

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0899/029/001

Case No: 2043122

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Goldshield Pharmaceuticals Ltd

NLA Tower, 12-16 Addiscombe Road,Croydon, Croydon, Surrey CRO 0XT, England

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fentazin 2mg Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **27/11/2007** until **17/09/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fentazin 2 mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg Perphenazine.

Excipients: Lactose monohydrate 130.95 mg
Sucrose 128.72 mg
Butyl parahydroxybenzoate 6 micrograms

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet

Biconvex, white, sugar-coated tablets with the code '1C' on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an adjunct to the short term management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour, schizophrenia, treatment of symptoms and prevention of relapse, other psychoses especially paranoid, mania and hypomania, nausea and vomiting.

Because of the hazard of severe extra-pyramidal reactions, Fentazin is not indicated for the treatment of agitation and restlessness in the elderly.

4.2 Posology and method of administration

For Oral Administration only.

Adults:

The usual total daily dose is 12 mg given in divided doses. As there may be variability of individual response and dosage requirement, the dose may be adjusted upwards or downwards according to patient response. The maximum dose in 24 hours should not exceed 24 mg.

Treatment should be started and dosage increased under close supervision.

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

Elderly:

One quarter or one half of the recommended adult dose for adults may be sufficient for a therapeutic response in the elderly.

Children:

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

Method of administration:

Oral.

4.3 Contraindications

Use in patients with a history of jaundice or with existent liver dysfunction.

Use in patients with uncontrolled cardiac decompensation.

Use in patients hypersensitive to the active ingredient.

Fentazin should not be administered to patients with leucopenia, or in association with drugs liable to cause bone marrow depression. It should not be given to patients in a comatose state.

4.4 Special warnings and precautions for use

Acute withdrawal symptoms including nausea, vomiting and insomnia have been reported after abrupt cessation of high doses of phenothiazines, and gradual withdrawal is advised.

Patients receiving phenothiazines over a prolonged period require regular and careful surveillance with particular attention for their potential for inducing eye changes, effects on haemopoiesis, liver dysfunction, myocardial conduction effects, particularly if other concurrently administered drugs also have potential effects on these systems.

Prolonged administration of phenothiazines may result in persistent or tardive dyskinesias, particularly in the elderly.

Phenothiazine should only be used with great caution in patients with coronary insufficiency or cardiac disease.

Caution is indicated in patients with cardiovascular disease or family history of QT prolongation. Baseline ECG is recommended in these patients before initiation of therapy with Fentazin. During the therapy, the need for ECG monitoring should be assessed on individual patient basis. Whilst on therapy, reduce dose if QT is prolonged and discontinue if QTc > 500ms. Periodic electrolyte monitoring of patient is recommended and use of concomitant antipsychotics should be avoided.

Use with caution in patients with epilepsy or predisposed to epilepsy.

Perphenazine rarely causes increased susceptibility to sunburn and patients should be warned to avoid excess exposure. Skin rashes have been reported rarely. Fine deposits in the cornea and lens and pigmented retinopathy have been reported after long-term therapy.

Perphenazine may impair body temperature regulation and cases of severe hypothermia or hyperpyrexia have been reported usually in association with moderate or high dosage of phenothiazines. The elderly or hypothyroid patient may be susceptible to hypothermia. The hazard of hyperthermia may be increased by especially hot or humid weather or by drugs, such as anti-Parkinsonian agents, which impair sweating.

Perphenazine can very rarely cause obstructive jaundice associated with stasis in biliary canaliculi. It has been thought to be a hypersensitivity reaction.

Transient abnormalities of liver function tests may occur in the absence of jaundice.

Adynamic ileus rarely occurs with phenothiazine therapy, but is of particular concern in psychiatric patients who may fail to seek treatment of the condition.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligo or amenorrhoea. Sexual function including, erection and ejaculation is sometimes impaired by perphenazine. Weight gain may occur. Oedema has been reported with phenothiazine medication. Perphenazine may also result in false-pregnancy tests.

Approximately 3-fold increases of cerebrovascular adverse events have been seen in randomised placebo-controlled clinical trials in dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk can not be excluded for other antipsychotics or other patient populations. Fentazin should be used with caution in patients with risk factors for stroke.

Patients with rare hereditary problems 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

Fentazin can increase the central nervous system depression produced by other CNS depressants including alcohol, hypnotics, sedatives or strong analgesics.

It may antagonise the action of adrenaline and other sympathomimetic agents and reverses the blood pressure lowering effects of adrenergic blocking agents such as guanethidine and clonidine. It may impair the metabolism of tricyclic antidepressants, the antiparkinson effects of levodopa, and anti-convulsants.

Undesirable anticholinergic effects can be enhanced by antiparkinson or other anti-cholinergic drugs.

Phenothiazines may enhance the cardiac depressant effects of quinidine, the effect of diazoxide, the effect of neuromuscular blocking agents, and the absorption of corticosteroids and digoxin.

Fentazin may affect diabetic control and anticoagulant therapy. Interaction with lithium must be considered when using Fentazin.

