IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Rennie 750 mg Medicated Chewing Gum
Calcium carbonate
PA1410/089/001

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 750 mg Medicated Chewing-gum, from Bayer Ltd on 22nd July 2022 for
"*Symptomatic relief of heartburn and acid related symptoms in adults and children from 12 years old*".

The application was submitted as a Well-Established Use application under Article 10a of Directive 2001/83/EC.

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 750 mg Medicated Chewing-gum
Name(s) of the active substance(s) (INN)	Calcium Carbonate
Pharmacotherapeutic classification (ATC code)	A02AC01
Pharmaceutical form and strength(s)	750 mg Medicated Chewing-gum
Marketing Authorisation Number(s) in Ireland (PA)	PA1410/089/001
Marketing Authorisation Holder	Bayer Limited
MRP/DCP No.	IE/H/1139/001/DC
Reference Member State	IE
Concerned Member State	FR HU IT NL SI

II. QUALITY ASPECTS

II.1. Introduction

This application is for Rennie 750 mg Medicated Chewing Gum

II.2 Drug substance

The active substance is Calcium Carbonate an 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 piece of medicated chewing-gum contains 750 mg of calcium carbonate.

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 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 the dosage form, 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 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 750 mg Medicated Chewing Gum.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The application is being submitted as a Well-Established Use application under Article 10a of Directive 2001/83/EC for Rennie 750 mg Medicated Chewing Gum. The product is composed of one active ingredient, calcium carbonate.

III.2 Pharmacology

No new pharmacology studies have been submitted by the Applicant. The mechanism of action of calcium carbonate is via raising the gastric pH by reacting with hydrochloric acid in the gastric juices resulting in the formation of calcium chloride, water and carbon dioxide. This is well established from clinical experience. Similarly, no studies on secondary pharmacology, safety pharmacology of pharmacodynamic drug interactions. For a well-established use application this is considered acceptable.<Insert text>

III.3 Pharmacokinetics

No new pharmacokinetic studies have been performed by the Applicant which is acceptable for a well-established use application. Following oral ingestion of CaCO3 systemic absorption of calcium occurs via a vitamin-D dependent absorption from the duodenum of the intestine. This process is saturable and is regulated on the basis of calcium intake. In addition, paracellular absorption of calcium from the intestine also occurs which is non-saturable. As an essential ion, calcium is widely distributed around the body. In the serum approx. 50% is protein bound and another 5-10% found in salt form with the remainder as free ions. Physiological concentrations of calcium are tightly controlled principally by the effects of parathyroid hormone, vitamin D and its metabolites, and calcitonin, on intestinal absorption, deposition in bone, and renal excretion. Unabsorbed calcium is eliminated from the GI tract via the faeces.

III.4 Toxicology

No new toxicology studies have been submitted by the Applicant, which is considered acceptable. Calcium carbonate is a well-known active ingredient and although the available toxicology data in the literature is limited, the overview of the toxicology of Rennie Gum is considered adequate and acceptable in the context of this well-established use application.

III.5 Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, calcium carbonate is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

No new nonclinical studies have been submitted by the Applicant which is in-line with the requirements for a well-established use application. Calcium carbonate is a well established antacid that has been in clinical use for decades with a known efficacy and safety profile. The use of literature references in-lieu of new nonclinical studies is acceptable and appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

As this was a well established use procedure, literature references were provided in lieu of clinical studies.

IV.2 Pharmacology

Insoluble calcium carbonate is transformed in the stomach to soluble calcium chloride. The ionized calcium is absorbed in the gut or transformed to insoluble salts (carbonate, stearate) for elimination in the feces. The absorbed fraction is mainly eliminated in the urine, depending on the creatinine clearance. Generally speaking, the absorption of calcium salts depends on the patient and the dose; the absorbed fraction is inversely proportional to total dose. The bioavailability of calcium carbonate is greatly influenced by gastric acidity. In particular, subjects achlorhydric in the fasting state do not absorb any calcium at all while absorption is normal when calcium carbonate is taken with food. In hyperchlorhydria, calcium absorption is increased. The degree of calcium absorption from insoluble $CaCO_3$ is modest (up to 20%). The absorbed fraction is mainly eliminated in the urine, the rate depending on the creatinine clearance.
However, the absorption of calcium is not related nor relevant to clinical efficacy because it acts locally by neutralizing acidic gastric contents.

