Public Assessment Report

UK PAR

Prochlorperazine maleate 3 mg Buccal Tablets

UK Licence No: PL 43659/0024

Primegen Limited
LAY SUMMARY

Prochlorperazine maleate 3 mg Buccal Tablets

This is a summary of the Public Assessment Report (PAR) for Prochlorperazine maleate 3 mg Buccal Tablets (PL 43659/0024). It explains how the application for Prochlorperazine maleate 3 mg Buccal 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 3 mg Buccal Tablets.

For practical information about using Prochlorperazine maleate 3 mg Buccal Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

Prochlorperazine maleate 3 mg Buccal Tablets may be referred to as Prochlorperazine maleate Buccal Tablets in this Lay Summary.

What are Prochlorperazine maleate Buccal Tablets and what are they used for?
Prochlorperazine maleate Buccal Tablets are a ‘hybrid medicine’. This means that Prochlorperazine maleate Buccal Tablets are similar to a ‘reference medicine’ already authorised in the UK called Stemetil 5 mg Tablets (PL 04425/0593; Aventis Pharma Limited), which was first authorised in the UK to May & Baker (PL 00012/5263R) on 05 August 1986.

Prochlorperazine maleate Buccal Tablets are effective in treating nausea (feeling sick) and vomiting (being sick) from whatever cause. They are also used to treat migraine and dizziness due to ear problems and other causes.

How do Prochlorperazine maleate 3 mg Buccal Tablets work?
The active substance, prochlorperazine, belongs to a large group of drugs known as phenothiazines, which have a variety of effects.

How are Prochlorperazine maleate Buccal Tablets used?
The patient should always take this medicine exactly as advised by the doctor. The patient should check with his/her doctor or pharmacist if they are not sure.

• Prochlorperazine maleate Buccal Tablets are held in the mouth high up along the top gum, under the upper lip, on either side if the mouth. The tablet(s) must not be swallowed whole or chewed.
• The tablet(s) will soften and adhere to the gum. The tablet(s) should be allowed to dissolve slowly and completely - this may take between 1 and 2 hours. Most people find that after a few minutes they no longer notice the tablet(s).
• The tablet(s) should NOT be moved about the mouth with the tongue as this will cause it (them) to dissolve too quickly.
• If the patient wears dentures, the tablet(s) may be placed in any comfortable position between the lip and gum.

The recommended dose is one or two tablets twice a day for adults and children over 12 years of age. The tablet(s) are best taken after meals.

Prochlorperazine maleate Buccal Tablets are not recommended for children under 12 years of age.
Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Prochlorperazine maleate Buccal Tablets can only be obtained on prescription.

**How have Prochlorperazine maleate Buccal Tablets been studied?**
Prochlorperazine maleate Buccal Tablets are a hybrid medicine and cross refer to the reference medicine Stemetil 5 mg Tablets (Aventis Pharma Limited). Reference is also made to the clinical data provided for Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK). Studies in patients have been limited to tests to determine that Prochlorperazine maleate Buccal Tablets are bioequivalent to Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Prochlorperazine maleate Buccal Tablets?**
Like all medicines Prochlorperazine maleate Buccal Tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Prochlorperazine maleate Buccal Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Prochlorperazine maleate Buccal Tablets.

**Why are Prochlorperazine maleate Buccal Tablets approved?**
It was concluded that, in accordance with EU requirements, Prochlorperazine maleate Buccal Tablets have been shown to have comparable quality and to be bioequivalent to Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK). Therefore, the view was that, as for Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals 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 Buccal Tablets?**
A Risk Management Plan has been developed to ensure that Prochlorperazine maleate Buccal Tablets are 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 Prochlorperazine maleate Buccal Tablets, 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 Prochlorperazine maleate Buccal Tablets**
A Marketing Authorisation was granted in the UK to Primegen Limited on 02 February 2016.

The full PAR for Prochlorperazine maleate Buccal Tablets follows this summary.

For more information about treatment with Prochlorperazine maleate Buccal Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I  Introduction  Page 5
II  Quality aspects  Page 6
III  Non-clinical aspects  Page 9
IV  Clinical aspects  Page 10
V  User consultation  Page 12
VI  Overall conclusion, benefit/risk assessment and recommendation  Page 12
Steps taken after Authorisation - Summary  Page 14
I Scientific discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Primegen Limited, a Marketing Authorisation for the medicinal product Prochlorperazine maleate 3 mg Buccal Tablets (PL 43659/0024) on 02 February 2016. This product is a Prescription-Only Medicine (POM) indicated for the following:

- symptomatic treatment of vertigo due to Ménière's Disease, labyrinthitis and other causes;
- nausea and vomiting from whatever cause;
- treatment of migraine.

The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended as a hybrid application and cross refers to Stemetil 5 mg Tablets (PL 04425/0593; Aventis Pharma Limited), which was authorised in the UK on 02 October 2006 following a series of change of ownership procedures of Stemetil 5 mg Tablets (PL 00012/5263R; May & Baker Limited). The licence for Stemetil 5 mg Tablets (PL 00012/5263R; May & Baker Limited) was originally granted in the UK on 05 August 1986.

The applicant refers also to the clinical data provided for Buccastem 3mg Buccal Tablets. This is in line with the position which has been discussed and agreed by the Co-Ordination Group for Mutual Recognition and Decentralised Procedures - human (CMDh) and is reflected in the CMDh Questions & Answers Generic applications, Question 4 (most recently updated 2012).

Buccastem 3mg Buccal Tablets (PL 16853/0101; Alliance Pharmaceuticals Ltd) was authorised in the UK on 16 February 2010 following a series of change of ownership procedures of Buccastem 3 mg Buccal Tablets (PL 00044/0089; Reckitt & Colman). Buccastem 3 mg Buccal Tablets (PL 00044/0089; Reckitt & Colman) was first approved in the UK on 20 May 1987. The marketing authorisation was granted based on Article 10(3) of Directive 2001/83/EC, as amended, cross-referring to the reference medicinal product Stemetil 5 mg Tablets.