Fentazin should not be taken with tea or coffee because absorption may be impaired by the formation of insoluble precipitates. Absorption may be impaired by antacids.

Fentazin should be administered with caution when concomitantly given with drugs which prolong QT interval or cause electrolyte imbalance.

Proper care should be taken in consuming the drugs which may inhibit the metabolism of Fentazin.

4.6 Pregnancy and lactation

The safety of Fentazin during pregnancy has not been established. Phenothiazines should only be used during pregnancy if it is considered essential by the physician.

Perphenazine is excreted in the breast milk and a mother on perphenazine should not breast feed.

4.7 Effects on ability to drive and use machines

Fentazin may induce drowsiness. Persons taking these drugs should not drive or operate machinery unless the drug has been shown not to interfere with physical or mental ability.

4.8 Undesirable effects

Drowsiness, sedation, dry mouth, postural hypotension, blurred vision, constipation, urinary retention, nausea, headache, eye changes, hormonal effects, agranulocytosis, raised cholesterol and glucose levels, skin rashes, photosensitivity, lens deposits, hypothermia, obstructive jaundice, oculogyric crisis, nasal stuffiness and ECG changes like QT prolongation, ventricular arrhythmias - VF, VT, sudden unexplained death, cardiac arrest & Torsades de pointes.

Use of phenothiazines at high (relative or absolute) doses may induce extrapyramidal side-effects, dyskinesia, akathisia, dystonia. These are likely to be particularly severe in children.

4.9 Overdose

With oral preparations of Fentazin, gastric lavage is recommended.

Emetics are likely to be of little value because Fentazin has potent anti emetic activity of the drug.

Hypotension is not usually a problem, especially if the patient is passing urine satisfactorily. Severe hypotension may

require fluid infusion therapy.

If a vasopressor is required, norepinephrine may be used.

Central nervous system depression is best treated conservatively.

Analeptics should not be used.

Rewarming measures should not be employed unless the body temperature falls below 30°C.

Convulsions may be controlled with by standard methods, but the use of barbiturates should be avoided.

Cardiac monitoring for at least 48 hours is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Perphenazine is a phenothiazine with potent tranquilliser and anti-emetic properties. It is a neuroleptic phenothiazine and it has antagonistic activity, in approximately the following order of potency, against α -receptor agonists, dopamine, serotonin, histamine (H_1 -receptor agonists), muscarinic agonists and bradykinin in peripheral tissues and presumably, in the central nervous system.

Neurotransmission depending on any one of the above receptors is impaired. In addition, there is impairment of transmitter release from adrenergic nerves; however, the neuronal uptake of monoamines is also inhibited and this tends to facilitate transmission. It is not clear to what extent its central effects are attributable to any one, or a combination of these actions.

It has been suggested that the tranquillising action is due to blockade of central adrenergic transmission, but there is evidence to suggest that blockade of serotonergic and dopaminergic transmission may underlie its antischizophrenic activity, and blockade of dopamine receptors appears to be involved in its antiemetic effect and the production of extrapyramidal side-effects.

5.2 Pharmacokinetic properties

Perphenazine undergoes extensive first-pass metabolism by the liver, after oral administration. The half life of Perphenazine is estimated at 8-12 hours but there may be a prolonged elimination phase of up to three weeks.

The elimination of Perphenazine is mainly by metabolism in the liver. It is able to cross the blood brain and placental barriers. The excretion of Perphenazine is detectable in the breast milk of nursing mothers.

5.3 Preclinical safety data

Acute short-term toxicity is available for Perphenazine in both the rat and the mouse, at doses exceeding those prescribed. Oral acute toxicity studies in the rat have shown a no toxic effect level of 318mg/kg. In mice, studies have shown that the level at which no toxic effect was observed at 120mg/kg after a single oral dose. Thus Perphenazine appears to exhibit low acute systemic toxicity.

Reproductive studies have been carried out in both rats and mice and show that specific abnormalities are found and effects on the reduction in fertility have been observed. Craniofacial abnormalities have been observed in mice at doses of 30mg/kg and in the rat at 90mg/kg. The specific mechanism of this has not been fully elucidated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Magnesium stearate

Maize starch

Pregelatinised maize starch

Tablet coating:

Dewaxed Shellac
Acacia
Sucrose
Butyl parahydroxybenzoate
Gelatin
Calcium phosphate
Maize starch
Titanium dioxide (E171)
Talc

Opaglos 6000:

Bleached Shellac
Beeswax, white
Carnauba wax

Printing ink:

Opacode Black containing:
Dewaxed Shellac
Iron oxide black (E172)
Lecithin (Soya)
Dimeticone (Antifoam DC 1510 (food grade))

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

Keep container in the outer carton.

6.5 Nature and contents of container

The tablets are supplied in aluminium foil strips containing 10 tablets, ten foil strips (100 tablets) are presented in a outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Surrey
Croydon CR0 0XT
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 899/29/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 July 1993

Date of last renewal: 18 September 2005

10 DATE OF REVISION OF THE TEXT

October 2006