Public Assessment Report

UKPAR

Trifluoperazine 5 mg/5 ml Oral Solution

(trifluoperazine hydrochloride)

UK Licence No: PL 20046/0300

Focus Pharmaceuticals Limited
LAY SUMMARY

Trifluoperazine 5 mg/5 ml Oral Solution

This is a summary of the Public Assessment Report (PAR) for Trifluoperazine 5 mg/5 ml Oral Solution (PL 20046/0300). It explains how Trifluoperazine 5 mg/5 ml Oral Solution was assessed and its authorisation recommended, as well as its condition of use. It is not intended to provide practical advice on how to use Trifluoperazine 5 mg/5 ml Oral Solution.

The product will be referred to as Trifluoperazine Oral Solution throughout the remainder of this public assessment report.

For practical information about using Trifluoperazine Oral Solution patients should read the package leaflet or contact their doctor or pharmacist.

What is Trifluoperazine Oral Solution and what is it used for?
Trifluoperazine Oral Solution is a ‘hybrid generic medicine’. This means that Trifluoperazine Oral Solution is similar to a ‘reference medicine’, already authorised in the UK called Stelazine 1mg/5ml Syrup/Trifluoperazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited) containing the same active substance but different strength to the reference product. For ease of reading the reference product will be referred to as Stelazine 1mg/5ml Syrup throughout the remainder of the PAR.

Trifluoperazine Oral Solution belongs to a group of medicines called phenothiazine tranquillisers, also referred to as a neuroleptic drug and is used to treat the following conditions:

- At a low dose, Trifluoperazine Oral Solution is used to manage anxiety and depression. It is used in this way for short periods of time. Trifluoperazine Oral Solution may also be used to treat nausea (feeling sick) and vomiting (being sick).
- At high doses, Trifluoperazine Oral solution is used to treat and prevent relapses of schizophrenia (a serious mental illness). It can also be used for short periods of time to treat bad agitation or dangerous behaviour.

How does Trifluoperazine Oral Solution work?
This medicine contains the active ingredient called trifluoperazine (as hydrochloride). Trifluoperazine works by influencing the activity of certain brain cells by decreasing the effect of dopamine, a natural chemical in the brain.

How is Trifluoperazine Oral Solution used?
The pharmaceutical form of this medicine is an oral solution taken by mouth (oral).

The patient should always use this medicine exactly as described in the package leaflet or as their doctor or pharmacist has advised. If unsure, the patient should ask the doctor or pharmacist.

A graduated oral syringe, a press-in syringe/bottle adaptor and a graduated dosing cup are provided with the product. Each 5ml of oral solution contains 5mg of the active ingredient, trifluoperazine. The recommended dose is described below:
During treatment the patient’s doctor should regularly check the patient for physical side effects, changes in their blood counts or liver function, and any heart problem, especially if the patient has been taking this medicine for a long time or are also taking other medicines.

This medicine can be obtained without a prescription.

For further information on how to use Trifluoperazine Oral Solution see section 3 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**What benefits of Trifluoperazine Oral Solution have been shown in studies?**
Studies in humans have been limited to tests to determine that Trifluoperazine Oral Solution is bioequivalent to an equivalent dose of the reference product; Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects from Trifluoperazine Oral Solution?**
The most common side effects with Trifluoperazine Oral Solution are blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood
vessels to the lungs causing chest pain and difficulty in breathing. If the patient notices any of these symptoms they must seek medical advice immediately.

For a full list of all the side effects reported with Trifluoperazine Oral Solution see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

**Why was Trifluoperazine Oral Solution approved?**
The MHRA decided that the benefits of Trifluoperazine Oral Solution are greater than the risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Trifluoperazine Oral Solution?**
A Risk Management Plan has been developed to ensure that Trifluoperazine Oral Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Trifluoperazine Oral Solution including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Trifluoperazine Oral Solution**
A Marketing Authorisation was granted in the UK on 17 July 2018.

The full PAR for Trifluoperazine Oral Solution follows this summary.

For more information about treatment with Trifluoperazine Oral Solution read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.
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I INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Focus Pharmaceuticals Limited a Marketing Authorisation for the medicinal product Trifluoperazine Oral Solution (PL 20046/0300) on 17 July 2018. The product is a prescription only medicine (POM), indicated for:

- Low dosage: Trifluoperazine oral solution is indicated as an adjunct in the short-term management of anxiety states, depressive symptoms secondary to anxiety and agitation. Orally it is also indicated in the symptomatic treatment of nausea and vomiting.

- High dosage: Trifluoperazine oral solution is intended for the treatment of symptoms and prevention of relapse in schizophrenia and in other psychoses, especially of the paranoid type, but not in depressive psychoses. It may also be used as an adjunct in short-term management of severe psychomotor agitation and of dangerously impulsive behaviour in, for example, mental subnormality.

