increase the proarrhythmic risk.

Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If possible, discontinue amitriptyline several days before surgery; if emergency surgery is unavoidable, the anaesthetist must be informed.

Great care is necessary if amitriptyline is administered to hyperthyroid patients or to those receiving thyroid medication.

Suicide/suicidal thoughts

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide. This risk persists until significant remission occurs. Patients should be closely monitored until such improvement occurs, as improvement may not occur during the first few weeks or more of treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Patients with a history of suicide-related events are at greater risk and should receive careful monitoring. Patients (and caregivers of patients) should be alerted to monitor for clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour, and to seek medical advice immediately.

Other psychiatric considerations

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

Other cautions

Use with caution in: patients with convulsive disorders; urinary retention; prostatic hypertrophy; hyperthyroidism; paranoid symptomatology; advanced hepatic or cardiovascular disease; pylorus stenosis; paralytic ileus. In patients with narrow anterior chamber angle, attacks of acute glaucoma due to dilation of the pupil may be provoked.

Hyperpyrexia has been reported with tricyclic antidepressants when administered with anticholinergic agents or neuroleptic medications, especially in hot weather. After prolonged administration, abrupt cessation may produce withdrawal symptoms such as headache, malaise, insomnia and irritability.

Diabetes

Amitriptyline may modify insulin and glucose responses, calling for adjustment of antidiabetic therapy.

Lactose content
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

MAOIs (contraindicated — see section 4.3):

Risk of serotonin syndrome (agitation, confusion, tremor, myoclonus, hyperthermia).

Sympathomimetic agents (not recommended):

Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

Adrenergic neurone blockers (not recommended):

Tricyclic antidepressants may counteract the antihypertensive effects of centrally acting antihypertensives (guanethidine, betanidine, reserpine, clonidine, methyldopa).

Anticholinergic agents (not recommended):

Tricyclic antidepressants may potentiate anticholinergic effects on the eye, CNS, bowel and bladder (increased risk of paralytic ileus, hyperpyrexia).

QT-prolonging drugs (not recommended):

Including antiarrhythmics (quinidine), antihistamines (astemizole, terfenadine), antipsychotics (pimozide, sertindole), cisapride, halofantrine, sotalol; may increase the likelihood of ventricular arrhythmias. Use caution with methadone (additive QT effects).

Thioridazine:

Co-administration should be avoided due to inhibition of thioridazine metabolism and consequent increased risk of cardiac side effects.

Tramadol:

Increased risk for seizures and serotonin syndrome; also inhibits metabolism of tramadol to its active metabolite, potentially causing opioid toxicity.

CYP2D6 inhibitors (fluoxetine, paroxetine, bupropion, quinidine, terbinafine):

May produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Monitor TCA plasma levels when co-administering with CYP2D6 inhibitors.

Fluvoxamine (CYP1A2 inhibitor):

Was shown to increase amitriptyline plasma concentrations; this combination should be avoided.

CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir):

Clinically relevant interactions may be expected.

Antifungals (fluconazole, terbinafine):

Increase serum concentrations of tricyclics and accompanying toxicity. Syncope and torsades de pointes have occurred.

CNS depressants (alcohol, barbiturates):

Amitriptyline may enhance sedative effects.

Cimetidine, methylphenidate, calcium-channel blockers (diltiazem, verapamil):

May increase plasma levels of tricyclic antidepressants.

CYP inducers (oral contraceptives, rifampicin, phenytoin, barbiturates, carbamazepine, St. John's Wort):

May increase metabolism of tricyclic antidepressants and reduce plasma levels.

Sodium valproate and valpromide:

Can increase amitriptyline plasma concentrations; clinical monitoring is recommended.

Diuretics (particularly those inducing hypokalaemia, e.g. furosemide):

Increased proarrhythmic risk; increased risk of postural hypotension.

