Public Assessment Report

UK PAR

Prochlorperazine Maleate 5 mg Buccal Tablets

UK Licence Number: PL 21880/0121

MEDREICH plc
LAY SUMMARY

Prochlorperazine Maleate 5 mg Tablets

This is a summary of the Public Assessment Report (PAR) for Prochlorperazine Maleate 5 mg Tablets (PL 21880/0121). It explains how the application for Prochlorperazine Maleate 5 mg Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Prochlorperazine Maleate 5 mg Tablets.

For practical information about using Prochlorperazine Maleate 5 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Prochlorperazine Maleate 5 mg Tablets and what are they used for?
Prochlorperazine Maleate 5 mg Tablets are a medicine that contains the active substance prochlorperazine maleate. Prochlorperazine Maleate 5 mg Tablets can be used to:
• treat balance problems or dizziness (vertigo). This includes problems of the inner ear such as ‘Meniere’s Syndrome’ or ‘labyrinthitis’;
• stop patients from feeling sick (nausea) or being sick (vomiting). This can be from any cause including migraines;
• treat anxiety in the short-term, when used in addition to other medicines;
• treat schizophrenia;
• treat over-active behaviour or thoughts (mania).

Prochlorperazine Maleate 5 mg Tablets are a ‘generic’ medicine. This means that Prochlorperazine Maleate 5 mg Tablets are similar to a reference medicine already authorised in the European Union (EU) called Stemetil 5 mg tablets (Aventis Pharma Limited, UK).

How are Prochlorperazine Maleate 5 mg Tablets used?
Prochlorperazine Maleate 5 mg Tablets are swallowed with water. The recommended dose depends on the condition being treated. Prochlorperazine Maleate 5 mg Tablets are not recommended in children under 12 years of age.

The tablets should not be handled more than is necessary as persons frequently handling the tablets may develop sore, red or blistered skin.

For further information on how Prochlorperazine Maleate 5 mg Tablets are used, please refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Prochlorperazine Maleate 5 mg Tablets can only be obtained on prescription.

How do Prochlorperazine Maleate 5 mg Tablets work?
The active substance, prochlorperazine maleate, belongs to a group of medicines called ‘phenothiazine antipsychotics’. It works by blocking the effects of a chemical in the brain.

How have Prochlorperazine Maleate 5 mg Tablets been studied?
As Prochlorperazine Maleate 5 mg Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Stemetil 5 mg tablets (Aventis Pharma Limited, UK). Two medicines are considered to be bioequivalent when they produce the same levels of the active substance in the body.
In addition, the Company (Medreich plc) provided data from the published literature on prochlorperazine maleate.

**What are the benefits and risks of Prochlorperazine Maleate 5 mg Tablets?**
Because Prochlorperazine Maleate 5 mg Tablets are a generic medicine and are bioequivalent to the reference medicine, their benefits and risks are taken as being the same as those of the reference medicine.

**Why are Prochlorperazine Maleate 5 mg Tablets approved?**
It was concluded that, in accordance with EU requirements, Prochlorperazine Maleate 5 mg Tablets have been shown to have comparable quality and to be bioequivalent to Stemetil 5 mg tablets (Aventis Pharma Limited, UK). Therefore, the view was that, as for Stemetil 5 mg tablets (Aventis Pharma Limited, UK), the benefits of these tablets outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Prochlorperazine Maleate 5 mg Tablets?**
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Prochlorperazine Maleate 5 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Prochlorperazine Maleate 5 mg Tablets.**
A Marketing Authorisation was granted in the UK on 09 January 2014.

The full PAR for Prochlorperazine Maleate 5 mg Tablets follows this summary.

For more information about treatment with Prochlorperazine Maleate 5 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2016.
## SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Medreich plc a Marketing Authorisation for the medicinal product Prochlorperazine Maleate 5 mg Tablets (PL 21880/0121) on 09 January 2014. This product is a prescription-only medicine (POM) indicated for vertigo due to Meniere's Syndrome, labyrinthitis and other causes, and for nausea and vomiting from whatever cause including that associated with migraine. Prochlorperazine Maleate 5mg Tablets may also be used for schizophrenia (particularly in the chronic stage), acute mania and as an adjunct to the short-term management of anxiety.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, cross referring to Stemetil 5 mg tablets (PL 04425/0593; Aventis Pharma), which was granted in the UK to Aventis Pharma Limited following a Change of Ownership (COA) procedure on the 02 October 2006 from Castlemead Healthcare Limited (PL 16946/0006). Stemetil tablets 5 mg (PL 16946/0006; Castlemead Healthcare Limited, UK) was granted on 01 July 1998 following a COA procedure from May & Baker Limited (PL 00012/5263R). Stemetil tablets 5 mg (PL 00012/5263R; May & Baker Limited) was originally authorised in the UK on 05 August 1986, hence the market exclusivity period of 10 years applied to the reference medicinal product has expired.

The active ingredient, prochlorperazine maleate belongs to a group of medicines known as phenothiazine derivatives. Prochlorperazine maleate is a potent phenothiazine neuroleptic. In the central nervous system, phenothiazines are powerful antagonists of the neurotransmitter action of dopamine in the basal ganglia and limbic system. They are also potent anti-emetics via effects on the chemoreceptor trigger zone and neuroleptic actions seem to change pain perception. In addition, they are adrenergic antagonists (which can lead to orthostatic hypotension).

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Prochloperazine Maleate 5 mg tablets (Medreich Limited) with the reference product Stemetil 5 mg tablets (Aventis Pharma Limited, UK) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Prochlorperazine Maleate 5 mg Tablets outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10(1) of Directive 2001/83/EC, as amended, and cross refers to Stemetil 5 mg Tablets (Aventis Pharma Limited).

