Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

UKPAR

Rennie 680 mg / 80 mg oral powder

(calcium carbonate, magnesium carbonate heavy)

UK Licence Number: PL 00010/0665

BAYER PLC.

LAY SUMMARY

Rennie 680 mg / 80 mg oral powder
(calcium carbonate, magnesium carbonate heavy)

This is a summary of the Public Assessment Report (PAR) for Rennie 680 mg / 80 mg oral powder (PL 00010/0665). It explains how Rennie 680 mg / 80 mg oral powder 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 Rennie 680 mg / 80 mg oral powder.

For practical information about using Rennie 680 mg / 80 mg oral powder, patients should read the package leaflet or contact their doctor or pharmacist.

What is Rennie 680 mg / 80 mg oral powder and what is it used for?
Rennie 680 mg / 80 mg oral powder is a medicine with 'well established use'. This means that the medicinal use of the active substances, of Rennie 680 mg / 80 mg oral powder, both individually and in combination are well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Rennie 680 mg / 80 mg oral powder quickly relieves heartburn, indigestion, dyspepsia, hyperacidity, nervous indigestion, flatulence, upset stomach, indigestion during pregnancy.

How does Rennie 680 mg / 80 mg oral powder work?
Rennie 680 mg / 80 mg oral powder contains the active substances calcium carbonate and magnesium carbonate heavy, which both reduce acidity by neutralising excess acid produced by the stomach.

How is Rennie 680 mg / 80 mg oral powder used?
The pharmaceutical form of this medicine is an oral powder and the route of administration is by mouth (oral).

Dose:
Adults and children over 12 years only
Preferably 1 hour after meals and before bedtime, 2 sachets should be taken orally by simply pouring the powder directly onto the tongue and swallowing. For heartburn, an extra 2 sachets may be taken between these times. Dosage should not exceed 10 sachets a day.

Not recommended in children under 12 years.

If symptoms persist after 14 days a pharmacist or doctor should be consulted. Prolonged use should be avoided.

If a patient has taken more Rennie oral powder than recommended:
The patient should drink plenty of water and consult their doctor or pharmacist. Symptoms of an overdose include nausea and vomiting, tiredness, constipation and muscular weakness.

If a patient has any further questions on the use of this medicine, they should ask their doctor or pharmacist.

The patient should always take this medicine exactly as the patient's doctor or pharmacist has told them and should check with their doctor or pharmacist if they are not sure.

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 can be obtained without a prescription.

What benefits of Rennie 680 mg / 80 mg oral powder have been shown in studies?
As calcium carbonate and magnesium carbonate heavy are well-known substances, and their combined use in the effective relief of the symptoms associated with excess acid in the stomach is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the combined use of calcium carbonate and magnesium carbonate heavy.

In addition, the Marketing Authorisation Holder (MAH) Bayer PLC, undertook a study to bridge their product to the information found in bibliographic sources to show that the combination of the active ingredients in a powder was comparable to administration of these active ingredients in a chewable tablet.

It was concluded from the study that Rennie 680 mg / 80 mg oral powder is therapeutically equivalent to another already approved similar medicinal product which contains the active substances calcium carbonate and magnesium carbonate heavy; Rennie Peppermint chewable tablet - Bayer PLC.

What are the possible side effects of Rennie 680 mg / 80 mg oral powder?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Rarely, allergic reactions to ingredients have been reported, e.g. rashes, itching, difficulty in breathing and swelling of the face, mouth or throat and anaphylactic shock (anaphylactic shock is a severe sudden allergic reaction, symptoms of which are low blood pressure, shock, palpitations, difficulty in breathing, bronchospasm, skin reactions, abdominal pain or cramps, vomiting and diarrhoea).

Long term use of high doses can cause high blood levels of calcium and magnesium, especially in people with kidney conditions. Symptoms of this may include nausea, vomiting, upset stomach, diarrhoea, tiredness, muscular weakness, headache, kidney problems and impaired sense of taste. In exceptional cases, long term use of high doses can lead to milk alkali syndrome, which can cause high blood levels of calcium.

For the full list of all side effects reported with Rennie 680 mg / 80 mg oral powder, see section 4 of the package leaflet available on the MHRA website.