IV.3 Clinical Efficacy

In gastro-oesophageal reflux which has failed to respond to dietary and lifestyle changes, antacids are fast and effective first line treatment options.
These products are cost-effective, safe and efficacious when used at the recommended doses and indications. The antacid effect of calcium carbonate antacids had been clearly demonstrated for doses ranging from 420 mg to 3'000 mg. These products are generally very safe and this explains such a huge variety in terms of doses currently available on the market.
The onset of the effect is fast, commencing in less than 5 min and had been shown to occur upon contact with stomach acid, which means that reaction of neutralization happens already in the oesophagus. The duration of effect depends on many factors, such as the food, its quantity and quality, the speed with which it was consumed, postprandial body position and many others (e.g. alcohol, cigarette smoking) but generally lasts from one to two hours. Chewing gums as antacids were investigated in three trials, including either $CaCO_3$, baking soda or no active ingredient. These studies demonstrate that $CaCO_3$ gums increase oesophageal pH as well as gastric pH and effectively neutralize oesophageal acidity. Use of bicarbonate chewing gums also resulted in higher oesophageal and pharyngeal pH and this buffering effect lasted longer than the chewing time. The third study analyzed the effect of chewing gum without active ingredient on oesophageal pH and showed that chewing sugar-free gum for half an hour after a meal can reduce acidic postprandial oesophageal reflux.
Bayer medicated chewing gum antacid, with 750 mg of calcium carbonate falls into the range of clinically tested antacids, which had demonstrated their ability to meaningfully elevate stomach / oesophageal pH. Given that calcium carbonate has wide therapeutic index there is no one fixed dose that would be optimal for heartburn and reflux symptoms relief. The choice of the single dose then is driven by available scientific data, acid neutralization capacity and safety profile. The totality of clinical and in-vitro data given above confirm that 750 mg calcium antacid in the pharmaceutical form of a medicated chewing gum is an antacid product with potent acid neutralizing capacity (ANC) and ability to meaningfully relief heartburn and acid reflux symptoms.

IV.4 Clinical Safety

Calcium carbonate based antacids (either as single ingredient or in combination products) have been marketed worldwide for more than 80 years with hundreds of millions of users exposed to it. This long and extensive experience allowed collection of sufficient evidence to establish safety profile of calcium-carbonate antacids, thus compensating for any limitations of adverse drug reactions (ADR) detection common to conventional clinical trial development programs. It has a well-established medicinal use and is generally recognised as safe and effective over the counter (OTC) available antacids.

Risk Management Plan
The applicant 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 calcium carbonate (Rennie).

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

The submitted Risk Management Plan, version 1.1, signed 06 August 2021 is considered acceptable. The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Reports (PSUR) submission

With regard to PSUR submission, the MAH should take the following into account:
• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
• In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.5 Discussion on the clinical aspects

It was noted that many of the literature references concerned slightly different doses, combinations and formulations, and mostly were chewable tablets rather than the gum proposed. However, the applicant submitted additional bridging data at a late stage of the procedure which can be accepted by the RMS; in particular the in vitro, comparative head to head testing, and the further discussion on the similarity between the chewable tablets and gum formulation. The additional data and justification provide a stronger bridge to the literature references than was presented in the initial dossier. The justifications

provided by the applicant explain why several potential differences in the physico-chemical properties between the proposed gum and chewable tablet formulations will not impact product efficacy and safety to a clinically relevant extent.
Calcium carbonate is a well established and well known antacid that has been in clinical use for decades. The efficacy and safety profile of calcium carbonate is well established. Overall, calcium carbonate is well tolerated with few adverse side effects which are usually mild.

V. OVERALL CONCLUSIONS

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 750 mg Medicated Chewing-gum demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

23.06.2027