The active substance, prochlorperazine (as maleate), belongs to a group of medicines known as phenothiazine derivatives. Prochlorperazine maleate is a dopamine and histamine antagonist. The mechanism of anti-emetic effect is due predominantly to blockade of the histamine H1 and dopamine D2 neurotransmitter receptors in the chemoreceptor trigger zone and vomiting centre. It also has a weak anticholinergic effect and prevents acid reflux by increasing the tone of the lower oesophageal sphincter.

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Prochlorperazine maleate 3 mg tablets (NRIM Ltd., UK) with Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK) under fasting conditions. The bioequivalence study is stated to have been conducted 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 3 mg Buccal 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(3) of Directive 2001/83/EC, as amended, and cross refers to Stemetil 5 mg Tablets (Aventis Pharma Limited). The applicant refers also to the clinical data provided for Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Ltd).

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 pale yellow, round, biconvex, uncoated tablet debossed with ‘PC’ on one side and plain on the other.

Each buccal tablet contains 3 mg of prochlorperazine maleate, as the active substance. The other ingredients are sucrose, locust bean gum, xanthan gum, hypromellose 2910, riboflavin sodium phosphate, magnesium stearate and talc.

The product is supplied in oriented polyamide/aluminium/polyvinylchloride/aluminium or polyvinylchloride/polyvinylidene chloride/aluminium blisters, in pack sizes of 30 and 50 buccal tablets. Not all pack sizes may be marketed.

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-methyl-piperazin-1-yl)propyl]-10H-phenothiazine bis[hydrogen (Z)-butenedioate]

Structure:

\[
\text{Structure:}
\]

Molecular formula: \( \text{C}_{20}\text{H}_{24}\text{ClN}_{3}\text{S},(\text{C}_{4}\text{H}_{4}\text{O}_{4})_{2} \)
Molecular weight: 606.0 g/mol
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 analysis 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 were comparable in performance to Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparable in-vitro dissolution and impurity profiles have been provided for this product and Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Limited, UK).

With the exception of locust bean gum, all the excipients comply with their respective European Pharmacopoeia monographs. Locust bean gum is controlled to a suitable in-house specification.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contains material of animal or human origin.

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 pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

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 that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months, with no special storage conditions, has been accepted.

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. The bioequivalence study is discussed in Section IV, Clinical Aspects.
II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application for Prochlorperazine maleate 3 mg Buccal Tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

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:
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 3mg Buccal Tablets from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC, as amended, and cross refers to Stemetil 5 mg Tablets (Aventis Pharma Limited). The applicant refers also to the clinical data provided for Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Ltd).

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study, comparing the applicant’s test Prochlorperazine maleate 3 mg tablets (2 x 3 mg; NRIM Ltd., UK) with Buccastem (Prochlorperazine maleate) 3 mg Buccal Tablets (2 x 3 mg; Alliance Pharmaceuticals Limited, UK) under fasting conditions.

The clinical pharmacology of prochlorperazine maleate is well-known. With the exception of data from the bioequivalence study detailed below, no new clinical 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 maleate 3 mg tablets (2 x 3 mg; NRIM Ltd., UK) versus Buccastem (Prochlorperazine maleate) 3 mg Buccal Tablets (2 x 3 mg; Alliance Pharmaceuticals Limited, UK) in healthy adult subjects under fasting conditions.
The subjects were administered a single 6 mg dose (two 3 mg tablets) of either the test or the reference product after at least a 10-hour overnight fast. Each tablet was placed high up along the top gum under the upper lip either side of mouth and was allowed to dissolve completely. Subjects were not allowed to move the tablet about the mouth. Subjects were instructed not to swallow, spit or to chew the tablets. Study drug administration was done under the supervision of trained study personnel in each period. Blood samples were collected before and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days. The pharmacokinetic results are presented below.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC$_{0-t}$ ng/ml/h</th>
<th>C$_{max}$ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>16412.1008 ± 6727.42007</td>
<td>919.8469 ± 472.91035</td>
</tr>
<tr>
<td>Reference</td>
<td>17149.6581 ± 7305.74568</td>
<td>945.2122 ± 451.15507</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>96.49 (88.64 - 105.03)</td>
<td>96.60 (86.67 - 107.66)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>20.83</td>
<td>26.80</td>
</tr>
</tbody>
</table>

*C$_{max}$ maximum plasma concentration  
AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours  
CV coefficient of variation  
*Ratios and 90% CI calculated from ln-transformed data

The Note for Guidance 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$_{max}$ values. Thus, the data support the claim that the applicant’s test product Prochlorperazine maleate 3 mg tablets (NRIM Ltd., UK) is bioequivalent to Buccastem (Prochlorperazine maleate) 3 mg tablets (Alliance Pharmaceuticals Limited, UK) under fasting conditions.

### IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of prochlorperazine maleate are well-known. No new clinical pharmacodynamic data have been submitted and none are required for this type of application.

### IV.4 Clinical Efficacy

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

### IV.5 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.6 Risk Management Plan

The MAH has submitted a risk management plan, 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 Prochlorperazine maleate 3 mg Buccal Tablets.

The MAH identified the following as safety concerns:
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION
A 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 pack leaflet 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Prochlorperazine maleate 3 mg Buccal 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 3 mg tablets (NRIM Ltd., UK) and Buccastem (Prochlorperazine maleate) 3 mg tablets (Alliance Pharmaceuticals 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. 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.
Prochlorperazine maleate 3 mg Buccal Tablets

PL 43659/0024

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>