Trifluoperazine 1mg and 5 mg Tablets
(trifluoperazine hydrochloride)

PL 08553/0097-8

TABLE OF CONTENTS

Lay Summary  Page 2
Scientific discussion  Page 3
Steps taken for assessment  Page 11
Steps taken after authorisation – summary  Page 12
Summary of Product Characteristics  Page 13
Product Information Leaflet  Page 21
Labelling  Page 22
Trifluoperazine 1mg and 5 mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0097-8

LAY SUMMARY

The MHRA granted Dr Reddy’s Laboratories (UK) Limited Marketing Authorisations (licence) for the medicinal products Trifluoperazine 1mg and 5 mg Tablets PL 08553/0097-8 on the 16th of February 2006. These products are prescription only medicines (POM) for schizophrenia and for the prevention of relapse. They are also indicated for paranoid psychosis; mania and hypomania and as an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement and violent or dangerously impulsive behaviour.

Trifluoperazine 1mg and 5 mg Tablets contain the active ingredient trifluoperazine hydrochloride.

This is a simple abridged application that cross refers to DDSA Pharmaceuticals Ltd terrazine / trifluoperazine 1mg and 5 mg (PL 00225/0032-0033) which were granted on the 3rd November 1978 and, as such, these products can be used interchangeably.

No new or unexpected safety concerns arose from these simple applications and it is, therefore, judged that the benefits of taking Trifluoperazine 1mg and 5 mg Tablets outweigh the risks, therefore Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction  Page 4
Pharmaceutical assessment  Page 5
Preclinical assessment  Page 8
Clinical assessment  Page 9
Overall conclusions and risk benefit assessment  Page 10
INTRODUCTION

The UK granted marketing authorisations for the medicinal products Trifluoperazine 1mg and 5 mg Tablets (Trifluoperazine Hydrochloride) PL 08553/0097-8 to Dr Reddy’s Laboratories (UK) Ltd on the 16th of February 2006. These products are prescription only medicines.

These marketing authorisations are informed consent abridged applications according to article 10.1(a) (i) of Directive 2001/83/EC. They have demonstrated essential similarity to the cross-reference products DDSA Pharmaceuticals Ltd terrazine / trifluoperazine 1mg and 5 mg (PL 00225/0032-0033, which were approved on the 3rd November 1978.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously approved cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no Public Assessment Reports has been generated for them.

This product contains the active ingredient trifluoperazine hydrochloride, which is indicated for schizophrenia and for the prevention of relapse. They are also indicated for paranoid psychosis; mania and hypomania and as an adjunct to the short-term management of anxiety, severe psychomotor agitation, excitement and violent or dangerously impulsive behaviour.
1. INTRODUCTION

These are informed consent applications for Trifluoperazine 1mg and 5mg Tablets submitted under Article 10.1(a)(i) of Directive 2001/83/EC. The proposed MA holder is Dr Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD.

These applications cross refer to the marketing authorisations for terrazine / triluoperazine 1mg and 5 mg (PL 00225/0032-0033), which were approved in the UK. These applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed name for these products is Trifluoperazine 1mg and 5mg Tablets. These products have been named in line with the current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

These products contain trifluoperazine hydrochloride equivalent to 1mg and 5mg. The immediate container for Trifluoperazine 1mg and 5mg Tablets is a high-density polystyrene container with polythene lid and/or polypropylene container with polypropylene or polythene lid and polyurethane/polythene insert. The pack sizes are 28, 30, 50, 56, 60, 84, 100, 250,500 and 1000.

The proposed shelf-life (36 months) and storage conditions (Store below 25°C in a dry place. Keep container well closed.) are consistent with the details registered for the cross-reference products.

2.3 Legal status

On approval, these products will be prescription only medicines.

2.4 Marketing authorisation holder/Contact Persons/Company

The proposed Marketing Authorisation holder is Dr Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD.
The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers

Evidence of GMP compliance has been provided for the proposed manufacturing sites.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference product.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification

The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specification for this product is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance

The magnesium stearate used is of vegetable origin and the lactose used is of pharmaceutical grade, in which the BSE-risk is negligible. This is consistent with the cross-reference products.

3. EXPERT REPORTS

Satisfactory statements have been provided.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearance of the product is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SPCs are consistent with the details registered for the cross-reference products.
6. PATIENT INFORMATION LEAFLET/CARTON

PIL

The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

Labelling

The proposed artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements.

