

Public Assessment Report

Gaviscon Liquid Sachets

**Sodium Alginate
Sodium Bicarbonate
Calcium Carbonate**

PL 00063/0159

Reckitt Benckiser Healthcare (UK) Ltd

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Lay Summary

Based on a review of the data of the quality, safety and efficacy, the UK granted Reckitt Benckiser Healthcare (UK) Ltd marketing authorisations (licenses) for the medicinal product Gaviscon Liquid Sachets (PL 00063/0159) on 12th November 2007. This product does not require a prescription and is for the treatment of gastrooesophageal reflux, acid reflux, heartburn and reflux oesophagitis.

The product contains the active ingredients sodium alginate, sodium bicarbonate and calcium carbonate. Gaviscon Liquid Sachets are indicated in the treatment of gastrooesophageal reflux, acid reflux, heartburn and reflux oesophagitis. On ingestion the medicinal product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-oesophageal reflux.

Scientific Discussion

INTRODUCTION

Based on a review of the data of the quality, safety and efficacy, the UK granted Reckitt Benckiser Healthcare (UK) Ltd marketing authorisations for the medicinal product Gaviscon Liquid Sachets (PL 00063/0159) on 12th November 2007. This medicine is on the General Sale List and does not require a prescription.

This application was submitted as a bibliographic application under Article 10a of EC Directive 2001/83/EC as amended. The cross-reference product is Gaviscon Peppermint Tablets (PL 00063/0134). The application is a line extension to change excipients and pharmaceutical form.

The product contains the active ingredients sodium alginate, sodium bicarbonate and calcium carbonate. Gaviscon Liquid Sachets are indicated in the treatment of gastrooesophageal reflux, acid reflux, heartburn and reflux oesophagitis. On ingestion the medicinal product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-oesophageal reflux.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. 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 the patients/users are able to act upon the information that it contains.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCES

1. Sodium Alginate

An appropriate specification based on the European Pharmacopoeia has been provided. Consideration has been given to the potential impurities arising from the natural origins of sodium alginate. Sodium alginate is a sodium salt of alginic acid obtained from the brown seaweed *Laminaria hyperborea*) and the extraction and blending process involved in its production. Appropriate control measures and specification requirements have been put in place.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Sodium alginate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

2. Sodium Bicarbonate

Sodium bicarbonate is the subject of a Ph Eur Monograph.

Sodium bicarbonate is adequately controlled by the Ph Eur monograph. No additional controls on solid state properties are considered necessary since sodium bicarbonate is readily soluble.

Representative Certificates of Analysis have been provided for three batches of sodium bicarbonate confirming compliance with the proposed specification.

3. Calcium carbonate

Calcium carbonate is the subject of a Ph Eur Monograph, and a current Certificate of Suitability was provided.

A satisfactory specification for calcium carbonate has been provided. The drug substance complies with the requirements of the Ph Eur monograph, in addition the specification includes additional tests for bulk density, soluble alkali and particle size. These specifications are the same as other licensed Gaviscon preparations (e.g. PL 00063/0140).

Representative Certificates of Analysis have been provided for three batches of calcium carbonate confirming compliance with the proposed specification.

Drug Substances Stability

Stability studies on calcium carbonate and sodium bicarbonate have not been performed since they are simple inorganic salts with long-established use as a pharmaceutical ingredient, defined by pharmacopoeial standards and the stability profile of these salts is well established.

Stability studies on sodium alginate have not been performed since it is a well established pharmaceutical ingredient with long established use and its stability profile well recognised.

The absence of stability data is acceptable considering the nature of the drug substances.

DRUG PRODUCT**Other ingredients**

Gaviscon Liquid Sachets contain the other ingredients listed below

Carbomer
Sodium hydroxide
Sodium saccharin
Natural mint flavour
Methyl p-hydroxybenzoate
Propyl p-hydroxybenzoate
Purified water

All excipients used comply with their respective European Pharmacopoeial monographs. Natural mint flavour LE2008WA is satisfactorily controlled by in-house specifications and a statement from the supplier of the natural mint flavour stating that it conforms to the requirements of EC Directive 2002/72/EC relating to flavourings in foodstuffs has been provided. A representative certificate of analysis has been provided for the mint flavouring. No excipients of human/animal origin are used.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Liquid stick packs (sachets) of heat sealable laminate: polyester/aluminium foil/polyethylene/ polyester/ polyethylene. The packaging components comply with Directive 90/128/EEC with respect to their suitability for contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Do not refrigerate or refreeze” and “Do not store above 25°C”.

Conclusion

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

PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided for this application and none were required.

