Public Assessment Report

UKPAR

Prochlorperazine Maleate 3mg Buccal Tablets
(prochlorperazine maleate)

UK licence Number: PL 20117/0263

Morningside Healthcare Limited
This is a summary of the Public Assessment Report (PAR) for Prochlorperazine Maleate 3mg Buccal Tablets (PL 20117/0263).

This summary explains how Prochlorperazine Maleate 3mg Buccal Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use this product.

The product will be referred to as Prochlorperazine tablets throughout the remainder of this lay summary for ease of reading.

For practical information about using Prochlorperazine tablets, patients should read the package leaflet available on the MHRA website or contact their doctor or pharmacist.

What are Prochlorperazine tablets and what are they used for?
Prochlorperazine Tablets are effective in treating nausea (feeling sick) and vomiting (being sick) associated with migraine.

How do Prochlorperazine tablets work?
Prochlorperazine tablets contain prochlorperazine maleate. This is one of a large group of medicines called phenothiazines that have a variety of effects. Prochlorperazine is thought to work by blocking the action of a chemical called dopamine in the vomiting centre of the brain.

How are Prochlorperazine tablets used?
Prochlorperazine tablets are placed high along the patient’s top gum, under the upper lip on either side of the patient’s mouth. The tablet must not be swallowed whole or chewed. The tablet will soften and stick to the gum. It should be allowed to dissolve slowly and completely—this may take between 1 and 2 hours. Most people will find that after a few minutes they no longer notice the tablet. The tablet should not be moved about the mouth with the tongue as this will cause it to dissolve too quickly. If the patient wears dentures, the tablet may be placed in any comfortable position between their lip and gum. Prochlorperazine Tablets are best taken after meals.

The recommended dose is one or two tablets twice a day for a maximum of 2 days, for adults aged 18 years or over.

Use in children and adolescents
Prochlorperazine Tablets should not be used in children and adolescents aged less than 18 years.

If a patient takes more Prochlorperazine Tablets than they should they must seek medical attention immediately.
If the patient forgets to take Prochlorperazine Tablets, they should take it as soon as they remember. However, if it is nearly time for their next dose, in that case, they should miss the forgotten dose and take it next time as instructed by their doctor or pharmacist. A double dose should not be taken to make up for a forgotten dose.

The patient should not stop taking Prochlorperazine Tablets without talking to their doctor first.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine is available in a pharmacy, without a prescription.

**What benefits of Prochlorperazine tablets have been shown in studies?**
As the strength, pharmaceutical form and indications of Prochlorperazine tablets differs from the reference medicine, Stemetil 5mg tablets (Aventis Pharma Limited), the application for Prochlorperazine tablets was submitted as a ‘hybrid’ application. Reference is also made to the clinical data provided for Buccastem M Buccal Tablets (Alliance Pharmaceutical Ltd). Studies in patients have been limited to tests to determine that the medicine is bioequivalent to the comparator product, Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Ltd). Two medicines are bioequivalent when they produce the same levels of active substance in the body.

**What are the possible side effects of Prochlorperazine tablets?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet available on the MHRA website.

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

**Why are Prochlorperazine tablets approved?**
It was concluded that, in accordance with EU requirements, Prochlorperazine tablets have been shown to have comparable quality and to be bioequivalent to the comparator product, Buccastem 3mg Buccal Tablets. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Prochlorperazine tablets outweigh the risks, and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Prochlorperazine tablets?**
A Risk Management Plan (RMP) has been developed to ensure that Prochlorperazine tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflets of Prochlorperazine Maleate 3mg Buccal Tablets, including the appropriate precautions to be followed by patients.

Known side-effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.
**Other information about Prochlorperazine tablets**

The UK granted a Marketing Authorisation for Prochlorperazine tablets on 25 April 2017.

The full PAR for Prochlorperazine tablets follows this summary.

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

This summary was last updated in June 2017.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA considered that the application for Prochlorperazine Maleate 3mg Buccal Tablets (PL 20117/0263) could be approved for marketing. This product is a ‘Pharmacy Medicine’ (legal status “P”).

Prochlorperazine Maleate 3mg Buccal Tablets are indicated for:

- nausea and vomiting in previously diagnosed migraine, in adults aged 18 years and over.

These applications were submitted according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application for a different strength, pharmaceutical form and indications of product compared to the reference product.

The reference product is Stemetil 5mg 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 from 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 also refers to the clinical data provided for Buccastem M Buccal Tablets (PL 16853/0102). 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 (re CMDh/272/2012, Rev 2 April 2017).

