

1. Trade name of the medicinal product

Triptafen Tablets

2. Qualitative and Quantitative Composition

Each pink sugar coated tablet contains 25mg amitriptyline hydrochloride BP and 2mg perphenazine BP.
100 tablets are supplied in cartons, with 10 foil strips of 10 tablets.

3. Pharmaceutical Form

Tablets

4.1 Therapeutic indications

Triptafen tablets are indicated for the treatment of 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 should not continue beyond three months.

Children
Triptafen tablets are not suitable for use in children under 18 years of age.

Method of Administration: Oral

4.3. Contraindications

Triptafen tablets should not be used in those who are hypersensitive to any of the ingredients of the tablets, in patients with glaucoma, porphyria, urinary retention, congestive heart failure, arrhythmias, coronary artery disease, recent myocardial infarction, heart block, epilepsy, severely impaired liver function, mania; concurrent administration of other antidepressant drugs especially monoamine oxidase inhibitors (MAOI'S). Triptafen 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 behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Exacerbation of schizophrenia or pre-existing agitation mania may occur. Patients with severe depression should be kept under close surveillance, particularly during the early stages of treatment.

Patients receiving this agent should be kept under regular surveillance with particular attention to effects on cerebral function, haemopoietic function, cardiac conduction disorders, liver function and the eye particularly if other concurrently administered drugs also have potential effects on these systems.

If patients on tricyclic anti-depressants require surgery, the anaesthetist should be informed of medications in advance in view of the risk of cardiovascular complication.

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant. (See section 4.8 Undesirable Effects).

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

The drug should only be used with great caution in the young and the elderly who are likely to show behavioural effects or postural hypotension and in patients with a history of epilepsy or recent convulsions, schizophrenia, hepatic insufficiency, urinary retention, narrow-angle glaucoma, hyperthyroidism, or cardiovascular disorders, or in conjunction with electroconvulsive therapy, or with existent blood dyscrasias.

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factor for VTE, all possible risk factors for VTE should be identified before and during treatment with Triptafen Tablets and preventive measures undertaken.

Increased Mortality in Elderly people with Dementia

Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Triptafen Tablets is not licensed for the treatment of dementia-related behavioural disturbances.

Excipient Warnings:

Butyl hydroxybenzoate is contained in this product which may cause allergic reactions (possibly delayed).

Triptafen Tablets contain lactose and sucrose. Patients with rare hereditary problem of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

MAO inhibitors: Triptafen should not be given concurrently with monoamine oxidase inhibitors (MAOIs). Because of the persistent action of MAOIs, at least 14 days must have elapsed after withdrawal of MAOI treatment before Triptafen therapy is started.

CNS depressants: Concomitant administration of this product with other medications such as central nervous system depressants (including alcohol and anaesthetics), may result in accentuation of their effects, while potentiation of action may occur with analgesics.

Anticholinergic agents: Excessive anticholinergic effects may occur when tricyclic antidepressants are combined with anticholinergic drugs. Paralytic ileus, urinary retention or acute glaucoma may be precipitated, especially in elderly patients. (see section 4.8)

Sympathomimetic agents: Adrenaline (epinephrine), Noradrenaline (norepinephrine), isoprenaline and phenylephrine: increased risk of hypertension and arrhythmias when given with tricyclics

Antihypertensive: In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but amitriptyline may block the antihypertensive action of guanethidine, and clonidine. Sudden withdrawal of amitriptyline from a patient stabilized on a postganglionic blocking agent may cause serious hypotension. All antihypertensive therapy should be reviewed following withdrawal of a tricyclic antidepressant as well as during treatment.

Anaesthetics, General: increased risk of arrhythmias and hypotension when tricyclics given with general anaesthetics

Anxiolytics & hypnotics: increased sedative effect when tricyclics given with anxiolytics and hypnotics.

Antiarrhythmics (amiodarone, disopyramide, flecainide, procainamide, propafenone, quinidine, sotalol): increased risk of ventricular arrhythmias when tricyclics given concomitantly

Antidepressants: plasma concentration of some tricyclics increased by SSRIs
Antiepileptics (barbiturates, carbamazepine, phenytoin, primidone): tricyclics antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration).

Antihistamines: increased antimuscarinic and sedative effects when tricyclics given with antihistamines

Antipsychotics: plasma concentration of tricyclics increased by antipsychotics, possibly increased risk of ventricular arrhythmias

Cimetidine: metabolism of amitriptyline inhibited by cimetidine (increased plasma concentration).

Coumarins: tricyclics may enhance or reduce anticoagulant effect of coumarins

Diltiazem, Verapamil: plasma concentration of tricyclics possibly increased

Disulfiram: concomitant amitriptyline reported to increase disulfiram reaction with alcohol. Delirium has been reported in patients taking Triptafen with disulfiram.