MEDICAL ASSESSMENT

INTRODUCTION

These peppermint flavoured sachets contain:

Sodium alginate 500mg / 10ml
Sodium bicarbonate 267mg / 10ml
Calcium carbonate 160mg / 10ml;

and are intended for the treatment of symptoms of gastro-oesophageal reflux following meals or, in particular, during pregnancy. The mode of action is physical and does not depend on absorption.

INDICATIONS

These are the treatment of symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion, for example, following meals or during pregnancy.

TOXICOLOGY

No new data are presented and none are required for this application. The active ingredients and the excipients are all well known and have been widely used.

CLINICAL PHARMACOLOGY

On ingestion, the liquid reacts rapidly with gastric acid to form a raft of alginic acid gel which has a pH very close to neutral. This floats on the stomach contents, thus impeding gastro-oesophageal reflux. In severe cases of reflux, the raft itself may enter the oesophagus, having a demulcent effect.

The mode of action of Gaviscon Liquid Sachets is physical and does not depend on absorption into the systemic circulation.

The mode of action of Gaviscon products is to impede reflux by the formation of an alginate raft which floats on the surface of the stomach contents. The other ingredient vital for formation of the raft is sodium bicarbonate, which acts as a source of carbon dioxide to provide buoyancy. Calcium carbonate provides a source of calcium ions which cross-link the alginate molecules and increase the raft strength. In addition, calcium carbonate and sodium bicarbonate have a neutralising effect on gastric acid.

Alginate preparations do not possess any pharmacology in the true sense since their mode of action in prevention of reflux is physical. Depending on the formulation, a gel is formed either by the rehydration of alginic acid or by reaction of an alginate salt with gastric acid to form alginic acid. This gel floats on top of the stomach contents by virtue of its reduced density, having entrapped carbon dioxide formed by reaction of a carbon dioxide source with gastric acid. Formation of such floating rafts has been demonstrated by X-ray, endoscopic and gamma scintigraphy studies. The raft prevents reflux because of its strength and cohesiveness, and may also be refluxed preferentially into the oesophagus where, by virtue of its neutral pH, it protects the oesophageal mucosa from corrosive attack. Calcium salts are included in some products to increase raft strength by formation of calcium ion cross-linkages between the alginate chains.

PHARMACODYNAMICS

The fundamental feature of all Gaviscon products is the formation of an alginate raft of nearly neutral pH which floats on the stomach contents. This either physically impedes reflux, or, in severe cases, is itself refluxed into the oesophagus where it acts as a demulcent. The raft is formed by the reaction of sodium alginate with gastric acid to form an alginic acid gel, which floats on the top of the stomach contents because of entrapped carbon dioxide formed by the reaction of bicarbonate with gastric acid. Calcium ions present increase the raft strength by forming cross-linkages between the alginate chains.

Raft Formation

A randomised, open three-way crossover study was performed to investigate the formation and retention of the alginate rafts assessed by gamma scintigraphy monitoring in healthy volunteers (males, aged 18-45 years) following administration of single doses of the two strengths of Gaviscon liquid (500mg sodium alginate)

An established gamma scintigraphic technique was used. Data was collected at 15 minute intervals over 4 hours and used to derive parameters relating to gastric emptying, etc.

The primary efficacy parameter was the gastric retention of the study drug in the whole stomach, which was compared between study drugs using analysis of variance of log-transformed data. Non-inferior gastric retention for the test liquid in comparison to Liquid Gaviscon was to be demonstrated by ln-transformed 95% Confidence Interval (CI) entirely above the non-inferiority limit of 0.8.

An open label design was employed since different dose volumes were to be compared. It was not considered that this would adversely affect the outcome of studies since the criteria for evaluation of raft formation were assessed objectively and could not be biased by either investigator or subject. Although crossover effects were considered unlikely, a washout period of three to seven days was allowed between study drugs to avoid potential carryover effects and randomisation was used to minimise the potential for confounding treatment and period effects.

Results

Gastric residence of both study drugs was significantly greater than that of the corresponding test meal in the upper (but not the whole) stomach and significantly greater proportions of both study drugs resided in the upper stomach. The times to half-emptying of both study drugs from the stomach were greater than for the corresponding test meals. These results clearly indicate that both Liquid Gaviscon and Gaviscon Advance formed effective alginate rafts which floated on top of the stomach contents and emptied after the test meal.

The gastric retention of the test liquid was not significantly different from that of Liquid Gaviscon and the 95% CI was, at 0.85-1.25, entirely above the pre-defined non-inferiority limit of 0.80. From the results, it is reasonable to conclude that the test liquid had non-inferior gastric retention to Gaviscon Liquid at doses containing 500mg sodium alginate.

PHARMACOKINETICS

Since the mode of action of these tablets is physical and not dependant on absorption into the systemic circulation, pharmacokinetic bioequivalence studies are not appropriate to indicate clinical equivalence.