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

Why is Rennie 680 mg / 80 mg oral powder approved?
The MHRA decided that the benefits of Rennie 680 mg / 80 mg oral powder are greater than its risks and recommended that it was approved for use.

What measures are being taken to ensure the safe and effective use of Rennie 680 mg / 80 mg oral powder?
A risk management plan (RMP) has been developed to ensure that Rennie 680 mg / 80 mg oral powder is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Rennie 680 mg / 80 mg oral powder 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 Rennie 680 mg / 80 mg oral powder
The Marketing Authorisation for Rennie 680 mg / 80 mg oral powder was granted on 5 September 2018.

The full PAR for Rennie 680 mg / 80 mg oral powder follows this summary.

For more information about treatment with Rennie 680 mg / 80 mg oral powder, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2018.

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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 the Marketing Authorisation Holder (MAH), Bayer PLC, a marketing authorisation for the medicinal product Rennie 680 mg / 80 mg oral powder (PL 00010/0665). This general sale list (GSL) medicine is for the symptomatic relief of acid-related gastro-intestinal symptoms such as indigestion, heartburn, nervous indigestion, hyperacidity, flatulence, upset stomach, dyspepsia, indigestion during pregnancy.

This application was submitted as an abridged national application according to Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing active substances of well-established use.

Rennie 680 mg / 80 mg oral powder is a medicine consisting of a combination of two active substances; calcium carbonate and magnesium carbonate heavy. Calcium and magnesium carbonates react with excess acid in the gastric medium to produce soluble chlorides. Calcium carbonate has a rapid and powerful neutralising action. This effect is increased by the addition of magnesium carbonate which also has a strong neutralising action.

Bibliographic data on calcium carbonate and magnesium carbonate heavy have been submitted to support this application. No new non-clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing active substances of well-established use.

In addition to the submission of published non-clinical and clinical references the MAH has also performed *in vitro* static and dynamic neutralising tests as a surrogate methodology to demonstrate therapeutic equivalence, in line with the draft CHMP guideline for the development of locally acting antacids products (CPMP/EWP/239/95 Rev. 1).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer/importer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No new or unexpected safety concerns arose during the review of information provided by the MAH and it was, therefore, judged that the benefits of taking Rennie 680 mg / 80 mg oral powder outweigh the risks and a Marketing Authorisation was granted on 5 September 2018.

II QUALITY ASPECTS

II.1 Introduction

Each sachet of oral powder contains 680 mg of calcium carbonate and 80 mg magnesium carbonate heavy. The other ingredients consist of xylitol, maltodextrin, cooling flavour (diethyl malonate, maltodextrin, menthol, menthyl lactate, modified starch E1450, iso-pulegol), mint flavour (maltodextrin, menthol, modified starch E1450), and saccharin sodium.

The finished product is packaged in polyester (PET) / aluminium / polyethylene (PE) foil sachets each containing 1250 mg of powder, placed in carboard cartons in pack sizes of 10 or 20 sachets.

Not all pack sizes may be marketed, however, the marketing authorisation holder has agreed to provide mock-ups of any pack size to the relevant regulatory authorities before marketing.

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

II.2 Drug Substances

1. Calcium carbonate

INN: Calcium carbonate
Chemical Name: Calcium carbonate
Molecular formula: CaCO3
Relative molecular mass: 100.1
Appearance: White or almost white, crystalline powder
Solubility: Practically insoluble in water.

Calcium carbonate is the subject of a European Pharmacopoeia monograph. All aspects of the manufacture and control of the active substance, calcium carbonate, are covered by an EDQM Certificate of Suitability.

2. Magnesium carbonate heavy

INN: Magnesium carbonate heavy
Chemical Name: Magnesium carbonate heavy
Molecular formula: $(MgCO_3)_4\ Mg(OH)_2,\ 5H_2O$
Relative molecular mass: 485
Appearance: White or almost white powder.
Solubility: Practically insoluble in water. It dissolves in dilute acids with effervescence.

Magnesium carbonate heavy is the subject of a European Pharmacopoeia monograph. All aspects of the manufacture and control of the active substance, magnesium carbonate heavy, are covered by an EDQM Certificate of Suitability.

