Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Gaviscon Instants Oral Powder Cool Mint
Gaviscon Instants Oral Powder Fresh Tropical

PL 00063/0173
PL 00063/0367

UK/H/942/001/DC
UK/H/943/001/DC

Reckitt Benckiser Healthcare (UK) Limited

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Reckitt Benckiser Healthcare (UK) Limited Marketing Authorisations (licences) for the medicinal products Gaviscon Instants Oral Powder Fresh Mint and Gaviscon Instants Oral Powder Fresh Tropical (Product Licence numbers: 00063/0173 and 00063/0367).

Gaviscon Instants Oral Powder contains the active ingredients sodium alginate, sodium hydrogen carbonate and calcium carbonate and belongs to a group of medicines called reflux suppressants. These form a protective layer on the top of the stomach contents to prevent stomach acid escaping into the food pipe, where it causes pain.

The data submitted in support of the applications for Gaviscon Instants Oral Powder raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Gaviscon Instants Oral Powder Cool Mint Gaviscon Instants Oral Powder Fresh Tropical
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10a Level 4 Chemical substance Level 5 GSL
Name of the active substance (INN)	Sodium alginate. Sodium hydrogen carbonate. Calcium carbonate
Pharmacotherapeutic classification (ATC code)	Other drugs for peptic ulcer and gastro-oesophageal reflux disease (A02BX13)
Pharmaceutical form and strength	Instant Oral Powder, 500 mg (sodium alginate), 267 mg (sodium hydrogen carbonate), 160 mg (calcium carbonate)
Reference numbers for the Mutual Recognition Procedure	UK/H/942/01/DC UK/H/943/01/DC
Reference Member State	United Kingdom
Member States concerned	BE, FR, IE, LU, NL
Date of start of the procedure	02 August 2006
End date of decentralised procedure	17 May 2007
Marketing Authorisation Number	PL 00063/0173 PL 00063/0367
Name and address of the authorisation holder	Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull HU8 7DS, United Kingdom

Module 2

Summaries of Product Characteristics

PL 00063/0173:

1 NAME OF THE MEDICINAL PRODUCT

Gaviscon Instants Oral Powder.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains sodium alginate 500 mg, sodium hydrogen carbonate 267 mg and calcium carbonate 160 mg.

Excipients: Aspartame E951.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral powder in sachet.

Cream coloured powder.

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

Oral administration.

Adults and children 12 years and over: One to two single dose containers after meals and at bedtime. The product is taken orally without water.

Elderly: No dose modifications necessary for this age group.

Hepatic Impairment: No modifications necessary.
Renal Insufficiency: Caution if highly restricted salt diet is necessary.
No data available for children under 12.

4.3 Contraindications

This medicinal product is contraindicated in patients with known or suspected hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

The sodium content of a single dose container is 123 mg (5.3 mmol). This should be taken into account when a highly restricted salt diet is recommended, e.g. in some cases of congestive cardiac failure and renal impairment.

Each single dose container 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.

Due to its aspartame content this medicinal product should not be given to patients with phenylketonuria.

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.

Consult your doctor if you are over 40 years and have never suffered with heartburn and acid indigestion before.

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. Nevertheless, taking into account the presence of calcium carbonate, it is recommended to limit the treatment duration as much as possible.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) ATC code: A02BX.

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

5.3 Preclinical safety data

No pre-clinical findings of any relevance to the prescriber have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Peppermint flavour
Macrogol 20,000
Macrogol 400
Aspartame (E951)
Citric acid anhydrous
Acesulfame potassium (E950)
Xylitol
Silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Eighteen months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pack sizes of 16, 20, 24 or 32 unit dose sachets. The sachets are composed of printed polyester/polyethylene/ aluminium foil/polyethylene.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 00063/0173

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/10/2007

10 DATE OF REVISION OF THE TEXT

10/10/2007

PL 00063/0367:

1 NAME OF THE MEDICINAL PRODUCT

Gaviscon Instants Oral Powder Fresh Tropical.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains sodium alginate 500 mg, sodium hydrogen carbonate 267 mg and calcium carbonate 160 mg.

Excipients: Aspartame E951.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral powder in sachet.

Cream coloured powder.

4 CLINICAL PARTICULARS

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Elderly: No dose modifications necessary for this age group.

