

1. Name of the Medicinal Product

Triptafen-M Tablets

2. Qualitative and Quantitative Composition

Each tablet contains 10mg amitriptyline hydrochloride BP and 2mg perphenazine BP.

3. Pharmaceutical Form

Tablets

4.1 Therapeutic indications

Triptafen-M tablets are indicated for the treatment of mild to moderate depression associated with anxiety.

4.2 Posology and method of administration

Dosage: Adults and Elderly

One tablet three times a day. An additional tablet may be taken at night if necessary. Failure to obtain a response within 4 weeks indicates that the treatment should be reviewed. Treatment with Triptafen-M should not continue beyond three months.

Children

Triptafen-M tablets are not suitable for use in children under 14 years old.

Method of Administration: Oral

4.3 Contraindications

Triptafen-M tablets should not be used by patients with glaucoma, urinary retention, congestive heart failure, coronary artery disease, epilepsy, severely impaired liver function; concurrent administration of other antidepressant drugs especially monoamine oxidase inhibitors (MAOIS). Triptafen-M should not be used for patients with leucopenia, or with drugs liable to cause bone marrow depression.

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.

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 behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Persistent oral dyskinesia has been reported occasionally, particularly in elderly female patients, after long-term treatment with potent phenothiazine drugs including perphenazine. Consequently triptafen M should be prescribed with regular patient re-assessments.

4.5 Interactions with other medicinal products and other forms of interaction

Triptafen-M should not be given concurrently with monoamine oxidase inhibitors (MAOIS). At least 14 days must have elapsed after withdrawal of MAOI treatment before Triptafen-M therapy is started.

Based on the known metabolism of amitriptyline, the protease inhibitor, ritonavir, may increase the serum levels of amitriptyline. Therefore careful monitoring of therapeutic and adverse effects is recommended when these drugs are administered concomitantly.

4.6 Pregnancy and lactation

Unless there are compelling reasons, Triptafen-M should not be used during pregnancy, particularly during the first and last trimesters, because there is inadequate evidence of its safety during human pregnancy.

Although it has been used without apparent ill-effects during pregnancy, there is animal data which indicates harmful effects occur when given at exceptionally high doses.

Lactation:

Triptafen-M should not be used during breast feeding.

4.7 Effects on ability to drive and use machines

Triptafen-M may cause drowsiness and blurred vision, and patients who drive or operate machinery should be warned about these effects.

4.8 Undesirable effects

Cases of suicidal ideation and suicidal behaviors have been reported during Triptafen-M therapy or early after treatment discontinuation (see section 4.4).”

Triptafen-M may cause dryness of the mouth, and occasionally tachycardia. It may cause a slight fall in blood pressure, tremor and extra-pyramidal side effects as well as pruritis, nausea, diarrhoea and indigestion.

4.9 Overdose

Amitriptyline

Ingestion of 750 mg or more by an adult may result in severe toxicity. The effects in overdose will be potentiated by simultaneous ingestion of alcohol and other psychotropic drugs.

Overdose effects are mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain. There is also a quinidine-like effect on the myocardium.

Peripheral symptoms

Commonly include sinus tachycardia, hot dry skin, dry mouth and tongue, dilated pupils and urinary retention.

The most important ECG feature of toxicity is prolongation of the QRS interval, which indicates a high risk of ventricular tachycardia. In very severe poisoning the ECG may be bizarre. Rarely, prolongation of the PR interval or heart block may occur. QT interval prolongation and torsade de pointes has also been reported.

Central symptoms

Commonly include ataxia, nystagmus and drowsiness, which may lead to deep coma and respiratory depression. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes may be abolished. A divergent squint may be present.

Hypotension and hypothermia may occur. Fits occur in >5% of cases.

During recovery confusion, agitation and visual hallucinations may occur.

Management

An ECG should be taken and in particular the QRS interval should be assessed since prolongation signifies an increased risk of arrhythmia and convulsions. Give activated charcoal by mouth or naso-gastric tube if more than 4 mg/kg has been ingested within one hour, provided the airway can be protected. A second dose of charcoal should be considered after two hours in patients with central features of toxicity who are able to swallow.

Tachyarrhythmias are best treated by correction of hypoxia and acidosis. Even in the absence of acidosis 50 millimoles of sodium bicarbonate should be given by intravenous infusion to adults with arrhythmias or clinically significant QRS prolongation on the ECG.

