

PERPHENAN TABLETS

Summary of Product Characteristics

1. Name of the medicinal product

Perphenan 4mg

Perphenan 8mg

2. Qualitative and quantitative composition

Perphenan 4mg - Each tablet contains 4mg Perphenazine

Perphenan 8mg - Each tablet contains 8mg Perphenazine

3. Pharmaceutical form

Film coated tablet

Perphenan 4 mg - White, round, bi-convex, coated tablets. Both sides plain.

Perphenan 8 mg - Gray, round, bi-convex, coated tablets. Both sides plain.

4. Clinical particulars

4.1 Therapeutic indications

Tranquilizer, antiemetic

4.2 Posology and method of administration

Adults:

4 mg perphenazine three times a day.

Dose may have to be adjusted upwards or downwards according to patient response. Total daily dose should not exceed 24mg.

Treatment should be started and dosage increased under close supervision.

Treatment should be reviewed at intervals to avoid indiscriminate or unduly prolonged use.

Elderly

One quarter or one half of the recommended adult dosage.

Perphenazine should be used with caution in the elderly, see section 4.4 for details.

Children

Perphenazine should not be given to children under the age of 14 years.

Method of administration: Oral

Withdrawal symptoms seen on discontinuation of Perphenazine:

Abrupt discontinuation should be avoided, see section 4.4 for details. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered.

Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Perphenazine should not be administered to patients with leucopenia, or in association with drugs liable to cause bone marrow depression, or to patients in comatose states.

Perphenazine should not be administered to patients with a known hypersensitivity to perphenazine or any of the other excipients.

4.4 Special warnings and precautions for use

The possibility of suicide in depressed patient's remains during treatment and until significant remission occurs. Perphenazine should not be used alone when depression is predominant.

Perphenazine should be used with caution in patients with liver disease; severe respiratory disease; renal failure; epilepsy and conditions predisposing to epilepsy such as alcohol withdrawal or brain damage; Parkinson's disease; patients who have shown sensitivity to other phenothiazines; personal or family history of narrow angle glaucoma; hypothyroidism, myasthenia gravis; phaeochromocytoma; or prostatic hypertrophy.

Perphenazine should be used with caution in patient with cardiovascular disease, such as cardiac arrhythmias, congestive heart failure, and a personal or family history of QT prolongation.

The concomitant use of other neuroleptics should be avoided because of possible potentiation of effects.

Since temperature regulation may be impaired, care should be taken in extremely hot and in cold weather, especially in the elderly and frail because of risk of hypothermia.

Acute withdrawal symptoms including nausea, vomiting, sweating and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore gradual withdrawal is advisable.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions affecting Perphenazine

Plasma concentrations of antipsychotics may increase when given with ritonavir or tricyclic antidepressants. Metabolism of perphenazine is inhibited when taken with paroxetine.

Kaolin or antacids may decrease the absorption of perphenazine. Memantine may reduce the effects of perphenazine

Interactions affecting other drugs

Perphenazine may enhance the hypotensive effect of other antihypertensive medication.

Risk of sedation and/or toxicity when perphenazine is administered with CNS depressants such as alcohol, antipsychotics, opioids, sedatives, and antihistamines.

Tramadol when given with perphenazine may increase the risk of convulsions.

Risk of extrapyramidal reactions/anticholinergic effects when perphenazine is administered with Lithium, metoclopramide, fluoxetine.

Perphenazine may antagonise the therapeutic effects of anticonvulsants.

Perphenazine may antagonise the therapeutic effects of drugs used for Parkinson's disease and other movement disorders.

Perphenazine antagonises the hypoglycaemic effect of sulphonylureas. Phenothiazines may enhance the absorption of corticosteroids and digoxin. May affect action of anticoagulants and increase the bleeding time.

Increased risk of toxicity when perphenazine is given with myelosuppressive drugs.

Use with concomitant QT prolonging drugs, drugs inhibiting the metabolism of perphenazine, and with drugs causing electrolyte imbalance is not recommended. If the benefit is considered to outweigh the risk in the individual patient, co-administration should be undertaken with caution and ECG monitoring should be considered (see section 4.4).

4.6. Pregnancy and lactation

The safety of perphenazine in pregnancy has not yet been established.

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.

Phenothiazines may be excreted in breast milk; breast feeding should be suspended during treatment.