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Renal Insufficiency: Caution if highly restricted salt diet is necessary.
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5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

No pre-clinical findings of any relevance to the prescriber have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mint flavour
Passion fruit flavour
Macrogol 20,000
Macrogol 400
Aspartame (E951)
Citric acid anhydrous granular
Acesulfame potassium (E950)
Xylitol
Silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Eighteen months.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
Pack sizes of 16, 20, 24 or 32 unit dose sachets. The sachets are composed of printed polyester/polyethylene/ aluminium foil/polyethylene.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling
No special requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL00063/0367

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
11/10/2007

10 DATE OF REVISION OF THE TEXT
11/10/2007

Module 3

Product Information Leaflet

These products have combined label-leaflets, see Module 4 for further information.

Module 4

Labelling

GAVISCON INSTANTS
ORAL POWDER
Cool Mint Flavour
16
Gaviscon Instants Oral Powder 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 is this product? Each single dose container of oral powder contains 500mg sodium alginate, 267mg sodium hydrogen carbonate and 160mg calcium carbonate as the active ingredients. It also contains macrogol 20,000, macrogol 400, peppermint flavour, aspartame (E951), citric acid anhydrous granular, acesulfame potassium, xylitol and silicon dioxide.
The product is sugar and gluten free. You can take this product if you are pregnant or breast-feeding. As with all medicines, the treatment duration should be limited as much as possible.
Dosage: For oral administration. Adults, including the elderly and children 12 years and over: One to two single dose containers after meals and at bedtime. Pour the contents of one single dose container directly onto the tongue.
Before taking this product: Each single dose container of oral powder contains 5.3 mmol of sodium and 1.6 mmol of calcium. If you have been advised to follow a diet restricted in any of these then please consult your doctor before taking this product. This product contains aspartame (E951) which contains a source of phenylalanine. This may be harmful for people with phenylketonuria. This treatment may be less effective if you have decreased amounts of gastric acid produced in your stomach. Consult your doctor if you are over 40 years and have never suffered with heartburn and indigestion before. If you forget a dose it is not necessary to double the dose next time, just carry on taking as before.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
After taking this product: If symptoms persist after 7 days consult your doctor. If you take too many single dose containers you may feel bloated. It is unlikely to cause you any harm, but please consult your doctor or pharmacist. Do not take if you know you are allergic to any of the ingredients as skin rashes and difficulty in breathing have been reported. Consult your doctor if you experience these or any other side-effects.
Do not store above 25°C. Store in the original package.
Fast Soothing Relief
Quick & Easy
Dissolves on Tongue
Heartburn & Indigestion
Manufacturer and Product Licence Holder in UK: Reckitt Benckiser Healthcare (UK) Limited, Hull, HU8 7DS.
Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, U.K.
PL 00063/0173
Gaviscon and are trademarks
BN
EXP
Do not use after expiry date shown. Date of preparation 03/2007.
RB001395

GAVISCON INSTANTS
ORAL POWDER
Cool Mint Flavour
Gaviscon Instants Oral Powder 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 is this product? Each single dose container of oral powder contains 500mg sodium alginate, 267mg sodium hydrogen carbonate and 160mg calcium carbonate as the active ingredients. It also contains maltrogol 20,000, maltrogol 400, peppermint flavour, aspartame (E951), citric acid anhydrous granular, acesulfame potassium, xylitol and silicon dioxide.
The product is sugar and gluten free. You can take this product if you are pregnant or breast-feeding. As with all medicines, the treatment duration should be limited as much as possible.
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GAVISCON INSTANTS
ORAL POWDER
Cool Mint Flavour
Fast Soothing Relief
Quick & Easy
Dissolves on Tongue
Heartburn & Indigestion
Manufacturer and Product Licence Holder in UK: Reckitt Benckiser Healthcare (UK) Limited, Hull, HU8 7DS.
Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, U.K.
PL 00063/0173
Gaviscon and are trademarks
BN
EXP
Do not use after expiry date shown. Date of preparation 03/2007.
HB001395

