SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TERRA-ZINE / Trifluoperazine 5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Trifluoperazine HCl BP 5.90 mg

3 PHARMACEUTICAL FORM

Sugar coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Terra-zine is indicated in the treatment of the symptoms of schizophrenia and for the prevention of relapse.

Paranoid Psychosis; mania and hypomania.

As an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour.

4.2 Posology and method of administration

ADULTS:
In the treatment of the symptoms of schizophrenia, paranoid psychosis and mania and hypomania, the recommended starting dose is 5 mg twice a day for physically fit adults. This dose may be increased after one week if necessary to 15 mg a day. Further increases may be made of 5 mg at 3-day intervals; this is the minimum time that should be allowed to elapse.

The dosage may be gradually reduced after satisfactory control has been achieved until an effective maintenance level is established.

When commencing treatment this should be undertaken under close supervision. Likewise, when it is necessary to increase dosage. Dosage requirement should always take into account the great variability of individual response.

After commencing treatment it may take several weeks for clinical improvement to become evident. There may be a delay before relapse after stopping treatment. It is essential that withdrawal from treatment should be gradual.

The recommended dosage when Terra-zine is used as an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour is: 2-4 mg a day in divided doses. This dosage may be increased to a maximum of 6 mg per day in divided doses. Treatment should be commenced under close supervision as should any increase in dosage. Likewise the variability of individual response and dosage requirement must be borne in mind.

ELDERLY:
A quarter or half the normal starting dose may be sufficient for therapeutic response in the elderly.

CHILDREN:
Not recommended for use in children.

GENERAL:
Terra-zine should always be used for the minimum possible time at the minimal effective dosage level except where it is established that long-term administration for conditions such as schizophrenia is required.

Route of administration: oral.

4.3 Contraindications

Terra-zine should not be used in comatose patients.

4.4 Special warnings and precautions for use

Liver disease; cardiac arrhythmias; cardiac disease; severe respiratory disease; renal failure; epilepsy, conditions predisposing to epilepsy (e.g. alcohol withdrawal or brain damage); Parkinson's disease; patients who have shown

hypersensitivity to other phenothiazines; personal or family history of narrow angle glaucoma - in very hot weather; the elderly, particularly if frail or at risk of hypothermia; hypothyroidism; depression; myasthenia gravis; phaeochromocytoma; prostatic hypertrophy; patients with a history of jaundice; blood dyscrasias.

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.

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

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 Trifluoperazine and preventive measures undertaken.

4.5 Interaction with other medicinal products and other forms of interaction

Terra-zine can increase the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics.

Terra-zine 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.

Terra-zine may impair the metabolism of tricyclic antidepressants, the anti-Parkinson effects of levodopa and the effects of anticonvulsants.

Terra-zine may possibly affect the control of diabetes, or the action of anticoagulants.

Antacids can impair absorption.

Tea and coffee may prevent absorption by causing insoluble precipitates.

Undesirable anticholinergic effects can be enhanced by anti-Parkinson (e.g. benzhexol) or other anticholinergic drugs (e.g. orphenedrine, benztropine).

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

Terra-zine may interact with anti-diabetic drugs.

The possibility of interaction with lithium should be borne in mind.

Desferrioxamine should not be used in combination with Terra-zine.

4.6 Pregnancy and lactation

Terra-zine should be avoided in pregnancy and lactation.

Neonates exposed to antipsychotics (including Trifluoperazine) 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.

Trifluoperazine has been shown to pass into the milk of lactating dogs.

4.7 Effects on ability to drive and use machines

Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment, until their susceptibility is known.

4.8 Undesirable effects

Drowsiness, sedation, dry mouth and nasal stuffiness may occur, particularly with high dosage and at the start of treatment.

Dose-related postural hypotension may occur, particularly in the elderly and after intramuscular Injections.

Other dose-related anticholinergic-type side effects include blurring of vision, tachycardia, constipation and urinary hesitancy or retention.

Terra-zine may impair alertness, especially at the start of treatment. These effects may be potentiated by alcohol.

Extrapyramidal reactions are common and sometimes occur at low dosage. Acute dystonias may occur early in treatment. Parkinsonian rigidity, tremor, akathisia tend to appear less rapidly. Oculogyric crises have been reported. Anti-Parkinson agents should not be prescribed routinely, because of the possible risks of aggravating anticholinergic side effects of Terra-zine, of precipitating toxic-confusional states or of impairing its therapeutic efficacy. They should only be given as required.

Tardive dyskinesia is a syndrome of irregularly repetitive involuntary movement, which may occur during administration or after withdrawal of Terra-zine and other neuroleptic drugs. It is characterised by abnormal writhing movements or protrusions of the tongue with lip-smacking, puckering and chewing movements and facial grimaces. Choreoathetoid movements of the extremities, or repetitive movements of the neck or trunk may accompany the orofacial dyskinesia or can occur alone. The syndrome is common among patients treated with moderate to high doses of antipsychotic drugs for prolonged periods of time and may prove irreversible, particularly in patients over the age of 50.

