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.

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

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.

PHARMACEUTICAL ASSESSMENT

LICENCE NO	PL 08553/0097-8
PROPRIETARY NAME:	Trifluoperazine 1mg and 5mg Tablets
ACTIVE:	Trifluoperazine Hydrochloride
COMPANY NAME:	Dr Reddy's Laboratories (UK) Ltd
E.C. ARTICLE:	Article 10.1(a)(i) of Directive 2001/83/EC
LEGAL STATUS:	POM

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 / trifluoperazine 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.

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

STEPS TAKEN FOR ASSESMENT

1	The MHRA received these marketing authorisation applications on the 15/10/2003.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10/01/2004.
3	Following assessment of these applications the MHRA requested further information on the 5/07/2004
4	The applicant responded to the MHRA's requests, providing further information on 28/11/2005.
7	These applications were determined on 16/02/2006.

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

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

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 Dyscraias: 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 alter 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

Trifluoperzine 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 malabsorbtion syndrome, or sucrase isomaltase deficiency.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorbtion 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 CNSdepressant 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 arid 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 dyskinesa 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 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 Dyscraias: Agraulocytosis 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.

Trifluopeazine 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 alter 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

Trifluoperzine 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 componets) 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

Component Code

PATIENT INFORMATION LEAFLET
Trifluoperazine Hydrochloride 1mg & 5mg tablets

PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU START TAKING THIS MEDICINE. KEEP THIS LEAFLET UNTIL YOU HAVE FINISHED ALL THE PRESCRIBED COURSE OF TRIFLUOPERAZINE. IF YOU HAVE ANY QUESTIONS CONCERNING YOUR MEDICINE ASK YOUR DOCTOR OR PHARMACIST FOR MORE INFORMATION.

What is in Trifluoperazine tablets?
The active ingredient of Trifluoperazine is trifluoperazine hydrochloride BP.

Trifluoperazine 1mg tablets contain trifluoperazine hydrochloride BP 1.18mg.
Trifluoperazine 5mg tablets contain trifluoperazine hydrochloride BP 5.90mg.

Trifluoperazine 1mg and 5mg are both dark green sugar coated tablets.
The tablets contain the following inactive ingredients: lactose, starch, pregelatinised maize starch, magnesium stearate, shellac, talc, titanium dioxide (E171), sucrose, povidone, beeswax, carnauba wax, opalux (trade name) as F-5922 which contains the following colourants E132, E104 and E211.

Both strengths of Trifluoperazine are available in containers of 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000 tablets.

The Manufacturer and licence holder of Trifluoperazine is:
Dr Reddy's Laboratories (UK) Ltd
6 Riverview Road,
Beverley, HU17 0LD
UK

The active ingredient in Trifluoperazine tablets, trifluoperazine, belongs to a group of drugs known as phenothiazines.

Why have you been prescribed Trifluoperazine?
This drug is used to help in the control of short-term anxiety, agitation, excitement, impulsive/violent behaviour and uncontrolled bodily shaking. It is also used in the management of the symptoms of schizophrenia, and other more serious psychological disorders (paranoia, mania, hypomania).

If you are not sure why you have been prescribed Trifluoperazine, then please ask your doctor.

Before taking you medicine.
Before taking this medicine, tell your doctor if any of the following apply:
- If you have experienced unusual or allergic reactions in the past to other drugs belonging to the same phenothiazine group as this medicine.
- If you have ever had liver, heart, kidney, or respiratory disease
- If you have Parkinson's disease
- If you have epilepsy
- If you have diabetes
- If there is a history of glaucoma (increased eyeball pressure) in your family
- If you are suffering from alcohol withdrawal
- If you are allergic to any foods, preservatives or dyes.
- If you suffer from hypothyroidism which is a condition of the thyroid gland
- If you suffer from myasthenia gravis which is a weakness of certain muscles.
- If you suffer from phaeochromocytoma which causes an increase in blood pressure.
- If you suffer from prostatic hypertrophy which is an enlargement of the prostate gland.

Use in pregnancy and whilst breast-feeding.
Tell your doctor if you are pregnant or planning a pregnancy and if you are breast-feeding, as Trifluoperazine should not be used in pregnancy or whilst breast-feeding.