GAVISCON INSTANTS
ORAL POWDER
Fresh Tropical Flavour
Gaviscon Instants Oral Powder 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 is this product? Each single dose container of oral powder contains 500mg sodium alginate, 267mg sodium hydrogen carbonate and 160mg calcium carbonate as the active ingredients. It also contains xylitol, citric acid anhydrous granular, macrogol 20,000, aspartame (E951), acesulfame potassium, macrogol 400, silicon dioxide, passion fruit flavour and mint flavour.
The product is sugar and gluten free. You can take this product if you are pregnant or breast-feeding. As with all medicines, the treatment duration should be limited as much as possible.
Dosage: For oral administeration. Adults, including the elderly and children 12 years and over: One to two single dose containers after meals and at bedtime. Pour the contents of one single dose container directly onto the tongue.
Before taking this product: Each single dose container of oral powder contains 5.3 mmol of sodium and 1.6 mmol of calcium. If you have been advised to follow a diet restricted in any of these then please consult your doctor before taking this product. This product contains aspartame (E951) which contains a source of phenylalanine. This may be harmful for people with phenylketonuria. This treatment may be less effective if you have decreased amounts of gastric acid produced in your stomach. Consult your doctor if you are over 40 years and have never suffered with heartburn and indigestion before. If you forget a dose it is not necessary to double the dose next time, just carry on taking as before.
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Fresh Tropical Flavour
Fast Soothing Relief
Quick & Easy
Dissolves on Tongue
Heartburn & Indigestion
BN
EXP
Do not use after expiry date shown. Date of preparation 03/2007.
Manufacturer and Product Licence Holder in UK: Reckitt Benckiser Healthcare (UK) Limited, Hull, HU8 7DS.
Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, U.K.
PL 00063/0367
Gaviscon and ® are trademarks
RB001396

GAVISCON INSTANTS
ORAL POWDER
Fresh Tropical Flavour
Gaviscon Instants Oral Powder 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 is this product? Each single dose container of oral powder contains 500mg sodium alginate, 267mg sodium hydrogen carbonate and 160mg calcium carbonate as the active ingredients. It also contains xylitol, citric acid anhydrous granular, macrogol 20,000, aspartame (E951), acesulfame potassium, macrogol 400, silicon dioxide, passion fruit flavour and mint flavour.
The product is sugar and gluten free. You can take this product if you are pregnant or breast-feeding. As with all medicines, the treatment duration should be limited as much as possible.
Dosage. For oral administration. Adults, including the elderly and children 12 years and over: One to two single dose containers after meals and at bedtime. Pour the contents of one single dose container directly onto the tongue.
Before taking this product: Each single dose container of oral powder contains 5.3 mmol of sodium and 1.6 mmol of calcium. If you have been advised to follow a diet restricted in any of these then please consult your doctor before taking this product.
This product contains aspartame (E951) which contains a source of phenylalanine. This may be harmful for people with phenylketonuria. This treatment may be less effective if you have decreased amounts of gastric acid produced in your stomach. Consult your doctor if you are over 40 years and have never suffered with heartburn and indigestion before. If you forget a dose it is not necessary to double the dose next time, just carry on taking as before.
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Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, U.K.
PL 00063/0367
Gaviscon and are trademarks
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Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Gaviscon Instants Oral Powder (in cool mint or fresh tropical flavour) used to relieve the pain and discomfort of heartburn and acid indigestion are approvable.

EXECUTIVE SUMMARY
Problem statement
These are abridged applications for marketing authorisations of Gaviscon Instants Oral Powder via the decentralised procedure. The UK is the Reference Member State and the concerned member states are Belgium, France, Ireland, Luxembourg and the Netherlands.

About the product
Gaviscon Instants Oral Powder contains the same active ingredients as Gaviscon Peppermint Tablets 500mg and Liquid Gaviscon (sodium alginate, sodium bicarbonate and calcium carbonate) in a format that would disperse quickly and easily on the tongue without the use of water. The powder is packed into sachet stick packs made of suitable materials, that are packed in a cardboard box containing 16, 20, 24 or 32 single dose containers.

Based on previously developed granules of Gaviscon Peppermint Tablets 500mg, the granules' organoleptic profile and physical characteristics were improved by replacing some of the excipients with more appropriate ones, which are commonly used in oral powder dosage forms. The product is presented in either cool mint (UK/H/942/01/DC) or fresh tropical (UK/H/943/01/DC) flavour.