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

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral powder with combined action of the active ingredients calcium carbonate and magnesium carbonate heavy.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective monographs. The cooling flavour and mint flavour comply with their in-house specifications and all other excipients comply with the European Pharmacopoeia monographs. Suitable batch analysis data have been provided for each excipient.

A dissolution profile of Rennie 680 mg / 80 mg oral powder has been supplied, showing the rapid dissolution of the product. The quantity of carbonates released/dissolved is directly related to the variation of pH.

None of the excipients used contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years for the unopened product, with the in-use storage condition 'store in the original package'.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacological, pharmacokinetic and toxicological properties of magnesium carbonate and calcium carbonate are well known. As these two active substances are well known, no further studies are required and the applicant has provided none. An overview based on a literature review is, thus, appropriate.

III.2 Pharmacology
No new data on pharmacology have been submitted and none are required for an application of this type.

III.3 Pharmacodynamics
No new data on pharmacodynamics have been submitted and none are required for an application of this type.

III.3.1 Pharmacokinetics
No new data on pharmacokinetics have been submitted and none are required for an application of this type.

III.4 Toxicology
The toxicological properties of magnesium carbonate and calcium carbonate are discussed in detail in the MAH's non-clinical overview. The summaries of these findings are presented below:

Impurities and Excipients
A discussion of impurities and excipients has been included in the non-clinical overview, and in addition the relevant sections of this application have also been reviewed.

Drug Substances

Calcium carbonate is manufactured in accordance with an EDQM Certificate of Suitability. Impurities in the drug substance and drug product are controlled as per the current version of the European Pharmacopoeia.

Magnesium carbonate is manufactured in accordance with an EDQM Certificate of Suitability. Impurities in the drug substance and drug product are controlled as per the current version of the European Pharmacopoeia.

Drug Product

All excipients in Rennie oral powder are substances with well-known toxicological profiles, are recognised as safe, and comply with the stipulations of the European Pharmacopoeia. Cooling flavour and mint flavour are also well known ingredients widely used in food and pharmaceutical products. These ingredients are suitably controlled according to in-house monographs. In conclusion, the concentrations of the excipients in the formulation under evaluation do not cause reason for concerns from a pharmacological-toxicological point of view.

The limits for residual solvents are acceptable and in line with ICH Q3C(R6). No impurities have been listed in the drug product specification.

Conclusion

The MAH provides a short discussion of impurities and excipients in the non-clinical overview. there are no toxicological concerns with impurities in the drug substances and drug product or use of excipients.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The applicant has provided suitable justification for not performing an environmental risk assessment in accordance with the guideline (CHMP/SWP/4447/00). The ERA refers to Rennie chewable tablet which contains 680 mg calcium carbonate and 80 mg magnesium carbonate heavy as active ingredients. These are the same concentrations as the proposed powder, Rennie oral powder. The ERA is acceptable.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

A discussion of impurity profiles in the drug substance and drug product has been included in the Non-Clinical Overview. Similarly, drug product excipients have been discussed in the non-clinical overview. Following additional review of the quality aspects of this application, there are no toxicological concerns with impurities in the drug substance or with impurities or excipients and drug product.

IV CLINICAL ASPECTS

IV.1 Introduction

Calcium carbonate and magnesium carbonate heavy are well-established active substances, with recognised efficacy and acceptable safety, and the active substances have been licenced and available as Rennie tablets, chewable tablets, and suspension products in the European Union for many years. The details of their pharmacology are documented in various publicly accessible sources and a comprehensive review of the published literature has been provided by the MAH, citing the well-established clinical pharmacology, efficacy and safety of calcium carbonate and magnesium carbonate heavy. The clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

A small amount of calcium and magnesium may be absorbed, but in healthy subjects is usually rapidly excreted by the kidneys.

The soluble chlorides produced by the reaction of calcium and magnesium with gastric acid react, in turn, with intestinal, biliary and pancreatic secretions to form insoluble salts, which are excreted in the faeces.

A bioequivalence study was not required or conducted.

IV.3 Pharmacodynamics

Calcium and magnesium carbonates react with excess acid in the gastric medium to produce soluble chlorides.