Control convulsions with intravenous diazepam or lorazepam. Give oxygen and correct acid base and metabolic disturbances. Phenytoin is contraindicated in tricyclic overdose, because, like tricyclic antidepressants, it blocks sodium channels and may increase the risk of cardiac arrhythmias. Glucagon has been used to correct myocardial depression and hypotension.

Perphenazine:

Emergency treatment should be started immediately. Patients should be hospitalised as soon as possible. Concurrent ingestion of alcohol or other drugs or some medical explanation for the patient's condition should be considered.

Symptoms:

Perphenazine overdose primarily involves the extrapyramidal system. Overdose symptomatology is generally an extension of the many pharmacologic effects of perphenazine.

CNS depression progressing from drowsiness to stupor or coma with areflexia may occur. Patients with early or mild intoxication may experience restlessness, confusion and excitement. Other symptoms include hypotension, tachycardia, hypothermia, miosis, tremor, muscle twitching, spasm, rigidity or hypotonia, convulsions, difficulty in swallowing and breathing, cyanosis and respiratory and/or vasomotor collapse, possibly with sudden apnea.

Treatment:

Treatment is symptomatic and supportive. There is no specific antidote. The patient should be induced to vomit even if emesis has occurred spontaneously. Pharmacologic vomiting by the administration of ipecac syrup is a preferred method. It should be noted that ipecac has central mode of action in addition to its local gastric irritant properties, and the central mode of action may be blocked by the antiemetic effect of perphenazine products. Vomiting should not be induced in patients with impaired consciousness. The action of ipecac is facilitated by physical activity and by the administration of 240 to 350 ml of water. If emesis does not occur within 15 minutes, the dose of ipecac should be repeated. Precautions against aspiration must be taken, especially in infants and children. Following emesis any drug remaining in the stomach may be adsorbed by activated charcoal administered as a slurry with water. If vomiting is unsuccessful or contraindicated, gastric lavage should be performed. Isotonic and one-half isotonic saline are the lavage solutions of choice. Saline cathartics, such as milk of magnesia, draw water into the bowel by osmosis and therefore may be valuable for their action in rapid dilution of bowel content.

5.1 Pharmacodynamic Properties

Triptafen-M contains amitriptyline hydrochloride which is a tricyclic antidepressant, and which does not inhibit monoamine oxidase. The action of amitriptyline hydrochloride is believed to be related to its ability to block the re-uptake of released monoamines into the pre-synaptic nerve endings. It has anticholinergic effects and sedative properties.

The perphenazine in Triptafen-M is a depressant which blocks dopamine receptors in the central nervous system.

5.2 Pharmacokinetic Properties

Triptafen-M is readily absorbed from the gastro-intestinal tract. Both amitriptyline hydrochloride and perphenazine are rapidly taken up by the tissues and widely distributed throughout the body. Amitriptyline hydrochloride may be secreted in breast milk: perphenazine readily crosses the placenta.

Amitriptyline hydrochloride is metabolised by demethylation, hydroxylation, conjugation with glucuronic acid with some N-oxide formation. The metabolites include nortriptyline, and didesmethylamitriptyline, their conjugates and their 10-hydroxy derivatives, and amitriptyline N-oxide. Perphenazine is metabolised by sulphoxidation, demethylation, hydroxylation, N-oxidation, glucuronic acid conjugation, and possibly ring fission.

About 90% of an intravenous dose of amitriptyline hydrochloride is excreted in the urine, of which 1 to 5% is excreted unchanged. About 8% is excreted in the faeces.

20% to 70% of perphenazine is excreted in the urine, very little is unchanged. 5% is excreted in the faeces.

5.3 Preclinical Safety Data

No further relevant data

6.1 List of Excipients

Tablet Core

Lactose BP

Magnesium Stearate 572 BP

Maize starch BP

Maize starch pregelatinised BP

Tablet Coat

Acacia E414 BP

Gelatin BP

Butyl hydroxybenzoate BP

Calcium phosphate BP

Calcium sulphate dihydrate

Maize starch BP

Sunset yellow E100

Erythrosine E127

Opaglos aqueous(Purified water EP, Beeswax white BP, Carnauba wax yellow BP,

Polysorbate 20 BP and Sorbic acid)

Sugar

Mineral water

6.2 Incompatibilities

None stated

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

No special conditions

6.5 Nature and Contents of Container

Cardboard carton containing 10 strips of 10 tablets of Triptafen-M packed in aluminium foil.

6.6 Instructions for Use/Handling

None

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 12762/0200

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 January 1994

10. DATE OF (PARTIAL) REVISION OF THE TEXT

February 2008