The applicant has conducted raft formation studies comparing Gaviscon Instants Oral Powder with Liquid Gaviscon and found that Gaviscon Instants Oral Powder, at the equivalent dose, is not inferior to Liquid Gaviscon.

General Comments on the submitted dossier
These Marketing Authorisation Applications (MAA) are made under Article 10a of Directive 2001/83/EC, as amended, so called well established use applications, using the decentralised procedure. The MAA are supported by full dossiers.

General Comments on Compliance with GMP, GLC, GCP and agreed ethical principles
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. There are no manufacturing sites outside the Community

No issues regarding GLP or GCP aspects have been identified during the review of these dossiers.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

Sodium bicarbonate and calcium carbonate are simple inorganic salts, long established in official standards, and adequately controlled by their pharmacopoeial specifications. Consequently, no further scientific data is provided. A copy of a valid certificate of suitability for calcium carbonate is provided. Sodium alginate is a well known pharmaceutical active ingredient, long established in official standards and adequately controlled by the pharmacopoeial specification, however, some controls in addition to the pharmacopoeial requirements have been applied during the manufacture of this product. Sodium bicarbonate, calcium carbonate and sodium alginate are the subjects of European Pharmacopoeia monographs.

The chemical-pharmaceutical documentation and expert report in relation to sodium alginate, sodium bicarbonate and calcium carbonate are of sufficient quality in view of present European regulatory requirements. The control tests and specifications for drug substances are adequately drawn up. No stability studies have been performed on any of the drug substances as they are well established pharmaceutical ingredients with long established use and are defined by pharmacopoeial standards.

Drug product

This application is for Gaviscon Instants Oral Powder containing sodium alginate, sodium bicarbonate and calcium carbonate as active ingredients presented in either cool mint or fresh tropical flavour.

The development of the product has been described and the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.

Batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up and the shelf life of 18 months when stored below 25ºC is acceptable.

Approval of the product licence applications is recommended.

Clinical aspects

One raft formation study was carried out using Gaviscon Instants Oral Powder with the aim of demonstrating non-inferior raft formation and duration in comparison to Liquid Gaviscon. (In brief, rafts are formed when, in the presence of gastric acid, alginates precipitate to form a gel. The carbonates in the formulation convert to carbon dioxide, which becomes trapped in the gel, converting it into a foam that floats on the surface of the stomach contents, creating the so-called ‘raft’. This raft prevents stomach acid escaping into the food pipe, where it causes pain). The lower dose of Gaviscon Instants Oral Powder, containing sodium alginate,

was compared with a dose of Liquid Gaviscon, containing the same amount of sodium alginate.

The Gaviscon Instants Oral Powder was shown to produce a robust raft which floated on top of, and emptied after, the stomach contents. Retention in the stomach of Gaviscon Instants Oral Powder was shown to be non-inferior to that of Liquid Gaviscon.

A raft formation study of the higher dose, containing 1000 mg sodium alginate, has not been undertaken, nor have reflux suppression studies of either the lower or higher dose (500 mg and 1000 mg sodium alginate) been performed. However, based on the results of the raft formation and reflux suppression studies performed on Gaviscon Peppermint Tablets, which demonstrated that Gaviscon Advance Peppermint Tablets were non-inferior to Liquid Gaviscon with respect to raft formation (500 mg and 1000 mg sodium alginate doses) and reflux suppression (1000 mg sodium alginate dose), it is anticipated that Gaviscon Instants Oral Powder would also be found to be non-inferior to Liquid Gaviscon with respect to raft formation using a 1000 mg sodium alginate dose and with respect to reflux suppression using 500 mg and 1000 mg sodium alginate doses. In terms of clinical efficacy, a single dose of one to two sachets of Gaviscon Instants Oral Powder (500 mg or 1000 mg sodium alginate) is, therefore, expected to be noninferior to a single dose of 10 ml or 20 ml Liquid Gaviscon.

Clinical data provided in the MAA for Gaviscon Advance included a raft formation study in healthy subjects comparing a 10ml dose of Gaviscon Advance and a 20 ml dose of Liquid Gaviscon, with both doses containing 1000 mg sodium alginate. The study concluded that the two doses were clinically equivalent. This was confirmed by a study showing equal clinical efficacy in relieving the symptoms of patients with GOR.