Can you take Trifluoperazine with other medicines?
It is very important to tell you doctor or pharmacist about all the medicines that you are taking, whether or not any medicines were prescribed by your doctor or bought without a prescription from the pharmacy or elsewhere. Your doctor will be able to identify medicines you should not take with Trifluoperazine.

If you are taking other medicines.
Some medicines will affect the actions of Trifluoperazine e.g. central nervous system depressant drugs such as alcohol, sedatives, barbiturates, sleeping pills. Other medicines which interfere with the actions of Trifluoperazine, or which are interfered with by the use of Trifluoperazine include:
- Guanethidine and Clonidine (for high blood pressure)
- Anti-Parkinsonian drugs such as levodopa, and Benzhexol, and other anticholinergic drugs (e.g. orphenadrine, benztropine)
- Anti-diabetic drugs (Metformin, chlorpropamide)
- Anticoagulant drugs (blood thinning medicines such as warfarin)
- Medicines used to treat heart conditions and high blood pressure (e.g. quinidine, corticosteroids, digoxin, diazoxide)
- Lithium, used for psychological disorders
- Sympathomimetic agents, which increase heart rate and contraction of heart muscle.
- Anti-depressants, which are used to treat depression
- Antacids, used to treat increased stomach acidity.

Tea and coffee can affect the absorption of Trifluoperazine. Antacids will also affect the absorption of Trifluoperazine.
If you go to a doctor, dentist or hospital for any reason, tell them you are taking Trifluoperazine.

This medicine contains lactose and sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains sodium benzoate. This can be a mild irritant to the eyes, skin and mucous membranes. It may also increase the risk of jaundice in newborn babies though these reactions are very rare.

Can you drive when taking Trifluoperazine?
Because of the risk of impaired alertness it is advisable not to drive or operate machinery.

When and how to take Trifluoperazine.
This medicine is to be taken by mouth and only in the doses prescribed by your doctor. Do not take more and do not take more often.

You will be prescribed the lowest possible dose necessary to control your symptoms, and for the shortest possible time except in certain conditions where your doctor believes that long term treatment is required.

Do not stop taking your medicine or change the dose unless your doctor tells you to.

Usual dosages are stated below:

ADULTS:
When taking this medicine for the first time or when your doctor increases your dosage you will need to be closely monitored in order to find the correct dosage to control your symptoms without increasing the risk of side effects.

The recommended dosage when Trifluoperazine is used together with other medicines for the short-term management of anxiety, agitation, excitement and impulsive behaviour is 2-4mg a day in divided doses. This dosage may be increased to a maximum of 6mg per day in divided doses.

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

After satisfactory control has been achieved the dosage may be gradually reduced until an effective dosage maintenance level is arrived at. After commencing treatment it may take several weeks for improvement to be felt. It is always necessary that withdrawal from treatment should be gradual to avoid a relapse of the condition if stopping treatment is sudden.

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 minimal possible time at the minimal effective dosage level excepting where it is established that long-term administration for conditions such as schizophrenia is required.

What to do if too many tablets are taken at the same time.
If you accidentally take more tablets than recommended contact your doctor or nearest hospital casualty department at once. Take any remaining tablets with you and keep in the original container or packaging so that they can be identified.

What if you miss a dose?
If you miss a dose, skip the missed dose and go back to your regular dosage schedule. Do not take two doses at once. If you feel that this medicine is not working as well after you have taken it for a short time (3-4 days) do not increase the dose, instead check with your doctor.

What side effects can Trifluoperazine have?
Common side effects noticed particularly at the start of treatment and with high dosages include drowsiness, sedation, dry mouth and nasal stuffiness.

Trifluoperazine may effect concentration and alertness, particularly at the start of treatment. These effects will be increased by the consumption of alcohol.

In very hot weather or very cold weather, and particularly with the elderly, there is a risk of heat stroke or hypothermia. The elderly also have increased risk of low blood pressure which can be caused by moderate to high doses of Trifluoperazine.

Other dose-related side effects include:
- Blurring of vision
- Alteration of heart beat
- Constipation
- Difficulty passing urine

Some reactions are common and can occur at low dosages though are more common at moderate to high dosage. These include muscle rigidity (stiffness), tremor (fine shaking of the hands), jerky body movements and the inability to control movements of the hand and body. There is a risk of sustained fixed movement of the eyes and head (oculogyric crises) though this is more common in patients with Parkinson's syndrome. Anti-Parkinson medicines (such as levodopa) used together with trifluoperazine may aggravate these conditions and therefore should be avoided. These side effects may present themselves immediately of shortly after you stop taking this medicine. Abrupt drug withdrawal can increase the risk of these side effects.