This application was submitted as an abridged national application, according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference product for the application is Stelazine 1mg/5ml Syrup, which was originally authorised on 06 November 1985 to the Marketing Authorisation Holder (MAH) SmithKline and French Laboratories Limited (PL 0002/5080R). A subsequent change of ownership procedure took place on 01 August 1998 to the current Marketing Authorisation Holder (MAH) Mercury Pharmaceuticals Limited (PL 12762/0029).

Trifluoperazine is one of the phenothiazine class of compounds and as such has many pharmacodynamic effects which relate to its therapeutic actions and side effects. The most notable action of phenothiazines is antagonism at dopamine receptors in the CNS. It is hypothesised that this action in the limbic system and associated areas of cerebral cortex is the basis of the antipsychotic action of phenothiazines, whilst in the medullary chemoreceptor trigger zone it appears to be responsible for the antiemetic effect of these agents. In addition, dopamine antagonism in the basal ganglia appears to be involved in some of the extrapyramidal side-effects of phenothiazines, whilst blockage of the dopaminergic inhibition of prolactin release from the anterior pituitary gland is thought to lead to hyperprolactinaemia.

Other central actions of phenothiazines include sedation and inhibition of the function of the hypothalmic heat regulatory center. Phenothiazines also lower the seizure threshold. Central actions of phenothiazines also affect the cardiovascular system, as does their antagonism of peripheral α-adrenergic receptors, which can cause hypotension.

Phenothiazines also have anti-muscarinic activity which causes certain side effects.

Trifluoperazine is one of the piperazine sub-class of phenothiazine drugs whose members have fewer sedative, antimuscarinic and hypotensive side effects but more extrapyramidal side effects than other types of phenothiazines.

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the test product Trifluoperazine 5 mg/5 ml Oral Solution (Focus Pharmaceuticals Limited) versus the reference product Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited) under fasting conditions, has been submitted to support the application.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being a hybrid medicinal product of the reference product that has been licenced for over 10 years.
The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A Marketing Authorisation was granted in the UK on 17 July 2018.

II QUALITY ASPECTS

II.1 Introduction
The finished product is formulated as an oral solution containing 5 mg trifluoperazine, present as the hydrochloride, per 5ml. Each 1 ml of Trifluoperazine 5 mg/5 ml Oral Solution contains 0.86 mg sodium, 0.005 mg ethanol, 1 mg sodium benzoate, 100.95 mg propylene glycol and 0.0257 mg benzyl alcohol.

Other pharmaceutical excipients present are sodium benzoate, propylene glycol, citric acid, anhydrous, sodium citrate, sucralose, orange flavour -SP 14104/04 (which includes propylene glycol, ethanol, benzyl alcohol), natracol curcumin (E100) (which includes propylene glycol), citric acid and purified water.

All excipients used comply with their respective European Pharmacopoeia monographs except the non-pharmacopoeial colourant and flavour. The orange flavour (SP 14104/04) and natracol curcumin (E100) including their individual constituents are controlled by in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used in this product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

The finished product is packaged in amber (Type III) glass bottles of 150ml fill volume, with child-resistant, tamper-evident screw cap with an LDPE liner.

A 5 ml dosing syringe with intermediate graduations of 0.1 ml and a “press-in” syringe/bottle adaptor is provided. A 20 ml dosing cup with intermediate graduations is also provided with the product.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN: Trifluoperazine hydrochloride

Chemical Name: 10H-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl-[2-(trifluoromethyl)-, dihydrochloride

Structure:
Molecular formula: $\text{C}_{21}\text{H}_{24}\text{F}_{3}\text{N}_{3}\text{S.2HCl}$

Molecular weight: 480.43 g/mol

Appearance: White to pale yellow, crystalline powder

Solubility: Freely soluble in water; soluble in alcohol; sparingly soluble in chloroform; insoluble in ether and in benzene

The drug substance, trifluoperazine hydrochloride is the subject of a European Pharmacopeia.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop safe, efficacious oral solution, containing 5 mg trifluoperazine (as the hydrochloride)/5 ml that could be considered as a hybrid medicinal product of the currently licensed product, Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited).

Suitable pharmaceutical development data have been provided for this application.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Process validation data on the minimum commercial scale batches have been provided. The results are satisfactory. The Marketing Authorisation Holder has committed to performing process validation studies on future full production-scale batches.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

The data from these studies support a shelf-life of 24 months for unopened bottles. The bottle should be kept in the original carton to protect from light. The in-use shelf life of the product is 2 months after first opening the bottle.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

### III NON-CLINICAL ASPECTS

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of trifluoperazine (as hydrochloride) are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

#### III.2 Pharmacology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

#### III.3 Pharmacokinetics

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

#### III.4 Toxicology

Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

#### III.5 Ecotoxicity/environmental risk assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. Since Trifluoperazine Oral Solution is intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

#### III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

### IV CLINICAL ASPECTS

#### IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of trifluoperazine (as hydrochloride) are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of trifluoperazine (as hydrochloride).
Based on the results of the bioequivalence study, Trifluoperazine Oral Solution can be considered bioequivalent to the reference product, Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited), at equivalent doses.