FFICACY

Four studies have been performed to evaluate the efficacy of Gaviscon Advance. Details are provided in the company's Clinical Summary (Module 2, Section 7.3, pp5 and 11-15 and Section 7.6) all four were conducted in accordance with European requirements for the GCP and the Declaration of Helsinki.

Two Studies compared the efficacy of Gaviscon Advance with placebo; one used a 5ml dose taken q.i.d. over two periods (Study Reference 0104601) and the second used in a 10ml dose taken q.i.d. over four weeks (Study Reference 0100901). Both studies were doubled-blinded, parallel-group comparisons. The third study was a single-blinded, parallel-group study comparing Liquid Gaviscon 20ml q.i.d. and Gaviscon Advance 10ml q.i.d. (Study Reference 0104601) which has already been discussed. The final open study (Study Reference 0103402) looked at 5-10ml doses of Gaviscon Advance taken as required by pregnant patients for an initial period of four weeks.

In total, 742 patients participated in the four studies. Of the 495 who were treated with Gaviscon Advance, 192 received 5ml doses and 196 received 10ml doses according to a q.i.d. regimen. A further 192 patients took 5-10ml doses on an as needed basis. The patient populations studied covered the common symptoms of GOR and Study 0103402 specifically evaluated efficacy in patients experiencing heartburn during pregnancy. The ages of the participating patients ranged from 18-85 years

The primary assessment criterion for all four studies was the investigators' overall assessment of efficacy. This assessment was made on a scale of very good, good, acceptable, poor or very poor after talking to the patients and reviewing patient diaries kept throughout the study. It is claimed that, although subjective, this method of measuring efficacy is frequently used in clinical studies of Gaviscon products and is appropriate given the nature of the condition which is generally diagnosed and managed on the basis of symptoms.

As discussed previously, study 0100902 showed Liquid Gaviscon (20ml q.i.d.) and Gaviscon Advance (10ml q.i.d.) to have equivalent efficacy as assessed by both investigators' and patients' overall impressions.

Overall, as the clinical expert states, the efficacy of both 10ml and 20ml doses of Liquid Gaviscon has been demonstrated in the relief of symptoms of gastro-oesophageal reflux (GOR). 10ml of Gaviscon Advance has been shown to have equivalent raft-forming capabilities as 20ml liquid Gaviscon. It has been shown that 5ml and 10ml doses of Gaviscon Advance taken q.i.d. are superior to placebo in the treatment of symptoms reflux. The same can be expected to be true for 10ml and 20ml doses of Liquid Gaviscon. Also 5-10ml doses of Gaviscon Advance taken as required up to a maximum of 40ml per day have been shown to relieve heartburn and regurgitation during pregnancy. The same level of efficacy would be expected for 10-

20ml doses of Liquid Gaviscon taken on the same basis, this being the active ingredient in Gaviscon Liquid Sachets.

SAFETY

In the study outlined above, there were only two mild adverse events which were considered to be unrelated to the study medication. In the previous studies for Gaviscon Advance, Gaviscon Peppermint Tablets and Liquid Gaviscon, the numbers of events considered to be possibly or probably related to treatment were low and of mild, or at most moderate, severity. Post-Marketing experience has produced a very low incidence of adverse events. Liquid Gaviscon has been widely used during pregnancy and lactation for the past 25+ years.

EXPERT REPORTS

There is a satisfactory clinical expert report.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is satisfactory.

PATIENT INFORMATION AND LABEL, COMBINED

This is satisfactory.

CONCLUSION

A Marketing Authorisation may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Gaviscon Liquid Sachets 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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

The report from the clinical expert supported the granting of a marketing authorisation.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 13 th December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 6 th January 2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 8 th February 2006, 18 th July 2007 and 5 th October 2007 and on the medical assessment on 10 th May 2005.
4	The applicant provided further information in regard to the quality assessment on 17 th May 2007, 16 th September 2007 and 16 th October 2007 and on the medical assessment on 1 st August 2005.
5	The application was determined on 12 th November 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gaviscon Liquid Sachets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gaviscon contains 500 mg sodium alginate, 267 mg sodium bicarbonate and 160 mg calcium carbonate per 10 ml dose.

Excipients: methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension in sachets.

An off-white suspension with the odour and flavour of peppermint.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion related to reflux, for example, following meals, or during pregnancy, or in patients with symptoms related to reflux oesophagitis.

4.2 Posology and method of administration

For oral administration.

Adults and children 12 years and over: One to two sachets after meals and at bedtime.

Children under 12 years: Should be given only on medical advice.

Elderly: No dose modifications necessary for this age group.

4.3 Contraindications

Hypersensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

Sodium content of a 10 ml, one sachet dose is 141 mg (6.2 mmol). This should be taken into account when a highly restricted salt diet is required, e.g. in some cases of congestive cardiac failure and renal impairment.