4.7 Effects on ability to drive and use machines

Perphenazine may impair alertness, particularly when treatment is started. This may be potentiated by alcohol. Perphenazine may cause sedation and patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Not all the following side-effects have been reported with this specific drug. However pharmacological similarities with other phenothiazine derivatives require that each be considered. Many of the side effects may be prevented by a reduction in dosage. 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, discoloration, aching and rounding of the tongue, tonic spasm of the masticatory muscles, tight feeling in the throat, slurred speech, dysphagia, akathisia, dyskinesia, parkinsonism and ataxia are more common, and others (e.g., sedation, jaundice, blood dyscrasias) are less frequent.

Frequencies of the ADRs is not defined, however the below mentioned ADRs have been reported.

Disorders of the Blood and the Lymphatic system

Agranulocytosis; Transient leucopenia.

Cardiac disorders

Tachycardia, Ventricular arrhythmias VF, VT. Sudden unexplained death, cardiac arrest and Torsades de pointes, QT prolongation.

Endocrine disorders

Hyperprolactemia.

Disorders of the eye

Oculogyric crisis; Visual disorders including blurring of vision Corneal and lens deposits; Pigmented retinopathy.

Gastrointestinal disorders

Nausea; Oral dryness and saliva altered.

Gastrointestinal atonic and hypomotility disorders including constipation, adynamic ileus

General disorders

Fatigue; Oedema, weight gain

Hepato-biliary disorders

Cholestasis and jaundice, Obstructive jaundice.

Disorders of the immune system

Antinuclear antibodies; Systemic lupus erythematosus (SLE).

Investigations

Hyperglycemia, false positive pregnancy tests; Raised serum cholesterol

Neurological disorder:

Headaches; 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

Psychiatric disorders

Confusional state, Agitation; Excitement; Insomnia.

Renal and urinary disorders

Urinary hesitancy or urinary retention

Disorders of the Reproductive system and breast

Menstruation with decreased bleeding Amenorrhea; Erectile dysfunction; impaired

ejaculation. Gynaecomastia; Galactorrhoea.

Respiratory, thoracic and mediastinal disorders

Nasal stuffiness.

Skin and subcutaneous tissue disorders

Photosensitivity; Rashes; Hyperhidrosis.

Pregnancy, puerperium and perinatal conditions:

Drug withdrawal syndrome neonatal (see 4.6) – Frequency not known.

Vascular disorders

Hypotension.

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

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@mo h.gov.il>

4.9 Overdose

In patients who have overdosed, general supportive measures must be instituted.

Gastric lavage should be considered up to 2 hours after ingestion. Emetics are unlikely to be effective because perphenazine is a potent anti-emetic.

If hypotension is severe, fluid infusion may be needed. Central nervous system depression is treated conservatively.

Temperature should be monitored to detect hypothermia, and this should be treated appropriately. If convulsions occur, these should be managed by standard means.

Continuous monitoring of ECG should be instituted to detect any regularities of rhythm or QT interval for at least 48 hours.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

Perphenazine is absorbed readily from the gastro-intestinal tract. It is distributed widely throughout the body, and crosses the placenta.

Perphenazine is metabolised extensively by sulfoxidation, demethylation, hydroxylation, N-oxidation, glucuronic acid conjugation, and possible ring fission.

20 to 70% 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. Pharmaceutical particulars

List of excipients

Perphenan 4 mg:

Lactose monohydrate, corn starch, microcrystalline cellulose, gelatin, magnesium stearate

Coating contains: Polyvinyl alcohol-partially hydrolyzed, titanium dioxide, PEG 3350 and talc

Perphenan 8 mg:

Lactose monohydrate corn starch, microcrystalline cellulose, gelatin, sodium starch glycolate and magnesium stearate

Coating contains: Hypromellose, Titanium dioxide, Polydextrose, PEG and Black iron oxide

Incompatibilities

None known

6.1 Shelf life

36 months.

6.2 Special precautions for storage

Do not store above 25°C.

6.3 Nature and contents of container

Perphenan 4 mg - PVC aluminum foil blister pack containing 30 tablets or 1000 tablets.

Perphenan 8 mg - PVC aluminum foil blister pack containing 20 tablets, 30 or 1000 tablets.

Nor all pack sizes may be marketed.

6.4 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder

Taro Pharmaceutical Industries Ltd

14 Hakitor Street

Haifa Bay, 2624761

8. Marketing authorisation number(s)

Perphenan 4 mg – 015.38.24729

Perphenan 8 mg – 123.49.24730

9. Date of revision of the text

March 2016