SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimipramine 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trimpramine 10mg tablets contain Trimipramine Maleate 13.948 mg equivalent to 10mg trimipramine per tablet.
Excipient(s) with known effect: Lactose Monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Trimipramine has a potent antidepressant action similar to that of other tricyclic antidepressants. It also possesses pronounced sedative action. It is, therefore, indicated in the treatment of depressive illness, especially where sleep disturbance, anxiety or agitation are presenting symptoms. Sleep disturbance is controlled within 24 hours and true antidepressant action follows within 7 to 10 days.

4.2 Posology and method of administration

Posology

Adults: For depression 50-75 mg/day initially increasing to 150-300 mg/day in divided doses or one dose at night. The maintenance dose is 75-150 mg/day.

Elderly: 10-25 mg three times a day initially. The initial dose should be increased with caution under close supervision. Half the normal maintenance dose may be sufficient to produce a satisfactory clinical response.

Paediatric population: Not recommended.

Method of administration
Oral

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 other cardiac arrhythmias.
Mania.
Severe liver disease
During breast feeding.

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening
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.
Other psychiatric conditions for which Trimipramine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder.
The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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.

Hyperglycaemia/Diabetes:
Epidemiologic studies have identified an increased risk of diabetes mellitus in depressed patients receiving tricyclic antidepressants. Therefore, patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on trimipramine, should get appropriate glycaemic monitoring (see section 4.8).

Serotonin Syndrome:
Serotonin syndrome may occur when tricyclic antidepressants are used concomitantly with other serotonergic active substances (see section 4.5). Serotonin Syndrome

which is caused by an excess in serotonin, may be fatal and includes the following symptoms:
• Neuromuscular abnormalities (clonus, hyperreflexia, myoclonus, rigidity),
• Autonomic instability (hyperthermia, tachycardia, changes in blood pressure, diaphoresis, tremor, flushing, dilated pupils, diarrhoea),
• Changed mental state (anxiety, agitation, confusion, coma),
• Gastrointestinal symptoms

Concomitant administration of Trimipramine and buprenorphine/opioids may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

QT interval prolongation:
Like other tricyclic antidepressants, trimipramine may dose-dependently prolong QT interval (see section 4.8).
Caution should be taken in patients with known risk factors for prolongation of QT interval such as:
- Congenital long QT syndrome, bradycardia
- Concomitant use of drugs that are known to prolong the QT interval, induce bradycardia or hypokalemia (see section 4.5)
- Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia).

The elderly are particularly liable to experience adverse reactions, especially agitation, confusion and postural hypotension.
Avoid if possible in the patients with narrow angle glaucoma, symptoms suggestive of prostatic hypertrophy and a history of epilepsy.
Patients posing a high suicidal risk require close initial supervision. Tricyclic antidepressants potentiate the central nervous depressant action of alcohol.
Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated.
It may be advisable to monitor liver function in the patients on long term treatment with Trimipramine.
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Trimipramine should not be given concurrently with, or within 2 weeks of cessation of, therapy with monoamine oxidase inhibitors. Trimipramine may decrease the antihypertensive effect of guanethidine, debrisoquine, betanidine and possibly clonidine. It would be advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

Trimipramine should not be given with sympathomimetic agents such as adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

Barbiturates may increase the rate of metabolism.

Trimipramine should be administered with care in the patients receiving therapy for hyperthyroidism.

Co-administration with other serotonergic active substances (such as SSRIs, SNRIs, MAOIs, lithium, triptans, tramadol, linezolid, L-tryptophan, and St John's Wort – Hypericum perforatum-preparations) may lead to serotonin syndrome (see section 4.4). Close clinical monitoring is required when these substances are co-administered with trimipramine.

Trimipramine should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III antiarrhythmics, macrolides, floroquinolones, some antifungals, some antipsychotics), induce hypokalemia (e.g. hypokalemic diuretics, stimulant laxatives, glucocorticoids, tetracosactides) or bradycardia (e.g. beta-blockers, diltiazem, verapamil, clonidine, digitalis) (see section 4.4).