Random repetitive unintentional movements (known as Tardive dyskinesia) are a symptom which can occur when taking Trifluoperazine. It is characterised by grimacing, lip smacking and sticking your tongue out without wishing to. It is more common in the elderly, but is also common among patients taking high doses of Trifluoperazine over a long time. Taking Anti-Parkinson medicines with Trifluoperazine can also cause it.

In low doses, Trifluoperazine can cause the following side effects, which will disappear on their own, or once the medicine is stopped. These side effects are: feelings of being mentally slowed down or dulled, sickness, dizziness, headache, excitement, agitation, and sleeplessness. Confusion and epileptic fits (seizures) can also occur. Stopping the medication suddenly can lead to sickness, difficulty in sleeping and vomiting.

Various types of blood disorders may occur. Be sure to tell your doctor if you are suffering from bruising or an unusually bad sore throat or fever.

Rarely Trifluoperazine may cause problems with your liver. If you notice a yellowing of your skin or eyeballs tell your doctor. You may have to stop taking your medicine.

Trifluoperazine rarely causes sunburn with exposure to sunlight and can cause skin rashes and sensitivity. **Excessive exposure to sunlight should therefore be avoided.** With long-term use trifluoperazine can change skin pigmentation (colour). Very rarely, and only with excessively high doses, vision may become impaired due to pigment deposits in the eye. Trifluoperazine can also cause thickening of the skin.

The use of trifluoperazine can lead to hormonal changes: enlargement of the breasts, production of breast milk, reduction or stopping of monthly periods. The use of Trifluoperazine can also affect sexual function. Weight gain is common.

Water retention and increased levels in the blood of cholesterol and sugar have been reported as side effects of trifluoperazine.

After withdrawal of Trifluoperazine the following may occur; writhing movements, smacking of the lips, protrusion of the tongue, chewing movements and facial grimaces. Repetitive movements of the neck or trunk may occur. These withdrawal symptoms are not likely to occur with low doses used as recommended. Because withdrawal symptoms may be related to length of treatment as well as daily dose, Trifluoperazine should always be given in the smallest effective dose for the shortest period of time.

If you notice any of the above reactions or side effects or if you notice other unusual or worrying changes contact your doctor.

Storing your medicine
You must keep this medicine in a safe place where children cannot get at it. Your medicine could harm them.

- Do not store above 25°C
- Store in a dry place, protect from light
- Keep in original container

If your doctor tells you to stop the treatment, return any remaining tablets/capsules to the pharmacist.

On the container, you will find the words "expiry date" followed by numbers indicating the day, month and year. This is the date after which the medicine is no longer fit for use. Do not use the medicine after this date but return it to your doctor or pharmacist.

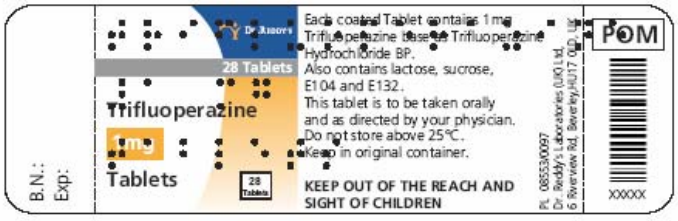
REMEMBER: this medicine is for you. Never give it to someone else, even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If you have questions or are not sure about anything, ask your doctor or pharmacist who have access to additional information.

Leaflet revision date: DATE
Trifluoperazine 1mg Tablets, PL08553/0097
Trifluoperazine 5mg Tablets, PL08553/0098

Component code

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

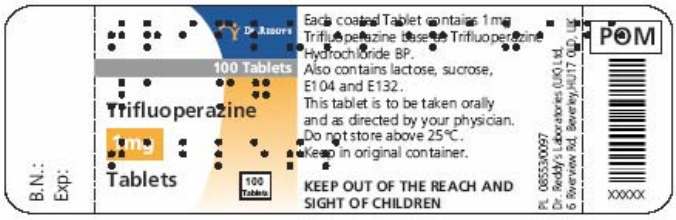


Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road, Beverley, HU17 0LD, UK

Title:	Trifluoperazine 1mg 28's
Date of origination:	31.01.2006
Dimensions:	112mm x 35mm
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 making POM larger to match 5mg label.