$CaCO_3 + 2HCl \Rightarrow CaCl_2 + H_2O + CO_2$
$MgCO_3 + 2HCl \Rightarrow MgCl_2 + H_2O + CO_2$

The mode of action of Calcium carbonate & magnesium carbonate is local, based on the neutralisation of gastric acid, and is not dependent on systemic absorption.

Calcium carbonate has a rapid 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 16 mEq H^+ (titration to endpoint pH 2.5).

The onset of neutralisation in healthy volunteers is rapid. In fasting subjects, the administration of two Rennie tablets, which contain the same amount of active ingredients as in two sachets of Rennie oral powder, produced an increase of more than one pH unit within 5 minutes and a significant increase in the pH of stomach contents above baseline pH was achieved within 2 minutes.

When determined using an artificial stomach model, the maximal theoretical antacid potency to return to pH 1.0 varies from 28 mmol H^+ to 41 mmol H^+ and 72 mmol H^+ for gastric emptying rates of 1.5 ml/min, 3 ml/min, and 4.5 ml/min, respectively, for one Rennie tablet.

IV.4 Clinical efficacy

The following supportive data have been submitted with the application:

Randomized clinical studies with either continuous pH monitoring by intragastric electrode (3 studies) or radio-telemetry (2 studies)

In total, five randomized clinical studies have been conducted with Rennie tablets (n=4) or the oral suspension (n=1) in comparison with other antacids and/or placebo; for details, please see Table 1.

Table 1 Randomised clinical studies

Randomized clinical studies

Study	Treatment	Type	pH	Antacid Effect	Rebound
Halter (8418)	Rennie 15 ml Maalox 15 ml Placebo 15 ml 4 doses	R, DB CO 12 Healthy subjects	24 h	4-60 min 4 periods	60-180 min 4 periods
Mignon (8419)	Rennie 2 tabs Talcid 2 tabs Placebo 2 tabs Single dose	R, DB+ CO 12 Subjects Pentagastrin	4 h	0-60 min	60-180 min
Ramdani (8420)	Rennie 1 tab Rennie 1 soft chew t Placebo 1 soft chew Single dose	R, DB++ CO 12 Healthy subjects	4 h	0-60 min	60-180 min
Lücker (8421)	Rennie 2 tabs Talcid 2 tabs Control Single dose	R, O CO+ 12 healthy subjects	19 h	-60-120 (0-60) min 4 periods	30-90 min (60-180) 4 periods
Martin (8422)	Rennie 2 tabs Aludrox 2 ct Milk Mag 2 tabs Milk Mag 2 tsp Setlers 2 tabs Alka-Seltzer 2 tabs Single dose	R, O CO 18 healthy subjects	HC ~4 h	+	-

HC: Heidelberg capsule; R: Randomized; DB: Double-blind; DB+: Double-blind Rennie vs placebo; DB++: Double-blind Rennie Gel soft chew tablet vs placebo; CO: Cross-over; CO+: Cross-over Rennie and Talcid; O: Open; Tab: Tablet; Tsp: teaspoon

Studies on the antacid effect with pH monitoring

The antacid effect was evaluated in 7trials:

- **tablets**: 4 trials in 54 healthy volunteers
- **soft chew tablets**: 1 trial in 12 healthy volunteers
- **oral suspension**: 2 trials in 12 healthy volunteers and 18 patients.

Table 2 Studies with the Heidelberg capsule

Study	Treatment	n	Peak pH	Onset of effect	Duration of effect
Martin (8422)	Rennie 2 tablets	18	6.1	2.7 min (pH ≥ 3.5)	38 min (pH 2 ≥ 3.5)
Monges (8423)	Rennie 10 ml	50	≥ 4.5 (all subjects)	30 s (pH ≥ basal pH)	75 min (pH ≥ basal pH)

Table 3 Overview of single dose studies; * significant vs placebo

Study	Treatment	Parameter (0 to 60 min)				
		peak pH	mean pH	Duration (min) onset	Duration (min) end	AUC
Mignon (8419)	Rennie 2 tabs	*4.25	2.02	5	60	*22.38
	Talcid 2 tabs	*2.94	1.61	10	60	*16.98
	Placebo	1.35	1.25			13.94
Ramdani (8420)	Rennie 1 tab	*5.96	2.64	1	60	31.38
	Rennie 1 soft chew tab	*5.51	2.39	1	35	28.68
	Placebo	3.74	1.99	-	-	23.89