Since a dose of two sachets of Gaviscon Instants Oral Powder has clinical efficacy at least equal to that of 20 ml Liquid Gaviscon, and since 20 ml Liquid Gaviscon is clinically equivalent to 10 ml Gaviscon Advance, a dose of two sachets of Gaviscon Instants Oral Powder must have at least equal clinical efficacy to a dose of 10 ml Gaviscon Advance. By extrapolation, a similar conclusion can also be reached regarding doses of one sachet of Gaviscon Instants Oral Powder, 10 ml Liquid Gaviscon and 5 ml Gaviscon Advance. This being the case, the clinical data provided in the MAA for Gaviscon Advance demonstrating efficacy of Gaviscon Advance and Liquid Gaviscon in the relief of symptoms of GOR is also relevant to the corresponding doses of Gaviscon Instants Oral Powder.

Two studies demonstrated the superiority compared to placebo of 5 ml (equivalent to one sachet of Gaviscon Instants Oral Powder) and 10ml (equivalent to two sachets of Gaviscon Instants Oral Powder) four times daily. The 5 ml dose was taken for up to a fortnight and the 10 ml dose for up to four weeks. A further two studies demonstrated the efficacy of Liquid Gaviscon. One study used 10-20 ml doses (equivalent to one to two sachets of Gaviscon Instants Oral Powder) taken after meals and 20 ml taken at bedtime for 15 days. The second (study reference Ward 1989) used 10 ml doses (equivalent to one sachet of Gaviscon Instants Oral Powder) taken four times daily for up to four weeks.

Therefore, a study in healthy volunteers has demonstrated that a dose of one sachet of Gaviscon Instants Oral Powder has clinical efficacy at least equivalent to 10 ml Gaviscon Instants Oral Powder (Gaviscon Instants Oral Powder), Liquid Gaviscon and hence to 5 ml Gaviscon Advance. By inference, a two sachet dose of Gaviscon Instants Oral Powder has clinical efficacy at least equivalent to 20 ml Liquid Gaviscon and 10 ml Gaviscon Advance.

The efficacy of 5-10 ml doses of Gaviscon Advance and 10-20 ml doses of Liquid Gaviscon in relieving symptoms in patients with GOR, when taken four times daily for periods of up to four weeks, has been demonstrated previously in clinical studies. Similar efficacy would be expected from doses of one to two sachets of Gaviscon Instants Oral Powder.

Assessors' overall conclusions on clinical efficacy
The efficacy of the product has been adequately demonstrated by reference to clinical trial data and published references to previously authorised, similar formulations.

CLINICAL SAFETY
In the study carried out in healthy subjects using Gaviscon Instants Oral Powder, 23 subjects received a single dose of Gaviscon Instants Oral Powder containing 500 mg sodium alginate and 24 subjects received a single dose of 10 ml Liquid Gaviscon containing 500 mg sodium alginate. The reason for withdrawal of one subject from the study was appropriate.

Six adverse events were reported by five of the 24 subjects who were randomised to receive the study investigational medicinal products. There were two reported adverse events of mild skin injury, two reported events of mild nasopharyngitis, one reported event of mild back pain and one reported event of moderate gastroenteritis.

All six events were considered to have either an unlikely relationship (two events) or to be unrelated (four events) to the study investigational medicinal products. One adverse event was considered to be moderate in severity. All other adverse events were considered to be mild in severity.

The safety data generated for Gaviscon Advance, Gaviscon Peppermint Tablets and Liquid Gaviscon, and provided in the MAAs for Gaviscon Advance and Gaviscon Peppermint Tablets, suggest that treatment was well-tolerated.

In the Gaviscon Advance studies a total of 197 patients received 5 ml Gaviscon Advance (500 mg sodium alginate), 155 received 10 ml Gaviscon Advance (1000 mg sodium alginate), 135 received 10 ml Liquid Gaviscon (500 mg sodium alginate) and 104 received 20ml Liquid Gaviscon (1000 mg sodium alginate).

The numbers of events considered to be possibly or probably related to treatment with Gaviscon Advance or Liquid Gaviscon were low and most were mild or moderate in severity.