Colours:	294 CV 423 CV Black 137 CV Profile (do not print)
Batch No. & Expiry	Printed

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

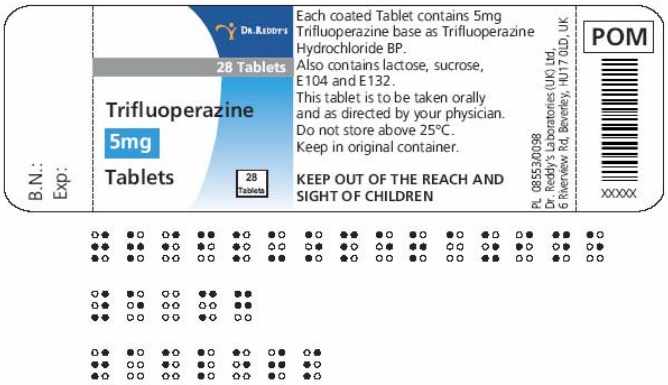


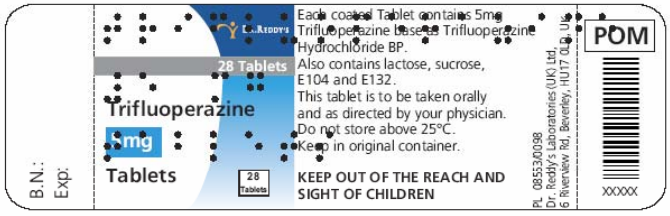
Dr. Reddy's Laboratories (UK) Ltd
6 Riverview Road, Beverley, HU17 0LD, UK

Title:	Trifluoperazine 1mg 100's
Date of origination:	31/01/2006
Dimensions:	112 x 35mm
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 making POM larger to match 5mg label.

Colours:	294 CV 423 CV Black 137 CV Profile (do not print)
Batch No. & Expiry:	Printed

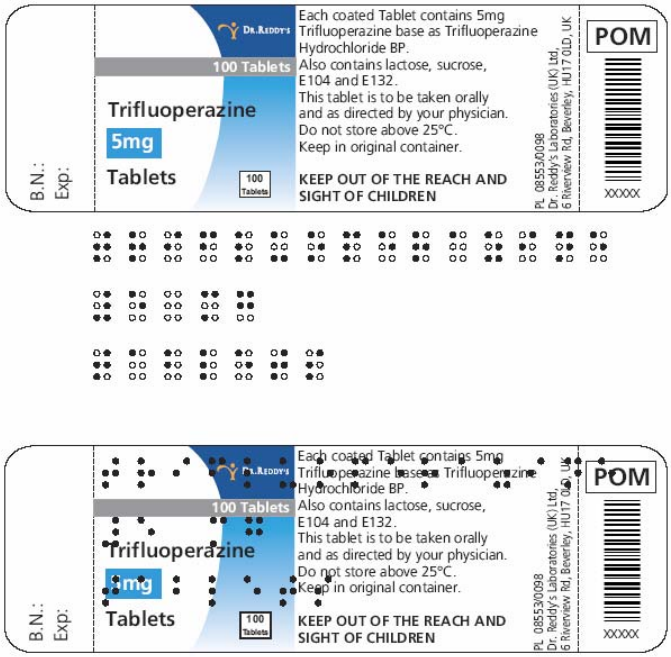
Trifluoperazine 5 mg Tablets
(trifluoperazine hydrochloride)
PL 08553/0098 Labels





Dr. Reddy's Laboratories (UK) Ltd 6 Riverview Road, Beverley, HU17 0LD, UK	Title:	Trifluoperazine 5mg 28's	Colours: 294 CV, 423 CV, Black, 299 CV, Profile (do not print)
	Date of origination:	31/01/2006	
	Dimensions:	112 x 35mm	
	Cutter ref:		
	Component code:		
	EAN number:		
	Software:	CorelDRAW 11.0	
	Version number:	2.0	
	Revision date:	01/02/06	Batch No. & Expiry: Printed
	Reason for revision:	Changes requested by John W. Removal of pictogram and moving braille to front.	

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 35mm
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.

Colours:	294 CV 423 CV Black 299 CV Profile (do not print)
Batch No. & Expiry:	Printed