Buccastem M Buccal Tablets (PL 16853/0102; Alliance Pharmaceuticals Ltd) was authorised in the UK on 16 February 2010 following a change of ownership procedure of Buccastem M (PL 00063/0107); Reckitt Benckiser Healthcare (UK) Ltd which was authorised 06 July 1999 as an identical licence (informed consent) to Buccastem 3 mg Buccal Tablets (PL 00063/0011); Reckitt Benckiser Healthcare (UK) Ltd and then varied to change the legal status from Prescription Only Medicine (POM) to Pharmacy medicine (P) on September 2001.

The comparator product, selected for use in the bioequivalence study, is Buccastem 3 mg Buccal Tablets (PL 16853/0101; Alliance Pharmaceuticals Limited). Buccastem 3 mg Buccal Tablets was authorised in the UK on 16 February 2010 following a change of ownership procedure from PL 00063/0011 (Reckitt Benckiser Healthcare (UK) Ltd). Buccastem 3 mg Buccal Tablets (PL 00063/0011; Reckitt Benckiser Healthcare (UK) Ltd) was authorised in the UK on 24 May 1995 following a change of ownership procedure from PL 00044/0089 (Reckitt & Colman), which was approved in the UK on 20 May 1987 in accordance with Article 10(3) of Directive 2001/83/EC, as amended, cross-referring to the reference medicinal product Stemetil 5 mg Tablets.

Prochlorperazine is a piperazine phenothiazine related to high-potency neuroleptics such as perphenazine. It shares many of the actions and adverse effects of antipsychotics. It is an antiemetic endowed with analgesic properties mediated by the presynaptic inhibition of the D2 heteroreceptor located on the cholinergic neurons. The mechanism of action of prochlorperazine has not been fully determined, but may be primarily related to its antidopaminergic effects. The drug blocks the D2 somatodendritic autoreceptor, resulting in the blockade of postsynaptic dopamine receptors in the mesolimbic system and an increased dopamine turnover.
Prochlorperazine also blocks anticholinergic and alpha-adrenergic receptors. The blockade of alpha(1)-adrenergic receptors results in sedation, muscle relaxation, and hypotension. The antidopamine action probably contributes to both the therapeutic effect and unwanted effects including extrapyramidal disorders and endocrine disturbances.

With the exception of a 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.

A bioequivalence study was conducted comparing the pharmacokinetics of the applicant’s test product Prochlorperazine Maleate 3mg Buccal Tablets versus Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited). The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture and assembly of this product.

A satisfactory summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) has been provided with this application.

A Marketing Authorisation was granted in the UK on 25 April 2017.
II QUALITY ASPECTS
II.1 Introduction
Prochlorperazine Maleate 3mg Buccal Tablets contains 3mg of prochlorperazine maleate per tablet.

Other ingredients consist of the pharmaceutical excipients locust bean gum (E410), xanthan gum (E415), compressible sugar, riboflavin sodium phosphate (E101), povidone K 30 (E1201), purified talc (E553b) and magnesium stearate (E470b).

The finished products are packaged into white opaque polyvinylchloride / polyvinylidene chloride / aluminium foil blisters, which are packaged in cardboard cartons in a pack size of 8 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

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

Structural formula:

![Structural formula of Prochlorperazine Maleate](image)

Molecular formula: C_{20}H_{24}ClN_{3}S \cdot 2C_{4}H_{4}O_{4}
Relative molecular mass: 606.09
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 (Ph.Eur) 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 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 specification limits. 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 supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The primary objective was to develop a generic formulation of Prochlorperazine Maleate 3 mg Buccal Tablets which is a safe and effective product, which could be considered equivalent to the product already on the market, Buccastem M Buccal Tablets of Alliance Pharmaceuticals Ltd, UK. A satisfactory account of the pharmaceutical development has been provided.

Comparable in vitro dissolution profiles have been provided for the test product and comparator product Buccastem 3 mg Buccal Tablets. Apart from the differences in the indications, Buccastem M Buccal Tablets (Alliance Pharmaceuticals Limited) and Buccastem 3mg Buccal Tablets (Alliance Pharmaceuticals Limited, PL 18853/0101) are considered identical products. Hence the use of Buccastem 3mg Buccal Tablets for bioequivalence studies is acceptable.

Locust bean gum is controlled to an in-house specification, compressible sugar is controlled to the United States Pharmacopoeia-national formulary, whilst xanthum gum and riboflavin sodium phosphate are controlled in accordance with their respective British Pharmacopoeia (BP) monographs. All other excipients comply with their respective Ph. Eur. monographs.