Repeated doses studies

Table 4 Halter Study: Comparison of median pH and duration of effect after intake of Rennie, Maalox or placebo

	Median pH (0-60 min)	Median pH (24 h)	Duration of effect (min)
Rennie 15 ml	*3.7 (2.7 – 4.2)	*1.7 (1.5 -1.9)	79.7 ± 20.2
Maalox 15 ml	*2.9 (2.5 – 3_6)	*1.7 (1.6 - 1.9)	83.5 ± 20.8
Placebo 15 ml	2.3 (1.8 – 2.7)	1.6 (1.5 - 1.7)	-

* significant versus placebo

Table 5 Lücker study: Change in pH values (antacid period pH vs premeal pH)

	9-10 h	14-15 h	19-20 h	23-24 h	Combined
Rennie (R) 2 tablets	0.450 ± 0.855	1.967 ± 2.045	1.225 ± 1.473	0.000 ± 0.241	0.910 ± 0.721
Talcid (T) 2 tablets	0.142 ± 0.535	0.775 ± 1.980	1.075 ± 0.721	0,033 ± 0.347	0.490 ± 0.689
R versus T	NS	R > T (S)	NS	NS	R > T (S)

Studies with monitoring of disease symptoms

Table 6 Brion study: Comparison of symptoms at inclusion versus end of trial

Symptom	Severity	Zero (Absent)	Slight	Moderate	Severe	Statistical comparison* (before/after)
Oral acidity	Inclusion	13	13	5	1	S
	End of trial	25	5	1	1	
Acid reflux	Inclusion	9	7	11	5	S
	End of trial	22	9	1	0	
Belching	Inclusion	9	14	7	2	S
	End of trial	27	5	0	0	
Waterbrash	Inclusion	13	8	9	2	S
	End of trial	28	3	1	0	
Retrosternal pain	Inclusion	19	7	3	3	S
	End of trial	30	2	0	0	
Epigastric pain	Inclusion	1	9	19	3	S
	End of trial	24	7	1	0	
Feelings of fullness	Inclusion	10	12	9	1	S
	End of trial	24	7	1	0	
Early satiety	Inclusion	13	11	5	3	S
	End of trial	29	3	0	0	
Bloating	Inclusion	4	7	16	5	S
	End of trial	21	10	1	0	
Slow/difficult digestion	Inclusion	7	11	10	4	S
	End of trial	22	10	0	0	
Nausea	Inclusion	16	9	6	1	S
	End of trial	28	4	0	0	
Vomiting	Inclusion	28	4	0	0	S
	End of trial	32	0	0	0	
Post-prandial drowsiness	Inclusion	20	8	2	2	NS
	End of trial	26	5	1	0	

*Rank test S = Significant NS = Non-significant

IV.4.1 THERAPEUTIC EQUIVALENCE

Following the CHMP draft guideline for the development of locally acting antacids products (CPMP/EWP/239/95 Rev. 1) and in order to demonstrate the evidence of therapeutic equivalence between Rennie 680 mg / 80 mg oral powder and suitable reference product (for which a global Rennie Peppermint chewable tablet formulation was chosen), *in vitro* static (acid neutralisation capacity (ANC)) and dynamic neutralising tests were performed as a surrogate methodology for therapeutic equivalence demonstration.

Rennie 680 mg / 80 mg oral powder contains 680 mg Calcium carbonate (CaCO3) and 80 mg Heavy Magnesium carbonate (MgCO3) as active pharmaceutical ingredients (APIs). Rennie Peppermint (chewable tablet) also contains 680 mg calcium carbonate (CaCO3) and 80 mg heavy magnesium carbonate (MgCO3) as active substances. The ANC was chosen for the static part of the test and it was performed as per USP (each test repeated three times for better accuracy). The results are shown in the Table 7 below.

Table 7: Rennie 680 mg / 80 mg oral powder and Rennie peppermint, individual ANC test results and their corresponding mean values.

