SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trimipramine 50mg Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Capsule, Hard contains 50 mg Trimipramine

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, Hard

Blue opaque cap/white opaque body, size “1” hard gelatin capsule shells, imprinted with “TRM” on cap and “50” on body with black ink, filled with white to off-white powder.

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.

Children

Not recommended.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to trimipramine maleate 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:

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 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 patients on long term treatment with Trimipramine.

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 patients receiving therapy for hyperthyrodism.

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 cautiously when co-administered with:

• Buprenorphine/opioids, as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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).

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.

Breastfeeding

Trimipramine is contraindicated during lactation.

Fertility

There is insufficient information available on the effects of trimipramine on human fertility.

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

Cases of suicidal ideation and suicidal behaviours have been reported during trimipramine therapy or early after treatment discontinuation (see section 4.4).

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. Other cardiac disorders include QT interval prolongation, torsade de pointes (see section 4.4).

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 micturation 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.

Serious adverse effects are rare; the following have been reported: depression of the bone marrow, including agranulocytosis, cholestatic jaundice, hypomania, convulsions and peripheral neuropathy. Psychotic manifestations including mania and paranoid delusions, may be exacerbated during treatment with tricyclic antidepressants.

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.

Hyperglycaemia. Epidemiologic studies have identified an increased risk of diabetes mellitus in depressed patients receiving tricyclic antidepressants (see section 4.4).

Withdrawal 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.

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 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

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 a 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 1mg (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

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

The absolute volume of distribution is 31 litres/kg.

The metabolic clearance is 16 ml/min/kg.

Plasma protein binding of trimipramine is about 95%. The plasma elimination half-life is around 23 hours. Trimipramine is largely metabolised by demethylation prior to conjugation yielding a glucuronide.

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

Capsule Core

Cellulose, Microcrystalline (E460)

Maize starch

Silica, colloidal anhydrous

Magnesium Stearate

Capsule Shell

Titanium Dioxide (E171)

Brilliant blue FCF (E133)

Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottles or Securitainers of 50 capsules, hard.

Cartons containing opaque PVdC coated PVC/aluminium blisters of 28 capsules, hard.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares Block,
Odyssey Business Park,
West End Road,
Ruislip, HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0682

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/06/2023

10 DATE OF REVISION OF THE TEXT

16/08/2024