None of the excipients contain materials of animal or human origin.

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

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at a commercial-scale batch size and shown satisfactory results.

Finished Product Specifications
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. In-house working standards are used, which are compared to European Pharmacopoeia reference standards, where available. Representative Certificates of Analysis have been provided for the reference standards.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, without any special storage conditions.
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

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

There are no objections to the approval of this product from a pharmaceutical perspective.

III **NON-CLINICAL ASPECTS**

III.1 **Introduction**

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

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

III.2 **Pharmacology**

The pharmacology of prochlorperazine maleate is well known and adequately described in the applicant’s non-clinical overview.

III.3 **Pharmacokinetics**

The pharmacokinetic properties of prochlorperazine maleate are well known and 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)**

As this product is intended for generic substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

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

There are no objections to the approval of this product from a non-clinical perspective.

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 M Buccal Tablets (Alliance Pharmaceuticals Limited).
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 Buccal Tablets (Morningside Healthcare Limited) versus Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited, formerly Reckitt Benckiser Healthcare, 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 has submitted results from the following bioequivalence study:

A randomised, open-label, balanced, two-treatment, two-sequence, single-dose, crossover study comparing the pharmacokinetics of the test product Prochlorperazine maleate 3mg buccal Tablets versus the comparator product Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited), in healthy, adult, human subjects under fasting conditions.

Subjects fasted for a minimum of 10 hours before receiving a single dose of the test or reference product. There was a washout period of 15 days between doses.

The ln-transformed pharmacokinetic parameters $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\infty}$ were calculated to evaluate bioequivalence.

Summary statistics for pharmacokinetic parameters for the test and reference products are shown below:

<table>
<thead>
<tr>
<th>PK Parameters (Unit)</th>
<th>Geometric Least Squares Means and it’s ratio (N = 24)</th>
<th>90% Confidence Interval</th>
<th>Intra-subject %CV</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test Product (T)</td>
<td>Reference Product (R)</td>
<td>(T/R) %</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (pg/mL)</td>
<td>267.436</td>
<td>276.905</td>
<td>96.58</td>
<td>82.34% - 113.28%</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (hr*pg/mL)</td>
<td>5332.170</td>
<td>5696.513</td>
<td>93.60</td>
<td>81.02% - 108.15%</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\infty}$ (hr*pg/mL)</td>
<td>5595.456</td>
<td>5976.869</td>
<td>93.62</td>
<td>81.05% - 108.13%</td>
</tr>
</tbody>
</table>

The 90% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for prochlorperazine maleate 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 applicant’s test product is bioequivalent to Buccastem 3 mg Buccal Tablets (Alliance Pharmaceuticals Limited) under fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for this type of application.
IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for this type of application.
IV.5 Clinical safety
With the exception of the safety data collected during the bioequivalence study, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed during the bioequivalence study.

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 this product.

A summary of safety concerns, as approved in the RMP is provided below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tr>
<td>Important identified risks</td>
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<tr>
<td>• Leucopenia and agranulocytosis</td>
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<tr>
<td>• Exacerbation of epilepsy</td>
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<tr>
<td>• Exacerbation of Parkinson’s disease</td>
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<tr>
<td>• Use in male patients with enlarged prostate</td>
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<tr>
<td>• Effects on the eyes (narrow angle glaucoma)</td>
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<td>• Photosensitivity</td>
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<tr>
<td>• Use during pregnancy</td>
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<tr>
<td>Important potential risks</td>
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<tr>
<td>• Dystonic reactions in children (after cumulative dose of 0.5 mg/kg) – POM product</td>
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<tr>
<td>• Tardive dyskinesia</td>
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<tr>
<td>• Neuroleptic malignant syndrome (NMS)</td>
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<tr>
<td>Missing information</td>
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<tr>
<td>• Use in children under the age of 12 years</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
There are no objections to the approval of this product from a clinical perspective.

V User consultation
The package leaflet has been evaluated, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to understand and act upon the information that it contains.

VI 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 prochlorperazine maleate is considered to have demonstrated the therapeutic value of the compound. The product is considered to be bioequivalent to the marketed comparator product and
their benefits and risks are considered similar. The benefit/risk balance is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Package Leaflet and Labels
In accordance with Directive 2010/84/EU the Summary of Product Characteristics (SmPCs) and package leaflet for the product granted a Marketing Authorisation at a national level is available on the MHRA website.

The approved labelling for Prochlorperazine Maleate 3mg Buccal Tablets is presented below:
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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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