7. CONCLUSIONS

The data submitted with the application is acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

As these are informed consent abridged applications for PL08553/0097-8, no new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications is consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Trifluoperazine hydrochloride is a well known drug and has been used for the treatment of schizophrenia and the prevention of relapse; paranoid psychosis; mania and hypomania and as an adjunct to the short-term management of anxiety; severe psychomotor agitation; excitement; and violent or dangerously impulsive behaviour for many years.

These applications are identical to previously granted applications terrazine / trifluoperazine 1mg and 5 mg (PL 00225/0032-0033).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT

The quality of these products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products and so are interchangeable. Extensive clinical experience with trifluoperazine hydrochloride is considered to have demonstrated the therapeutic value of this compound. The risk benefit is therefore considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<td>The MHRA received these marketing authorisation applications on the 15/10/2003.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 10/01/2004.</td>
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<td>Following assessment of these applications the MHRA requested further information on the 5/07/2004</td>
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<td>The applicant responded to the MHRA’s requests, providing further information on 28/11/2005.</td>
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Trifluoperazine 1mg and 5 mg Tablets  
(trifluoperazine hydrochloride)  
PL 08553/0097-8

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

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Trifluoperazine 1mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0097

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trifluoperazine 1 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.18mg trifluoperazine hydrochloride equivalent to 1mg Trifluoperazine

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Coated tablet
Dark green sugar coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Route of administration: oral

### 4.3 Contraindications

Trifluoperazine should not be used in comatose patients.

Unsuitable in hereditary fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase-isomaltase deficiency.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine

### 4.4 Special Warnings And Special 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.
4.5 **Interactions with other Medicaments and other forms of Interaction**

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

Trifluoperazine 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.

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

Trifluoperazine 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-Parkinsonian medications (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.

Trifluoperazine 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 Trifluoperazine.

4.6 **Pregnancy and Lactation**

Trifluoperazine should be avoided in pregnancy and lactation. 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.

Trifluoperazine 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 Trifluoperazine, 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 Trifluoperazine and other neuroleptic drugs. It is characterised by abnormal writhing movements or protrusions of the tongue with lip-smacking, packering 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 Trifluoperazine have been used for a few months. Since its occurrence may be related to duration of treatment as well as daily dose, Trifluoperazine 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.

Trifluoperazine, 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, gynacomastia and oligo-or amenorrhoea.

Sexual function, including erection and ejaculation is sometimes impaired by Trifluoperazine.

Weight gain may occur.

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.

Trifluoperazine 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 hyperthermia. The hazard of hyperthermia may be increased by especially hot or humid weather or by drugs, such as anti-Parkinson agents, which impair sweating.

Trifluoperazine 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 Trifluoperazine 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 phenothazines. Gradual withdrawal is advisable.

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 30°C. 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 242°C 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.

ATC code: NO5A
Psycholeptic, antipsychotic phenothiazine with piperazine structure
5.2 Pharmacokinetic Properties

Trifluoperazine is really 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 monohydrate
Starch
Pregelatinised maize starch
Magnesium stearate
Shellac
Talc
Titanium dioxide (E171)
Sucrose
Povidone
Purified water
Industrial methylated spirit
Beeswax
Carnauba wax

Opalux AS-F-5922 Green (The approximate solids content (non volatile components) of AS-F-5922 is 67%)

Sucrose
Purified water
FD&C Blue #2/Indigo Carmine Aluminium Lake
Quinoline Yellow Aluminium Lake
Titanium Dioxide
Sodium Benzoate

6.2 Incompatibilities

None known.
6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Do not store above 25°C. Keep 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 Instructions for Use/Handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Dr Reddy’s Laboratories (UK) Limited,
6 Riverview Road
Beverley
HU17 0LD

8. MARKETING AUTHORISATION NUMBER

PL 08553/0097

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2006

10 DATE OF REVISION OF THE TEXT

17/02/2006
Trifluoperazine 5 mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0098

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trifluoperazine 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5.90 mg trifluoperazine hydrochloride equivalent to 5mg trifluoperazine.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Coated Tablet

Dark green sugarcoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Trifluoperazine is indicated in the treatment 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 Trifluoperazine 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:
Trifluoperazine 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

Trifluoperazine should not be used in comatose patients.

Unsuitable in hereditary fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase isomaltase deficiency.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption syndrome should not take this medicine.

4.4 Special Warnings And Special 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.
4.5 Interactions with other Medicaments and other forms of Interaction

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

Trifluoperazine 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.

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

Trifluoperazine 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.

Trifluoperazine 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 Trifluoperazine.

4.6 Pregnancy and Lactation

Trifluoperazine should be avoided in pregnancy and lactation. 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.