Each 10 ml, one sachet dose contains 160 mg (1.6 mmol) of calcium carbonate. Care needs to be taken in treating patients with hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi.

There is a possibility of reduced efficacy in patients with very low levels of gastric acid.

If symptoms do not improve after seven days, the clinical situation should be reviewed.

Treatment of children younger than 12 years of age is not generally recommended, except on medical advice.

Contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216) which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Open controlled studies in 281 pregnant women did not demonstrate any significant adverse effects of Gaviscon on the course of pregnancy or on the health of the foetus/new-born child. Based on this and previous experience, the medicinal product may be used during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Very rarely ($\leq 1/10,000$) patients may develop allergic manifestations such as urticaria or bronchospasm, anaphylactic or anaphylactoid reactions.

4.9 Overdose

In the event of overdosage, symptomatic treatment should be given. The patient may notice abdominal distension.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: A02BX. Other drugs for peptic ulcer and gastro-oesophageal reflux disease.

On ingestion the medicinal product reacts rapidly with gastric acid to form a raft of alginic acid gel having a near neutral pH and which floats on the stomach contents effectively impeding gastro-oesophageal reflux. In severe cases the raft itself may be refluxed into the oesophagus, in preference to the stomach contents, and exert a demulcent effect.

5.2 Pharmacokinetic properties

The mode of action of the medicinal product is physical and does not depend on absorption into the systemic circulation.

5.3 Preclinical safety data

There is limited evidence in some reports in animals of delay in calcification of foetal skeleton/bone abnormalities relating to calcium carbonate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer 974P
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Saccharin sodium
Natural mint flavour
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 25°C and store in the original package. Do not freeze or refrigerate.

6.5 Nature and contents of container

A cardboard outer carton containing unit dose stick pack style sachets.
Pack sizes: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 and 36.
Not all pack sizes may be marketed.
The sachets are composed of polyester, aluminium and polyethylene.
Each sachet contains 10 ml of Gaviscon.

6.6 Special precautions for disposal

No special requirement.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Healthcare (UK) Limited,
Dansom Lane,
Hull,
HU8 7DS.
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00063/0159.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/11/2007

10 DATE OF REVISION OF THE TEXT

12/11/2007

Leaflet and Label (Combined)

3
?TON

3E
7D

3 EASY STEPS
TEAR SQUEEZE TAKE

Gaviscon Liquid Sachets bring fast, soothing and long lasting relief from the pain and discomfort of heartburn and acid indigestion which, for example, can occur after meals or during pregnancy. They belong to a group of medicines called 'reflux suppressants', which form a protective layer on top of the stomach contents to prevent stomach acid escaping from the stomach where it works into the food pipe where it hurts.

What's in this sachet? Each sachet (10ml) of oral suspension contains 500 mg sodium alginate, 267 mg sodium bicarbonate and 160 mg calcium carbonate as the active ingredients. It also contains carbomer, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E219), sodium saccharin, sodium hydroxide, natural mint flavour and purified water. The product is sugar-free and colour-free. You can take the product if you are pregnant or breastfeeding.

Warnings: Read the instructions. Adults, including the elderly and children 12 years and over: One to two 10 ml sachets after meals and at bedtime as directed.

Before taking this product: Each sachet (10ml) of oral suspension contains 6.3 mmol of sodium and 1.6 mmol of calcium. If you have been advised a diet restricted in either of these please consult your doctor before taking this product. This product contains methyl (E218) and propyl (E219) parahydroxybenzoates which may cause allergic reactions (possibly delayed). Do not take if you know you are allergic to any of the ingredients or skin rash or oral difficulty in mouth if they have been reported. Consult your doctor if you experience these or any other side effects.

After taking this product: If you forget to dose it is not necessary to double the dose next time, just carry on taking as before. If symptoms persist after seven days consult your doctor. If you take too much of the medicinal product you may feel bloated. It is unlikely to cause you any harm, but please consult your doctor or pharmacist.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not store above 25 °C and store in the original packaging. Do not freeze or refreeze.

GAVISCON LIQUID SACHETS

NEW SACHETS 12

GAVISCON LIQUID SACHETS

Oral Suspension
Sodium alginate
Sodium bicarbonate
Calcium carbonate

Mint Flavour

Fast soothing relief

- Heartburn & Indigestion
- Long lasting

12 x 10ml

UNPRINTED & UNVARNISHED AREA

Do not use this medicine after the expiry date shown. BN EXP

Manufacturer and Product Licence Holder in UK:
Reckitt Benckiser Healthcare (UK) Limited, H41, W11 70S,
Eggar Road, Basingstoke, Hants & Colman (Overseas) Ltd, H41, U.K.,
PL 00063/0159

Gavisconed enters facts
Date of preparation 04/2009.