Diuretics: increased risk of postural hypotension when tricyclics given with diuretics

Duloxetine: possible increased serotonergic effects when amitriptyline given with duloxetine

Lithium: risk of toxicity when tricyclics given with lithium

Moxifloxacin: increased risk of ventricular arrhythmias when tricyclics given with moxifloxacin —avoid concomitant use

Nitrates: tricyclics reduce effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth)

Pimozide: increased risk of ventricular arrhythmias when tricyclics given with pimozide —avoid concomitant use

Rifampicin: plasma concentration of tricyclics possibly reduced by rifampicin

Ritonavir: 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.

St. John's Wort: plasma concentration of amitriptyline reduced by St John's wort

Selegiline: CNS toxicity reported when tricyclics given with selegiline

Sibutramine: increased risk of CNS toxicity when tricyclics given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Thioridazine: increased risk of ventricular arrhythmias when tricyclics given with thioridazine —avoid concomitant use

Thyroid Hormones: effects of amitriptyline enhanced by thyroid hormones
Patients should be closely supervised, and the dosage of all medications carefully adjusted when these drugs are administered concomitantly.

Tramadol: increased risk of CNS toxicity when tricyclics given with tramadol.

4.6. Pregnancy and lactation

Pregnancy:

Unless there are compelling reasons, Triptafen 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.

Neonates exposed to antipsychotics (including Perphenazine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation:

Breast feeding mothers: Triptafen is detectable in breast milk. Because of the potential for serious adverse reactions in infants from Triptafen, a decision should be made whether to discontinue breast feeding or discontinue the drug.

4.7. Effects on ability to drive and use machines

Triptafen may cause drowsiness, blurred vision or affect concentration. Patients receiving this medication should not drive or operate machinery unless it has been shown not to interfere with physical or mental capacity.

4.8. Undesirable effects

Amitriptyline:

Cases of suicidal ideation and suicidal behaviours have been reported during Triptafen therapy or early after treatment discontinuation (see section 4.4). Abrupt withdrawal after prolonged administration has caused nausea, headache and malaise. Reports have associated gradual withdrawal with transient symptoms including irritability, restlessness, as well as dream and sleep disturbances during the first two weeks or dosage reduction.

Frequencies of the ADRs is not known (cannot be estimated from the available data).

System Organ Class	Adverse Reactions
Blood and Lymphatic system disorders	bone marrow depression including agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia
Immune system disorders	skin rash, urticaria, photosensitisation, oedema of face and tongue
Endocrine disorders	testicular swelling, gynaecomastia, breast enlargement, galactorrhoea, increased or decreased libido, impotence, interference with sexual function, elevation or lowering of blood sugar levels, syndrome of inappropriate ADH (antidiuretic hormone) secretion
Psychiatric disorders	confusional states, disturbed concentration, disorientation, delusions, hallucinations, hypomania, excitement, anxiety, restlessness, insomnia, nightmares
Nervous system disorders	peripheral neuropathy, numbness, tingling and paraesthesiae of the extremities, inco-ordination, ataxia, tremors, coma, convulsions, alteration of the EEG, extrapyramidal symptoms including abnormal involuntary movements and tardive dyskinesia, dysarthria and tinnitus. Anticholinergic: dry mouth, blurred vision, disturbance of accommodation, increased intra-ocular pressure, constipation, paralytic ileus, hyperpyrexia, urinary retention, urinary tract dilatation
Cardiovascular disorders	stroke, myocardial infarction, heart block, syncope, postural hypotension, hypertension, palpitations, tachycardia, non-specific ECG changes and changes in AV-conduction. Arrhythmias and severe hypotension are likely to occur with high dosage or overdose
Gastro-intestinal disorders	nausea, epigastric distress, vomiting, anorexia, stomatitis, unpleasant taste, diarrhoea, parotid swelling, black tongue
Hepatobiliary disorders	rarely hepatitis (including altered liver function and jaundice).
Skin and subcutaneous tissue disorders	Increased perspiration and alopecia
Renal and urinary disorders	Urinary frequency
General Disorders	dizziness, headache, weakness, fatigue, weight loss, mydriasis, drowsiness, increased appetite and weight gain (may be a drug reaction or due to relief of the

	depression)
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Class effects

Mania or hypomania has been reported rarely within 2-7 days of stopping chronic therapy 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.

Paediatric population

Adverse reactions such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers had taken tricyclic antidepressants in the last trimester of pregnancy.

Perphenazine:

Frequencies of the ADRs is not known (cannot be estimated from the available data).

