IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific discussion

Rennie Direct 680 mg/80 mg Powder
CALCIUM CARBONATE
MAGNESIUM CARBONATE
PA1410/053/005

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Rennie Direct 680 mg/80 mg Powder, from Bayer Limited on <date of authorisation> for relief of stomach upsets due to hyperacidity and heartburn.

This is an application under Article 10a of Directive 2001/83/EC referred to as a "well-established use" application. The application is supported by bibliographic data.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Rennie Direct 680 mg/80 mg Powder
Name(s) of the active substance(s) (INN)	CALCIUM CARBONATE MAGNESIUM CARBONATE
Pharmacotherapeutic classification (ATC code)	A02AX
Pharmaceutical form and strength(s)	680 mg/80 mg Powder
Marketing Authorisation Number(s) in Ireland (PA)	PA1410/053/005
Marketing Authorisation Holder	Bayer Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Rennie Direct 680 mg/80 mg oral powder.

II.2 Drug substance

The active substances are calcium carbonate and heavy magnesium carbonate, both established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each sachet contains calcium carbonate 680 mg (equivalent to 272 mg elemental calcium) and heavy magnesium carbonate 80 mg.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is based an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for oral powders, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. /EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Rennie Direct 680 mg / 80 mg oral powder.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Rennie ICE 680mg/80mg Chewable Tablet on the Irish market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A.

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

N/A

IV CLINICAL ASPECTS

IV.1 Introduction

This is an Article 10a well-established use application supported by bibliographic data. This is a line extension application for an addition of a new pharmaceutical form of Calcium carbonate 680mg and Heavy Magnesium carbonate 80mg combined as an oral powder formulation delivered from a sachet. The powder is to be taken orally without water. The posology is the same as that for the reference produce Rennie ICE 680mg/80mg Chewable Tablets. Rennie Direct 680 mg/80 mg Powder has the same qualitative and quantitative composition (apart from some differences in excipients) as Rennie Ice Chewable Tablets.
Calcium carbonate 680mg and heavy magnesium carbonate 80 mg in combination are well-known active substances with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for similar Rennie products marketed by the MAH.

As this product is an antacid and acts locally in the stomach to neutralise stomach acid, no bioequivalence studies have been submitted.

	Rennie Ice	Rennie Direct 680 mg / 80 mg Powder
	Calcium carbonate 680 mg (272 mg elemental calcium)	Calcium Carbonate 680 mg (272 mg elemental calcium)
	Heavy Magnesium Carbonate 80 mg	Heavy Magnesium Carbonate 80 mg
	Sucrose 475 mg	Xylitol
	Maize starch, pregelatinised	Maltodextrin
	Potato starch	
	Talc	
	Magnesium stearate	
	Paraffin, light liquid	
	Xylitab 100 (xylitol (min. 95%), polydextrose)	
	Cooling flavour (diethyl malonate, maltodextrin (maize), menthol, menthyl lactate, modified starch E1450 (waxy maize), iso-pulegol)	Cooling flavour (diethyl malonate, maltodextrin (maize), menthol, menthyl lactate, modified starch E1450 (waxy maize), iso-pulegol)
	Mint flavour (maltodextrin (maize), menthol, modified starch E1450 (waxy maize))	Mint flavour (maltodextrin (maize), menthol, modified starch E1450 (waxy maize))
		Saccharin sodium

There is no requirement to submit PSURs.

Calcium carbonate and magnesium carbonate in combination are well known active substance with established efficacy and tolerability. This medicinal product is the same as Rennie ICE 680mg/80mg Chewable Tablets on the Irish market.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Rennie ICE 680mg/80mg Chewable Tablets marketed by MAH.

IV.2 Pharmacokinetics

In the stomach, calcium carbonate and magnesium carbonate react with the acid in the gastric juice, forming water and soluble mineral salts.

$CaCO_3 + 2HCl \Rightarrow CaCl_2 + H_2O + CO_2$

$MgCO_3 + 2HCl \Rightarrow MgCl_2 + H_2O + CO_2$

Calcium and magnesium can be absorbed from these soluble salts. However, the degree of absorption is dependent on the subject and the dose. Less than 10% calcium and 15-20% magnesium is absorbed.
The small quantities of calcium and magnesium absorbed are usually excreted rapidly via the kidneys in healthy individuals. In the case of impaired renal function, plasma concentrations of calcium and magnesium may be increased.
Due to the effects of various digestive juices outside the stomach, the soluble salts are converted to insoluble salts in the intestinal canal and then excreted with the faeces.

IV.3 Pharmacodynamics

Rennie Direct is a combination of two antacids, calcium carbonate and magnesium carbonate. The mode of action of calcium carbonate and magnesium carbonate is local, based on the neutralisation of gastric acid, and is not dependant on systemic absorption. Calcium carbonate has a rapid, long lasting and powerful neutralising action. This effect is increased by the addition of magnesium carbonate which also has a strong neutralising action. In vitro, the total neutralising capacity of the product is 15.5 mEq H+ (titration to endpoint pH 2.5)

IV.4 Clinical Efficacy

The efficacy of the combination of Calcium carbonate 680mg and magnesium carbonate 80 mg in combination is well characterised.

IV.5 Clinical Safety

The safety of the combination of Calcium carbonate 680mg and magnesium carbonate 80 mg in combination is well characterised.

Pharmacovigilance System

The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan (RMP)

The MAH has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities designed to identify, characterise, prevent or minimise risks relating to Rennie Direct 680 mg/ 80 mg Powder.
The summary of safety concerns is presented below:

Summary of safety concerns	
• Important identified risks	• Hypersensitivity • Hypercalcaemia • Milk alkali syndrome/alkalosis • Drug interactions- due to complex formation and reduced absorption e.g. tetracyclines, quinolones, cardiac glycosides, fluorides, phosphates, eltrombopag, due to reduced absorption e.g. iron, levothyroxine, due to reduced urinary excretion of calcium e.g. thiazides
Important potential risks	• Hypermagnesemia • Nephrolithiasis
Missing information	• None

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

IV.6 Discussion on the clinical aspects

This is an Article 10a well-established use application supported by bibliographic data. This is a line extension application for an addition of a new pharmaceutical form. The reference for the line extension is Rennie ICE 680mg/80mg Chewable Tablets which has the same qualitative and quantitative composition (apart from some differences in excipients).
The product acts locally in the stomach to neutralise gastric acid (HCl). See IV.2.
The efficacy and safety of the reference product is well characterised.
The applicant has submitted sufficient bibliographic data to support the application. The application can be approved from a clinical point of view.

V OVERALL CONCLUSIONS

Rennie Direct 680mg / 80mg powder contains the same active substance as Rennie Ice Chewable tablet. Rennie Ice Chewable tablet is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.
The product like the reference product acts locally within the stomach. No bioequivalence studies were required.
The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Rennie Direct 680mg / 80mg powder demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.