Following treatment with 10 ml Gaviscon Advance, there were two reports of nausea and one of palpitations in one study, and 22 events in another study, the most commonly reported being nausea. In one study of 5 ml Gaviscon Advance there were 73 events, mostly GI in nature. Treatment with 10 ml Liquid Gaviscon resulted in three cases of vomiting and one of nausea in the Chevrel study, and five reports of nausea, three reports of constipation and one report of dyspepsia during the Ward study. Following treatment with 20 ml Gaviscon Liquid, there were 24 adverse events, the most frequently reported being flatulence (five events). The rates of withdrawal resulting from adverse effects amongst patients treated with Gaviscon Advance or Liquid Gaviscon were low, ranging from 0% in the Chevrel study to 8% in another.

In the three studies carried out in healthy subjects using Gaviscon Peppermint Tablets, a total of 14 subjects received a single dose of two Gaviscon Peppermint Tablets containing 500 mg

sodium alginate, and 47 subjects received a single dose of four Gaviscon Peppermint Tablets containing 1000 mg sodium alginate. A total of 14 subjects received a single dose of 10 ml Liquid Gaviscon containing 500 mg sodium alginate, and 46 subjects received a single dose of 20 ml Liquid Gaviscon containing 1000 mg sodium alginate

Following administration of two Gaviscon Peppermint Tablets, only one adverse event was recorded, increased flatulence, which was mild in severity and considered possibly related to treatment. After administration of four Gaviscon Peppermint Tablets, only three of the seven events reported were considered either possibly or probably treatment-related; these were upper abdominal pain and pharyngolaryngeal pain (both moderately severe) and mild paraesthesia. Neither of the two adverse events reported in a further study were considered treatment-related. Following administration of 10ml Liquid Gaviscon, only two adverse events were recorded, both by the same subject who reported adverse events after dosing with 250 mg Tablets. Both events, increased flatulence and frequent bowel movements, were mild in severity and considered to be possibly related to treatment. After administration of 20 ml Liquid Gaviscon, only one of the three events reported, mild nausea, was considered to be possibly treatment-related. Neither of the two adverse events reported in another study were considered treatment-related.

Given the similarities of the other Reckitt Benckiser alginate based formulae, the adverse reaction profiles of these products are considered relevant to this application since they are indicative of what might be expected for Gaviscon Instants Oral Powder.

As of 31 December 2005, a total of 1435 adverse event reports relating to Reckitt Benckiser alginate-based formulae have been received. This group includes adverse events following treatment with a range of Reckitt Benckiser Gaviscon products, including Gaviscon Advance, Liquid Gaviscon, Gaviscon Nourrisson, Project Avon and Project Trent. Not included are presentations based on alginic acid, which includes the tablet formulae prior to the introduction of Projects Avon and Trent and also the UK Infant Gaviscon formula. The total of 1435 adverse event reports includes reports received directly from the medical professions, those notified via the Medicines and Healthcare Products Regulatory Agency Surveillance Scheme and those reported during clinical trials. Reports are categorised according to their relationship with the Gaviscon products. The majority of the reports arising from everyday clinical use originate from the UK. Viewed in the context of the volume of Liquid Gaviscon manufactured in 2005 (5,412,254 litres) this represents a very low incidence of adverse events, even when the potential for under-reporting associated with OTC products is taken into account.

BENEFIT RISK ASSESSMENT

The active ingredients in one Gaviscon Instants Oral Powder sachet are the same as those in 10 ml Liquid Gaviscon, a well established authorised product. The indications currently approved indications for Gaviscon Advance are: "Treatment of symptoms of GOR such as acid regurgitation, heartburn, indigestion occurring due to the reflux of stomach contents, for instance, after gastric surgery as a result of hiatus hernia, during pregnancy or accompanying reflux oesophagitis". These indications are appropriate for this application. The wording of the indication has been modified to assist patients in deciding whether the product is appropriate for their symptoms: "Treatment of symptoms of GOR 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". Since the mode of action relies on the reaction of sodium alginate and bicarbonate with gastric acid to form an