IV.2 Pharmacokinetics

As the proposed product and the reference product are different strengths the applicant has submitted one bioequivalence study in support of the application. Trifluoperazine (as hydrochloride) is a substance with a well-known safety and efficacy profile and the applicant is not making any new clinical claims. The proposed indications and the posology are identical to those of the reference product.

STUDY 1

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the test (T) product Trifluoperazine 5 mg/5 ml Oral Solution (Focus Pharmaceuticals Limited) versus the reference (R) product Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited) under fasting conditions.

The study was conducted in two periods and in each period, the subjects received either test or reference products randomly.

Following an overnight fast of at least 10 hours, subjects were given a dose of 25 ml of the reference solution (1 mg/5 ml) or 5ml of the test solution (5 mg/5 ml) which was administered orally using a disposable syringe with 240 ml of drinking water.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after the drug administration. The washout period between treatment phases was 14 days.

The main pharmacokinetic results for trifluoperazine are presented below:

**Descriptive PK results for Trifluoperazine**

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Arithmetic Mean ± SD (%CV) (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference product (R)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>0.389 ± 0.1477 (38.00%)</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>6.000 (0.75 - 12.00)</td>
</tr>
<tr>
<td>AUC_{0-72} (hr*ng/mL)</td>
<td>8.532 ± 3.9382 (46.16%)</td>
</tr>
</tbody>
</table>

# For T_{max} median (min – max)
Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C<sub>max</sub> values for trifluoperazine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the test product Trifluoperazine 5 mg/5 ml Oral Solution (Focus Pharmaceuticals Limited) is bioequivalent to the reference product Stelazine 1mg/5ml Syrup (Mercury Pharmaceuticals Limited), at equivalent doses.

IV.3 Pharmacodynamics
No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy
No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sodium Cromoglicate.

A summary of safety concerns, as approved in the RMP, are listed below:
## Summary of safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blood dyscrasias</td>
<td>• Potentiation of effect on concomitant use with central nervous system (CNS) depressants,</td>
</tr>
<tr>
<td>• Liver dysfunction</td>
<td>antihypertensives, anticholinergics or antidepressants</td>
</tr>
<tr>
<td>• Use in patients hypersensitive to the active ingredient or related compounds</td>
<td>• Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>• Extrapyramidal symptoms including tardive dyskinesia</td>
<td>• Increased mortality in elderly patients with dementia</td>
</tr>
<tr>
<td>• Cardiac conduction defects</td>
<td>• Worsening of myasthenia gravis or prostatic hypertrophy</td>
</tr>
<tr>
<td>• Concomitant use with lithium</td>
<td>• Worsening of symptoms and reversal of effects of levodopa in patients with Parkinson’s disease</td>
</tr>
<tr>
<td>• Extrapyramidal and/or withdrawal symptoms in neonates when used during the third trimester of pregnancy</td>
<td>• Worsening of epilepsy</td>
</tr>
</tbody>
</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**
The grant of Marketing Authorisation is recommended, from a clinical viewpoint.

**V User consultation**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

**IV OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with trifluoperazine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The SmPC and PIL are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for this medicine is presented below:
Parfluperozine 5 mg/5 ml Oral Solution

150ml Trifluoperazine 5 mg/5ml Oral Solution

Each 5 ml contains 5 mg trifluoperazine as hydrochloride. The product also contains sodium, ethanol, sodium benzoate, propylene glycol and benzyl alcohol. See the leaflet for further information.

For oral use.

Read the package leaflet before use.

Keep out of the sight and reach of children.

Keep the bottle in the original carton to protect from light. Once opened use within 2 months.

Marketing Authorisation Holder:
Focus Pharmaceuticals Limited
Capita House, 85 King William Street,
London EC4N 7BL, UK
PL 20046/0300
Trifluoperazine 5 mg/5 ml Oral Solution

Each 5 ml contains 5 mg trifluoperazine present as hydrochloride. The product also contains sodium, ethanol, sodium benzoate, propylene glycol and benzyl alcohol. See the leaflet for further information.

For oral use. Read the package leaflet before use. Keep out of the sight and reach of children. Keep the bottle in the original carton to protect from light. Once opened use within 2 months.

Marketing Authorisation Holder:
Focus Pharmaceuticals Limited
Capital House, 85 King William Street, London EC4N 7BL, UK

PL 20046/0300
LB-104105-01
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>