Replicate Number	Rennie Powder Lot number: BT11827 (mEq/stick)	Rennie Peppermint Lot number: L8R751 (mEq/tablet)
1	15.14	15.10
2	15.29	15.15
3	14.99	15.15
Mean	**15.14**	**15.13**

Very slight variability in the results was attributed to measurement error and not considered relevant. Both tests were performed in a standardised manner as per USP.

Based on the ANC test results it can be concluded that both products are equivalent in their acid neutralising capacity.

Dynamic neutralising test was also conducted in a standardised way using a validated pH meter. To verify the assumption of equality between the two products the mean pH values and their confidence intervals (CI) were calculated for each time point (see Figure 1 below). There were no differences between the two products as pH mean values and their corresponding CI were similar.

Based on the data available from the static ANC test as well as the dynamic pH measuring it can be confirmed that Rennie 680 mg / 80 mg oral powder and Rennie Peppermint chewable tablets are therapeutically equivalent.

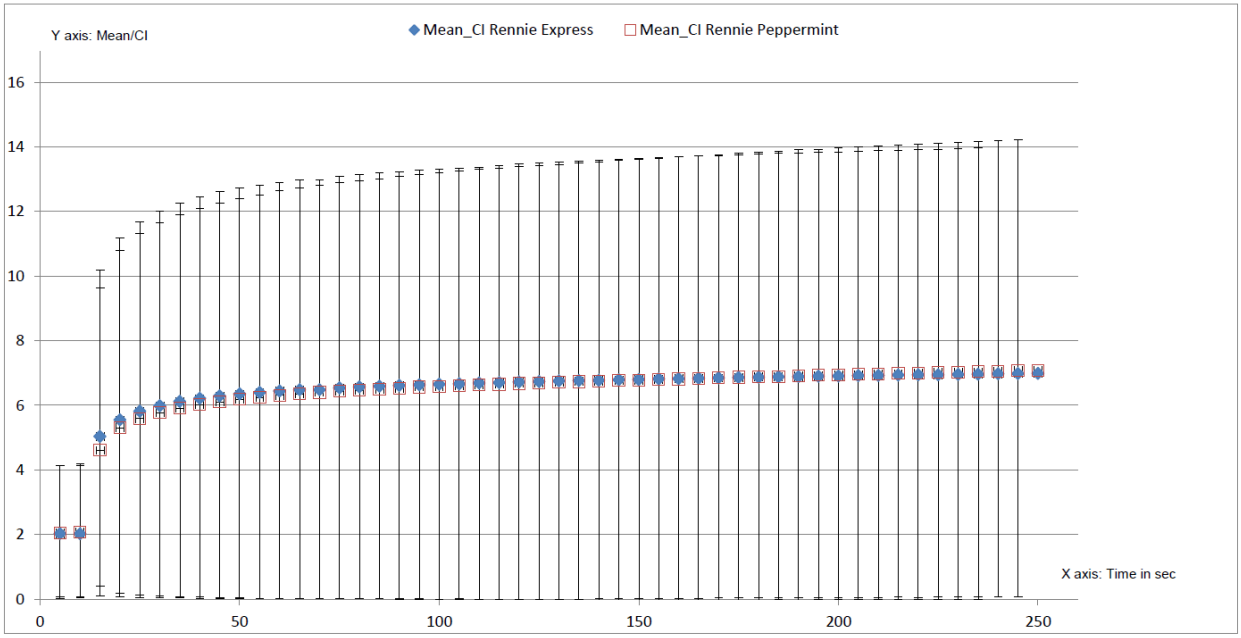

Figure 1: Mean pH values and their CIs (confidence intervals) for Rennie 680 mg / 80 mg oral powder and Rennie Peppermint, constructed from source data generated in dynamic acid neutralising test (some values do not have CIs because all measurements were equal and therefore no Standard Deviation (SD) could be calculated).

IV.4.2 OVERALL CONCLUSIONS ON CLINICAL EFFICACY

The applicant's overall summary of the use of the combination of calcium carbonate and magnesium carbonate heavy, in the proposed indications, is based on data obtained from the already available Rennietablets, chewable tablets and suspension products. The Applicant has satisfactorily met the requirement to provide *in vitro* static and dynamic tests as surrogate methodology for demonstration of therapeutic equivalence as required by the CHMP draft guideline for the development of locally acting antacid products (CPMP/EWP/239/95 Rev 1).