System Organ Class	Adverse Reactions
Blood and Lymphatic system disorders	Agranulocytosis; Transient leucopenia
Immune system disorders	Antinuclear antibodies; Systemic lupus erythematosus (SLE)
Endocrine disorders	Hyperprolactemia
Psychiatric disorders	Confusional state, Agitation; Excitement; Insomnia.
Nervous system disorders	Choreiform movements of the extremities; Dyskinesias and movement disorders including akathisia, orofacial dyskinesia, extrapyramidal disorder and tardive dyskinesias; Dystonia; Hyperreflexia; Disturbances in consciousness including somnolence, stupor; Dizziness. Parkinsonism; Tremors; Epileptic fits; CSF protein abnormalities; Impaired regulation of body temperature. Neuroleptic malignant syndrome has been reported in patients treated with neuroleptic drugs. It is a relatively uncommon, potentially lethal syndrome, characterized by severe extrapyramidal dysfunction, with rigidity and eventual stupor or coma, hyperthermia and autonomic disturbances, including cardiovascular effects.
Eye Disorders	Oculogyric crisis; Visual disorders including blurring of vision, Corneal and lens deposits; Pigmented retinopathy
Cardiovascular disorders	Sudden unexplained death, cardiac arrest and Torsades de pointes , QT prolongation, Ventricular arrhythmias VF ,VT, Tachycardia, hypotension
Respiratory, thoracic and mediastinal disorders	Nasal stuffiness
Gastro-intestinal disorders	Nausea; Oral dryness and saliva altered, Gastrointestinal atonic and hypomotility disorders including constipation, paralytic ileus

Hepatobiliary disorders	Cholestasis and jaundice, Obstructive jaundice
Skin and subcutaneous tissue disorders	Photosensitivity; Rashes; Hyperhidrosis
Renal and urinary disorders	Urinary hesitancy or urinary retention
Pregnancy, puerperium and perinatal conditions	Drug withdrawal syndrome neonatal (see 4.6) – Frequency not known.
Reproductive system and breast disorders	Menstruation with decreased bleeding Amenorrhea; Erectile dysfunction; impaired ejaculation. Gynaecomastia ; Galactorrhoea.
General Disorders	Fatigue; Oedema, weight gain, Headaches
Investigations	Hyperglycemia, false positive pregnancy tests; Raised serum cholesterol

Class effects

With the piperazine group (of which perphenazine is an example), the extrapyramidal symptoms like Opisthotonus, trismus, torticollis, retrocollis, aching and numbness of the limbs, motor restlessness, oculogyric crisis, hyperreflexia, dystonia, including protrusion, slurred speech, dysphagia, akathisia, dyskinesia, parkinsonism and ataxia are more common, and others (e.g., sedation, jaundice, blood dyscrasias) are less frequent.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs- Frequency unknown

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.

Standard measures (oxygen, i.v. fluids, corticosteroids) should be used to manage circulatory shock or metabolic acidosis. An open airway and adequate fluid intake should be maintained.

Body temperature should be regulated. Hypothermia is expected, but severe hyperthermia may occur and must be treated vigorously.

An ECG should be taken and close monitoring of cardiac function instituted for not less than 5 days. Cardiac arrhythmias may be treated with neostigmine, pyridostigmine or propranolol. Digitalis should be considered for cardiac failure.

Vasopressors, such as norepinephrine or phenylephrine, may be used to treat hypotension, but epinephrine should not be used.

Anticonvulsant agents, such as an inhalation anesthetic, diazepam or paraldehyde, are recommended for control of seizures, but not barbiturates, since perphenazine increases the CNS depressant action but not the anticonvulsant action of barbiturates. Since phenothiazines lower the convulsive threshold, convulsant stimulants such as picrotoxin or pentylenetetrazol should not be given.

If acute parkinson-like symptoms result from perphenazine intoxication, benztropine mesylate, trihexyphenidyl or diphenhydramine may be administered.

Arousal may not occur for 48 hours following toxic overdose, despite supportive and contra-active measures. Dialysis is of no value in treatment.

5.1. Pharmacodynamic properties

Triptafen 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 is a depressant which blocks dopamine receptors in the central nervous system.

5.2 Pharmacokinetic Properties

Triptafen 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.

Perphenazine is extensively metabolised by Sulphoxidation, Demethylation, Hydroxylation, N-Oxidation, Glucuronic Acid Conjugation and possibly Ring Fusion.

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 B.P.
Magnesium Stearate B.P.
Maize Starch Special B.P.
Maize starch pregelatinised B.P.

Tablet Coat

Acacia (E414) B.P.
Gelatin B.P.
Butyl hydroxybenzoate B.P.
Calcium phosphate B.P.
Calcium sulphate dihydrate 516
Maize starch B.P.
Tartrazine Ariavit 311840 (E120)
Erytbrosine Ariavit 311807 (E127)
Opaglos aqueous(Purified water EP, Beeswax White BP,Carnauba wax yellow BP,
Polysorbate 20 BP and Sorbic acid.)
Sugar
Mineral water
Opacode black(Shellac glaze, Iron oxide black (E172),N-Butyl alcohol,Purified water,
Propylene glycol (E1520),Industrial Methylated Spirit and Isopropyl Alcohol)

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 packed in aluminium foil.

6.6 Instructions for Use/Handling

None

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surry
CR0 0XT
UK

8. MARKETING AUTHORISATION NUMBER

PL 12762/0201

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

09/12/2011