4.6 Fertility, pregnancy and lactation

Pregnancy

For amitriptyline, only limited clinical data are available. 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 may occur (irritability, hypertonia, tremor, irregular breathing, poor drinking, loud crying, and possibly anticholinergic symptoms).

Breast-feeding

Amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6–1% of the maternal dose); the estimated daily infant exposure (amitriptyline + nortriptyline) averages 2% of the corresponding maternal weight-related 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 amitriptyline therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

Amitriptyline reduced the pregnancy rate in rats. No data on effects on human fertility are available.

4.7 Effects on ability to drive and use machines

Amitriptyline is a sedative drug. Patients who are prescribed psychotropic medication may be expected to have some impairment in general attention and concentration and should be cautioned about their ability to drive or operate machinery. These adverse effects can be potentiated by the concomitant intake of alcohol.

4.8 Undesirable effects

Summary of the safety profile

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

System Organ Class	Frequency	Preferred Term
Blood and lymphatic disorders	Rare	Bone marrow depression, agranulocytosis, leucopenia, eosinophilia, thrombocytopenia and purpura
Metabolism and nutrition disorders	Rare / Not known	Decreased appetite (rare); elevation or lowering of blood sugar, increased appetite, anorexia (not known)
Psychiatric disorders	Very common / Common / Uncommon / Rare	Aggression (very common); confusional state, libido decreased, agitation (common); hypomania, mania, anxiety, insomnia, nightmare (uncommon); delirium (elderly), hallucination, suicidal thoughts or behaviour* (rare)
Nervous system disorders	Very common / Common / Uncommon / Very rare / Not known	Somnolence, tremor, dizziness, headache, drowsiness, dysarthria (very common); disturbance in attention, dysgeusia, paraesthesia, ataxia (common); convulsion (uncommon); akathisia, polyneuropathy (very rare); peripheral neuropathy, inco-ordination, extrapyramidal disorder (not known)
Eye disorders	Very common / Common / Very rare	Accommodation disorder (very common); mydriasis (common); acute glaucoma (very rare)
Cardiac disorders	Very common / Common / Uncommon / Rare / Very rare	Palpitations, tachycardia (very common); AV block, bundle branch block (common); collapse, worsening of cardiac failure (uncommon); arrhythmia (rare); cardiomyopathies, torsades de pointes (very rare)
Vascular disorders	Very common / Uncommon	Orthostatic hypotension (very common); hypertension (uncommon)
Gastrointestinal disorders	Very common / Uncommon / Rare	Dry mouth, constipation, nausea (very common); diarrhoea, vomiting, tongue oedema (uncommon); salivary gland enlargement, paralytic ileus (rare)
Hepatobiliary disorders	Rare / Uncommon / Not known	Jaundice (rare); cholestatic liver disease (uncommon); hepatitis (not known)
Skin and subcutaneous tissue disorders	Very common / Uncommon / Rare	Hyperhidrosis (very common); rash, urticaria, face oedema (uncommon); alopecia, photosensitivity (rare)
Renal and urinary disorders	Common / Uncommon	Micturition disorders (common); urinary retention (uncommon)
Reproductive system and breast	Common / Uncommon / Rare	Erectile dysfunction (common); galactorrhoea (uncommon); gynaecomastia (rare)
General disorders	Common / Rare	Fatigue, feeling thirst (common); pyrexia (rare)

System Organ Class	Frequency	Preferred Term
Investigations	Very common / Common / Uncommon / Rare	Weight increased (very common); ECG abnormal, QT prolonged, QRS prolonged, hyponatraemia (common); intraocular pressure increased (uncommon); weight decreased, liver function test abnormal (rare)

** Case reports of suicidal thoughts or behaviour were reported during treatment with or just after conclusion of treatment with amitriptyline (see section 4.4).*

Class effects: Epidemiological studies, mainly in patients ≥50 years of age, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9 Overdose

Symptoms

Anticholinergic symptoms: mydriasis, tachycardia, urinary retention, dry mucous membranes, reduced bowel motility. Convulsions. Fever. CNS depression progressing to coma. Respiratory depression. Hypothermia may occur.