Trimipramine should be used cautiously when co-administered with buprenorphine/opioids as the risk of serotonin syndrome, a potentially life threatening condition, is increased (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Do not use in pregnancy especially during the first and last trimesters unless there are compelling reasons. There is no evidence from animal work that it is free from hazard.

Breast-Feeding

Trimipramine is contra-indicated during lactation.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Trimipramine may initially impair alertness. Patients should be warned of the possible hazard when driving or operating machinery.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention:

Common (≥1/100 to <1/10)

Rare (≥1/10,000 to <1/1,000)

Not known (cannot be estimated from the available data)

The following adverse effects, although not necessarily all reported with trimipramine, have occurred with other tricyclic antidepressants:-

Atropine-like side effects including dry mouth, disturbance of accommodation, tachycardia, constipation and hesitancy of micturition are common early in treatment but usually lessen. Other common adverse effects include drowsiness, sweating, postural hypotension, tremor and skin rashes. Interference with sexual function may occur.

System Organ Class (Soc)	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Rare	Bone marrow failure, agranulocytosis
Metabolism and nutrition disorders	Not known	Hyperglycaemia- Epidemiologic studies have identified an increased risk of diabetes mellitus in depressed patients receiving tricyclic antidepressants (see section 4.4).
Psychiatric disorders	Rare	Hypomania, mania, delusion may be exacerbated during treatment with tricyclic antidepressants
	Not known	Cases of suicidal ideation and suicidal behaviours have been reported during trimipramine therapy or early after treatment discontinuation (see section 4.4).
Nervous system disorders	Rare	Seizure, Neuropathy peripheral
Cardiac disorders	Not known	Cardiac arrhythmias and severe hypotension are likely to occur with high dosage or in deliberate overdosage. They may also occur in patients with pre-existing heart disease taking normal dosage. Torsade de pointes (see section 4.4).
Hepatobiliary disorders	Rare	Cholestatic jaundice
General disorders and administration site conditions	Not known	Withdrawal syndrome: symptoms may occur on abrupt cessation of therapy and include insomnia, irritability and excessive perspiration. Adverse effects such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken trimipramine during the last trimester of pregnancy.
Investigations	Not known	Electrocardiogram QT prolonged (see section 4.4).

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reaction

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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and management

Acute overdosage may be accompanied by hypotensive collapse, convulsions coma, QT interval prolongation, torsades de pointes. Overdose may result in a fatal outcome. Provided coma is not present, gastric lavage should be carried out without delay even though some time may have passed since the drug was ingested. Patients in coma should have an endotracheal tube passed before gastric lavage is started. Absorption of trimipramine is slow but, as cardiac effects may appear soon after the drug is absorbed, a saline purge should be given. Electrocardiography monitoring is essential.

It is important to treat acidosis as soon as it appears with, for example, 20 ml per kg of M/6 sodium lactate injection by slow intravenous injection. Intubation is necessary, and the patient should be ventilated before convulsions develop. Convulsions should be treated with diazepam administered intravenously.

Ventricular tachycardia or fibrillation should be treated by electrical defibrillation. If supraventricular tachycardia develops, pyridostigmine bromide 1 mg (adults) intravenously or propranolol 1 mg (adults) should be administered at intervals as required.

Treatment should be continued for at least three days even if the patient appears to have recovered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; Non-selective monoamine reuptake inhibitors, ATC code: N06AA06.

Trimipramine is a tricyclic antidepressant. It has marked sedative properties.

5.2 Pharmacokinetic properties

Absorption

Trimipramine undergoes high first-pass hepatic clearance, with a mean value for bioavailability of about 41% after oral administration.

Distribution

The absolute volume of distribution is 31 litres/kg and total metabolic clearance is 16 ml/min/kg. Plasma protein binding of trimipramine is about 95%.

Biotransformation

Trimipramine is largely metabolised by demethylation prior to conjugation yielding a glucuronide.

Elimination

The plasma elimination half-life is around 23 hours.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber additional to those already included in other section of SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Sodium lauryl sulphate
Maize starch
Calcium hydrogen phosphate dihydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25˚C. Store in the original packaging.

6.5 Nature and contents of container

PVC/Aluminium blister strips packed in cardboard cartons. Packs of 28 and 84 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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