alginate raft, there is the possibility of reduced efficacy in patients with very low levels of gastric acid. For Gaviscon Advance, Gaviscon Peppermint/Lemon Tablets, Gaviscon Peppermint/Lemon Tablets 500 and Gaviscon Instants Oral Powder, the recommended dose of sodium alginate for adults and children over 12 years of age is 500-1000 mg taken four times daily (after meals and at bedtime). No limit is placed on the duration of treatment. A clinical pharmacology study has demonstrated that doses of one sachet of Gaviscon Instants Oral Powder (500 mg sodium alginate) has non-inferior raft formation properties in comparison to 10 ml Liquid Gaviscon. Utilising previous clinical studies performed on Gaviscon Advance, Liquid Gaviscon and Gaviscon Peppermint Tablets, this permits inference of clinical efficacy for Gaviscon Instants Oral Powder at least equal to that of Gaviscon Advance and Liquid Gaviscon at both the lower (500 mg sodium alginate - 5 ml and 10 ml respectively) and higher (1000 mg sodium alginate - 10 ml and 20 ml respectively) doses for which efficacy in the treatment of symptoms of GOR has been demonstrated in clinical studies. The adult dose is considered to be equally appropriate for use by children aged 12 years and over, and the elderly. Use in children under 12 is, though, proposed only on medical advice. No limit is placed on the duration of treatment, although it is recommended that patients should seek medical advice if symptoms do not improve within seven days. Since, in rare cases, the symptoms associated with gastric reflux may actually result from a more serious underlying condition such as gastric carcinoma, this is a sensible measure to guard against prolonged self-medication resulting in such conditions going undiagnosed.

Each sachet contains 123 mg (5.3 mmol) sodium and 160 mg (1.6 mmol) of calcium carbonate. This should be taken into account when a highly restricted salt diet is recommended, as in some cases of congestive heart failure and renal impairment, and by patients with hypercalcaemia, nephrocalcinosis and recurrent calciumcontaining renal calculi. The medicinal product also contains aspartame and should not be taken by patients with phenylketonuria.

Gaviscon Instants Oral Powder may be used during pregnancy and lactation. The physical mode of action of the Gaviscon formulations makes them suitable for use in pregnancy and lactation. Gaviscon Advance, Gaviscon Peppermint/Lemon Tablets and Gaviscon Peppermint/Lemon Tablets 500 are specifically indicated for use in pregnancy, and Liquid Gaviscon has been widely used in pregnancy and lactation since its first introduction in the UK over 20 years ago. Open, controlled studies in 281 pregnant women have not shown any significant adverse effects of the Gaviscon formulations on the course of pregnancy or on the health of the foetus/new born child.
Gaviscon Instants Oral Powder has no effect on ability to drive or operate machines.

There are no known interactions with Gaviscon Instants Oral Powder. Although antacids are known to interfere with the absorption of some drugs, such as tetracyclines and digoxin, the amounts of antacid components in Gaviscon Instants Oral Powder are low. The intakes from the maximum daily dose of eight Gaviscon Instants Oral Powder sachets are 2136mg sodium bicarbonate and 1280mg of calcium carbonate compared with single doses of 1000-5000 mg and up to 1500 mg of the two ingredients respectively, taken as required in antacid products. No undesirable effects which could be attributed as possibly or probably related to treatment during the single clinical study performed for Gaviscon Instants Oral Powder were observed and the expected rarity of adverse events is confirmed by long-term marketing experience of Liquid Gaviscon and more limited experience of Gaviscon Advance. There is a history of very rare allergic-type reactions to Liquid Gaviscon. Such reactions, including urticaria and

bronchospasm, are most likely to have been triggered by reaction to the alginate, paraben preservatives or erythrosine used as a colouring agent in the fennel flavour variant. Since Gaviscon Instants Oral Powder contains neither preservatives nor colouring agents, a reduced incidence of allergic reactions may be expected.

The most likely consequence of overdosage is abdominal distension and bloating. Symptomatic treatment should be given as necessary. The overall conclusion of the clinical programme is that Gaviscon Instants Oral Powder is a suitable product for the indications which it is intended to treat, and will have appropriate efficacy and safety when used in accordance with the proposed SPC.

RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

The legal status of the product is that it is not subject to medical prescription.

Overall conclusion

QUALITY

The important quality characteristics of Gaviscon Instants Oral Powder 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.

PRECLINICAL

No preclinical data is needed for these applications.

No new or unexpected safety concerns arise from these applications.

EFFICACY

Clinical studies have demonstrated the efficacy of Gaviscon Instants Oral Powder in the treatment of symptoms of gastro-oesophageal reflux, such as acid regurgitation, heartburn and indigestion (related to reflux).

The product literature is satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.