Trifluoperazine 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 Trifluoperazine, 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 Trifluoperazine and other neuroleptic drugs. It is characterised by abnormal writhing movements or protrusions of the tongue with lip-smacking, packering and chewing movements and facial grimaces. Choreaathetoid 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 Trifluoperazine have been used for a few months. Since its occurrence may be related to duration of treatment as well as daily dose, Trifluoperazine 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.

Trifluoperazine, 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.

MHRA PAR Trifluoperazine 1mg and 5 mg Tablets
(Trifluoperazine Hydrochloride) PL 08553/0097-8
Confusional states or epileptic fits can occur.

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, gynacomastia and oligo-or amenorrhea.

Sexual function, including erection and ejaculation is sometimes impaired by Trifluoperazine

Weight gain may occur.

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.

Trifluoperazine, 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.

Trifluoperazine 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 hyperthermia. The hazard of hyperthermia may be increased by especially hot or humid weather or by drugs, such as anti-Parkinson agents, which impair sweating.

Trifluoperazine 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.

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 Trifluoperazine 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 phenothazines. Gradual withdrawal is advisable.

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 30°C. 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 242°C 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.

ATC Code: N05A B06
Psycholeptic, antipsychotic phenothiazine with piperazine structure

5.2 Pharmacokinetic Properties

Trifluoperazine is really 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 monohydrate
Starch
Pregelatinised maze starch
Magnesium stearate
Shellac
Talc
Titanium dioxide (E171)
Sucrose
Povidone
Purified water
Industrial methylated spirit
Beeswax
Carnauba wax

Opalux AS-F-5922 Green (The approximate solids content (non-volatile components) of AS-F-5922 is 67%)

Sucrose
Purified water
FD&C Blue#2 /Indigo Carmine Aluminium Lake
Quinoline Yellow Aluminium Lake
Titanium Dioxide
Sodium Benzoate

6.2 Incompatibilities

None known

6.3 Shelf Life

36 months
6.4 Special Precautions for Storage

Store below 25°C 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 Instructions for Use/Handling

No special instructions.

7. MARKETING AUTHORISATION HOLDER

Dr Reddy’s Laboratories (UK) Limited,
6 Riverview Road
Beverley
HU17 0LD

8. MARKETING AUTHORISATION NUMBER

PL 08553/0098

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/02/2006

10 DATE OF REVISION OF THE TEXT

17/02/2006
Trifluoperazine 1mg and 5 mg Tablets (trifluoperazine hydrochloride) PL 08553/0097-8

Trifluoperazine 1mg and 5 mg Tablets (trifluoperazine hydrochloride) PL 08553/0097-8

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Trifluoperazine 1mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0097 Labels
Trifluoperazine 1mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0097 Labels

Each coated tablet contains 1 mg Trifluoperazine base as Trifluoperazine Hydrochloride 89. Also contains lactose, sucrose, E104 and E152.
This tablet is to be taken orally and as directed by your physician.
Do not store above 25°C.
Keep in original container.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Dr. Reddy’s Laboratories (UK) Ltd
8 Riverview Road, Beverley, HU17 8LD, UK

Title: Trifluoperazine 1mg 100’s
Date of origination: 31/01/2016
Dimension: 112 x 300mm
Cutter ref.:
Component code:
EAN number:
Software: CorelDRAW 11.0
Version number: 2.0
Revision date: 01/02/06
Reason for revision: Changes requested by John W.

MHRA PAR Trifluoperazone 1mg and 5 mg Tablets
(Trifluoperazine Hydrochloride) PL 08553/0097-8
- 31 -
Trifluoperazine 5 mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0098 Labels

Each coated tablet contains 5 mg
Trifluoperazine base as Trifluoperazine
Hydrochloride BP.
Also contains lactose, sucrose, E104 and E132.
This tablet is to be taken orally
and as directed by your physician.
Do not store above 25°C.
Keep in original container.
KEEP OUT OF THE REACH AND
SIGHT OF CHILDREN
Trifluoperazine 5 mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0098 Labels

Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road, Beverley, HU17 0LD, UK

| Title: Trifluoperazine 5mg 100's |
| Date of origination: 31/01/2006 |
| Dimensions: 112 x 36mm |
| Cutter ref: |
| Component code: |
| EAN number: |
| Software: CorelDRAW 11.0 |
| Version number: 2.0 |
| Revision date: 01/02/06 |
| Reason for revision: Changes requested by John W. Removal of pictogram and moving braille to front. |

MHRA PAR Trifluoperazine 1mg and 5 mg Tablets
(Trifluoperazine Hydrochloride) PL 08553/0097-8