IV.5 Clinical safety

No new safety data were submitted, and none are required for this bibliographic application. The safety discussion is based on literature data and clinical studies conducted with the already approved tablets, chewable tablets, and oral suspension formulations. The sweeteners and flavours in Rennie oral powder have GRAS status (US FDA, Generally Regarded As Safe) and considered safe as used as sweeteners or in flavouring agents, respectively. The sweeteners are also authorised as per European Regulation EU 1333/2008 and both flavours are compliant with food regulation (EC) 1334/2008 and therefore, the flavourings and sweeteners are all approved for use in food products. The inference is made that potential adverse events of Rennie 680mg/80 mg oral powder would be related to the active ingredients (calcium carbonate and magnesium carbonate heavy) and would be similar to the marketed products, therefore, no specific data on the powder formulation is provided. The clinical safety properties of the single active and combination of the actives are discussed in detail in the MAH's non-clinical overview.

Local tolerability

Rennie 680 mg / 80 mg oral powder is not likely to lead to local tolerability issues. Calcidol tablets containing similar active ingredients to Rennie 680 mg / 80 mg oral powder were not irritating in an oral mucous irritation test. The sweeteners and flavouring agents present in Rennie 680 mg / 80 mg oral powder are approved for use and present at similar levels in food products. The active ingredients in Rennie 680 mg / 80 mg oral powder are identical to those found in Rennie products which have been marketed in Europe for over 30 years. The Rennie products are also currently registered in more than 70 countries worldwide. Rennie 680 mg / 80 mg oral powder behaves like an oral product and its residence time in the buccal cavity is similar or less than other Rennie products, such as tablets to be sucked or chewed.

POST MARKETING EXPERIENCE
Post-marketing observations of the marketed Rennie formulations have not found any additional adverse effects which are not already indicated in section 4.8 of the proposed SmPC of Rennie 680 mg / 80 mg oral powder.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC, as amended.

There are no differences from the reference product in terms of proposed uses, maximum pack size / strength or pharmaceutical form / formulation that would have any implications for safety. Only routine pharmacovigilance and routine risk minimisation measures for all safety concerns (labelling in the SmPC and the patient information leaflet (PIL)) will be performed.

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 Competent Authority
- 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 Periodic Safety Update Report and the update of an RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application from a clinical viewpoint.

V User consultation

A user consultation with target patient groups on the PIL has been performed on the basis of a bridging report making reference to Rennie Sugar Free, PL 00010/0362. The bridging report submitted by the applicant is acceptable.

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 calcium carbonate and magnesium carbonate heavy is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for this medicine, no label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Rennie
680mg / 80mg oral powder

Calcium Carbonate
Magnesium Carbonate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bayer Cross

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

To be taken orally without water

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rennie
680mg / 80mg oral powder
Calcium Carbonate,
Magnesium Carbonate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains: Calcium Carbonate 680mg, Heavy Magnesium Carbonate 80mg.

3. LIST OF EXCIPIENTS

Mint flavour
Sugar free

4. PHARMACEUTICAL FORM AND CONTENTS

10 sachets
20 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Prolonged use should be avoided.
If symptoms persist after 14 days consult your pharmacist or doctor.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package. Do not keep an opened sachet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PL Holder: Bayer plc, Consumer Care Division, Newbury, Berkshire, RG14 1JA, UK.
consumerhealthuk@bayer.com

Rennie® is a registered trademark.

12. MARKETING AUTHORISATION NUMBER(S)

PL 00010/0665

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Fast effective relief from heartburn and indigestion

Rennie oral powder is a mint flavoured antacid powder which quickly relieves heartburn, indigestion, acid indigestion, dyspepsia, hyperacidity, nervous indigestion, upset stomach, indigestion during pregnancy.

Dosage: Adults and children over 12 years: Take 2 sachets orally. Simply pour powder directly onto the tongue, preferably 1 hour after meals and before bedtime. These doses may also be sued during pregnancy and breast-feeding. Do not take more than 10 sachets per day.
Children under 12: Not recommended.

16. INFORMATION IN BRAILLE

RENNIE ORAL POWDER

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)