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as a white to off white coloured, circular-shaped, biconvex tablet, with monogram ‘P5’ on one side and plain on the other.
Each tablet contains 5 mg of prochlorperazine maleate, as the active substance. The other ingredients are lactose monohydrate, maize starch, colloidal anhydrous silica and magnesium stearate.

The tablets are packaged in aluminium/polyvinylchloride/polyvinylidene chloride (Alu/PVC/PVdC) blisters. The blisters are packed with the Patient Information Leaflet in cartons, in pack sizes of 28 and 84 buccal tablets.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance
Prochlorperazine maleate

INN: Prochlorperazine maleate
Chemical name: 2-chloro-10-[(3-(4-methylpiperazin-1-yl)propyl]-10H-phenothiazine bis[hydrogen (Z)-butenedioate]

Structure:

Molecular formula: \( C_{20}H_{24}ClN_3S,(C_4H_4O_4)_2 \)
Molecular weight: 606
Appearance: A white or pale-yellow, crystalline powder
Solubility Very slightly soluble in water and in ethanol (96 per cent).

Prochlorperazine maleate is the subject of a European Pharmacopoeia monograph.

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. 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.

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

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

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe efficacious, stable tablets that could be considered a generic medical product of the innovator product Stemetil 5 mg Tablets (Aventis
Pharma Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparable in-vitro dissolution profiles have been provided for this product and the innovator product, Stemetil Tablets, (Aventis Pharma Limited, UK).

Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contains material of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material, other than calf rennet, is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full-scale production-scale batches that have shown satisfactory results.

**Control of Finished Product**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided, which comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Stability of the product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with the special storage conditions ‘Do not store above 25°C. Store in the original package’.

A suitable post approval stability commitment has been provided to continue stability studies on batches of finished product.

**Bioequivalence**
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of prochlorperazine maleate are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

The non-clinical overview 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 Pharmacokinetics
The pharmacokinetic properties of prochlorperazine maleate are well known and adequately described in the applicant’s non-clinical overview.

III.3 Pharmacodynamics
The pharmacodynamic properties of prochlorperazine maleate are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of prochlorperazine maleate are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Prochlorperazine Maleate 5 mg Buccal Tablets from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of prochlorperazine maleate is well-known.

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

A randomised, open label, two-treatment, two-sequence, two-period, single-dose, crossover study to compare the pharmacokinetics of the test product Prochlorperazine 5 mg tablets (Medreich Limited) versus the reference product Stemetil 5 mg tablets (Aventis Pharma Limited, UK) in healthy adult subjects under fasting conditions.
The subjects were administered a single dose (one 5 mg tablet) of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 72 hours after each administration. The washout period between the treatment phases was 14 days. The pharmacokinetic results are presented below:

### Bioequivalence results for log-transformed data with 90% confidence intervals (CI) for prochlorperazine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test (T) (Geometric mean)</th>
<th>Reference (R) (Geometric mean)</th>
<th>Ratio of T/R (%)</th>
<th>Intra-subject % CV</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>93.48</td>
<td>96.57</td>
<td>95.96</td>
<td>30.28</td>
<td>83.34 – 110.49</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (pg.h/mL)</td>
<td>932.65</td>
<td>1025.56</td>
<td>91.18</td>
<td>23.59</td>
<td>81.62 – 101.87</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (pg.h/mL)</td>
<td>1343.38</td>
<td>1423.49</td>
<td>93.30</td>
<td>23.30</td>
<td>83.01 – 104.86</td>
</tr>
</tbody>
</table>

C<sub>max</sub> maximum plasma concentration  
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours  
AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity  
CV coefficient of variation  
Ratios and 90% CI calculated from ln-transformed data

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**) defines the confidence limits as 80.00% to 125.00% for AUC and C<sub>max</sub> values. Thus, the data support the claim that the applicant’s test product Prochlorperazine 5 mg tablet (Medreich Limited) is bioequivalent to the reference product Stemetil 5 mg tablet (Aventis Pharma Limited, UK) under fasting conditions.

### IV.3 Clinical efficacy

The efficacy of prochlorperazine maleate is well-known. No new efficacy data have been submitted and none are required for this type of application.

### IV.4 Clinical safety

With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

### IV.5 Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for non-submission of a Risk Management Plan (RMP) for this application which was received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the application is for a generic version of an already authorised product, for which safety concerns requiring additional risk minimisation have not been identified, there is no need for a detailed European Risk Management Plan and the routine pharmacovigilance activities are sufficient. The reference product has been in use for many years and the safety profile of the active ingredient is well-established.

### CONCLUSION

The grant of a Marketing Authorisation is recommended.
V USER CONSULTATION
User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant that makes reference to the successful user test of the PIL for Prochlorperazine Maleate 3 mg Buccal Tablets (PL 21880/0122; Medreich plc). The justification on the rationale for bridging is accepted.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Prochlorperazine Maleate 5 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of prochlorperazine maleate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s Prochlorperazine Maleate 5 mg tablet and the reference product Stemetil 5 mg tablet (Aventis Pharma Limited, UK) under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of prochlorperazine maleate is well-known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and Stemetil 5mg Tablets are interchangeable. Extensive clinical experience with prochlorperazine maleate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
Prochlorperazine Maleate 5 mg Buccal Tablets

PL 21880/0121

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists an update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>03/11/2014</td>
<td>Type IB</td>
<td>To extend the shelf life of Prochlorperazine Maleate 5 mg Tablets from 24 months to 36 months</td>
<td>Approved on 05/12/2014</td>
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