Cardiac symptoms: Arrhythmias (ventricular tachyarrhythmias, torsades de pointes, ventricular fibrillation). Characteristic ECG changes include prolonged PR interval, widened QRS complex, QT prolongation, T-wave changes and AV block. Heart failure, hypotension, cardiogenic shock.

Ingestion of 750 mg or more by an adult may result in severe toxicity. Children are especially susceptible to cardiotoxicity, seizures and hyponatraemia.

Treatment

Hospital admission (intensive care) if required. Treat symptomatically and supportively: ABC assessment; IV access; close monitoring. Gastric lavage only if within one hour of a potentially fatal overdose. Administer 50 g of charcoal if within one hour of ingestion. Continuous ECG monitoring for 3–5 days. Treat wide QRS intervals, cardiac failure, ventricular arrhythmias, circulatory failure, hypotension, hyperthermia, convulsions and metabolic acidosis as required. Unrest and convulsions may be treated with diazepam. Monitor for rhabdomyolysis if the patient has been unconscious for a considerable time.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-selective monoamine reuptake inhibitor (tricyclic antidepressant). 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. The mechanism of action also includes ion-channel blocking effects on sodium, potassium and NMDA channels at central and spinal cord level. Tricyclic antidepressants possess affinity for muscarinic and histamine H1 receptors.

5.2 Pharmacokinetic properties

Absorption

Maximum serum levels in about 4 hours after oral administration. Mean Cmax after 50 mg approximately 31 ng/ml. Mean absolute oral bioavailability 53%.

Distribution

Apparent volume of distribution approximately 1,221 L (16 L/kg). Plasma protein binding approximately 95%. Amitriptyline and the main metabolite nortriptyline cross the placental barrier and are excreted in small amounts in breast milk (milk/plasma ratio approximately 1:1).

Biotransformation

Metabolism proceeds mainly by demethylation (CYP2C19, CYP3A4) and hydroxylation (CYP2D6) followed by conjugation with glucuronic acid. CYP1A2 and CYP2C9 are also involved. The main active metabolite is nortriptyline.

Elimination

Elimination half-life approximately 25 hours. Mean systemic clearance 39.24 L/h. Excretion proceeds mainly with urine; renal elimination of unchanged amitriptyline is insignificant (approximately 2%). Steady-state plasma levels reached within a week.

Pharmacokinetic/pharmacodynamic relationship

Therapeutic plasma concentration in major depression approximately 80–200 ng/ml (amitriptyline + nortriptyline). Levels above 300–400 ng/ml are associated with increased risk of cardiac conduction disturbances.

5.3 Preclinical safety data

Amitriptyline inhibited hERG channels in the upper micromolar range of therapeutic plasma concentrations, suggesting a risk for cardiac arrhythmia. The genotoxic potential has shown partially contradictory results; a potential to induce chromosome aberrations cannot be excluded. Long-term carcinogenicity studies have not been performed. In reproductive studies, teratogenic effects were not observed in mice, rats or rabbits at doses up to 13 times the maximum recommended human dose; however, literature data suggested a risk for malformations at 9–33 times the maximum recommended dose. There was a possible association with reduced fertility in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch BP, dibasic calcium phosphate BP, povidone K-30 BP, isopropyl alcohol BP, microcrystalline cellulose BP, purified talc BP, sodium starch glycolate BP, plasticised cellulose colour, methylene dichloride BP, Ponceau 4R, magnesium stearate BP, colloidal silicon dioxide BP.

Note: Lactose is present in this formulation (declared as an excipient with known effect in section 2).

6.2 Incompatibilities

None known.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container, tightly closed. Keep out of the reach and sight of children.

6.5 Nature and contents of container

Blister pack of PVC/PVdC – Aluminium, containing 28 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

ZAIN PHARMA LIMITED

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8. MARKETING AUTHORISATION NUMBER (PPB REGISTRATION NUMBER)

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