It is unlikely to occur in the short term when low or moderate doses are used as recommended, but tardive dyskinesia has been reported even when low doses of Terra-zine have been used for a few months. Since its occurrence may be related to duration of treatment as well as daily dose, Terra-zine should be given in the minimal effective dose for the minimum possible time, unless it is established that long-term administration for the treatment of schizophrenia is required.

The potential seriousness and unpredictability of tardive dyskinesia and the fact that it has occasionally been reported to occur when neuroleptic antipsychotic drugs have been prescribed for relatively short periods in low dosage means that the prescribing of such agents requires especially careful assessment of risks versus benefit. Tardive dyskinesia can be precipitated or aggravated by anti-Parkinson drugs. Short-lived dyskinesias may occur after abrupt drug withdrawal.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Terra-zine, even in low dosage in susceptible (especially non-psychotic) individuals, may cause unpleasant subjective feelings of being mentally dulled or slowed down, nausea, dizziness, headache or paradoxical effects of excitement, agitation-or insomnia.

Confusional states or epileptic fits can occur.

The elderly are more susceptible to the sedative and hypotensive effects.

The effects of phenothiazines on the heart are dose-related. ECG changes, with prolongation of the QT interval and T-wave changes have been reported commonly in patients treated with moderate to high dosage; they are reversible on reducing the dose. In a very small number of cases, they have been reported to precede serious arrhythmias, including ventricular tachycardia and fibrillation, which have also occurred after overdosage.

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 Terra-zine.

Weight gain may occur.

Pregnancy, puerperium and perinatal conditions: drug withdrawal syndrome neonatal (see 4.6), Frequency: not known.

Oedema has been reported with phenothiazine medication. These effects may be prevented by reduction in dosage.

Raised serum cholesterol and, rarely, hyperglycaemia have been reported in association with phenothiazines.

Blood Dyscrasias: Agranulocytosis has been reported very rarely, most commonly in the first three months of treatment, but occasionally later. Blood counts should be performed if the patient develops signs of a persistent infection. Transient leucopenia can also occur.

Terra-zine, rarely, causes increased susceptibility to sunburn and patients should be warned to avoid excessive exposure. Skin rashes have occurred rarely. The occurrence of lenticular opacities has been reported.

Terra-zine 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 particularly susceptible to hypothermia. The hazard of hyperthermia may be increased by especially hot or humid weather or by drugs, such as anti-Parkinson agents, which impair sweating.

Terra-zine can, very rarely, cause obstructive jaundice associated with stasis in billiary canaliculi. It has been thought to be a hypersensitivity reaction. Transient abnormalities of liver function tests may occur in the absence of jaundice.

Neuroleptic malignant syndrome is a rare but occasionally fatal complication of treatment with various neuroleptic drugs and is characterized by hyperpyrexia, muscle rigidity, altered consciousness and autonomic instability. Intensive symptomatic treatment, following discontinuation of trifluoperazine, should include cooling. Intravenous dantrolene has been suggested for muscle rigidity.

With long-term usage, very rarely Terra-zine can cause increased melanin pigmentation of the skin, which eventually may develop a bluish-grey colouration.

Pigment deposits also occur in the eye and other tissues.

Permanent deposits, leading to impairment of vision, may develop in the lens. Epithelial keratophathy has been reported.

Acute withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high doses of phenothiazines. Gradual withdrawal is advisable.

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

There is no specific antidote. Treatment should include gastric lavage. Acute hypotension should be countered by the adoption of a head-down or supine position and noradrenaline may be administered by intravenous drip Infusion. Adrenaline is contra-indicated.

The symptomatic treatment of central nervous depression should be instituted including the administration of antibiotics to prevent bronchopneumonia. Extrapyramidal symptoms may be treated with anticholinergic anti-Parkinsonian drugs.

It is advisable to institute cardiac monitoring because of the likelihood of the occurrence of cardiac arrhythmias particularly when body temperature falls

below 30ºC. A special watch should also be kept for the development of bladder and intestinal distension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Trifluoperazine is a white to pale yellow, odourless, hygroscopic, crystalline powder with a bitter taste. Melting point 242ºC with decomposition, soluble 1 in 2 of water, 1 in 11 of alcohol and 1 in 100-of chloroform, practically insoluble in ether. A 5% solution in water has a pH of 1.7 to 2.6.
In aqueous solutions it is readily oxidised by atmospheric oxygen.

5.2 Pharmacokinetic properties

Trifluoperazine is readily absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the gut wall. It is also excessively metabolised in the liver and excreted in the urine and faeces in the form of active and inactive metabolites.

Plasma half-life is only about 2 hours but the terminal elimination phase can be up to 3 weeks.

Trifluoperazine is extensively bound to plasma protein. The drug crosses the blood/brain barriers and its metabolites also cross the placental barriers and are excreted in milk.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Starch
Pregelatinised maize starch
Magnesium stearate
Shellac
Talc
Titanium dioxide
Sucrose
Povidone
Opalux AS-F-5922 Green
Beeswax
Carnauba wax

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25ºC in a dry place. Keep container well closed.

6.5 Nature and contents of container

High-density polystyrene with Polythene lids and/or polypropylene containers with polypropylene or Polythene lids and polyurethane/polythene inserts.
Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500, and 1000.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

05/01/2012