Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

GAVISCON ADVANCE

UK/H/0222/001/E02
UK MA no: PL 00063/0097

Reckitt Benckiser Healthcare (UK) Limited

GAVISCON ADVANCE

LAY SUMMARY

On 16th June 2008, Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain and Sweden granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Gaviscon Advance (PL 00063/0097; UK/H/0222/001/E02). This product is available on a general sales licence (GSL) to treat the symptoms of gastro-oesophageal reflux, such as acid regurgitation, heartburn and indigestion related to reflux, such as following meals, during pregnancy or in patients with symptoms associated with reflux oesophagitis.

Gaviscon Advance contains the ingredients sodium alginate and potassium bicarbonate, and belongs to a group of medicines known as “reflux suppressants”. Reflux in a process in which the acid stomach juices flow back up into the food pipe. Unlike the stomach, the food pipe is not resistant to acid so that when reflux occurs, it causes pain and discomfort commonly known as heartburn. Gaviscon Advance forms a protective layer that floats on top of the stomach contents and keeps the stomach contents away from the lining of the food pipe to relieve the symptoms of heartburn and acid indigestion.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Gaviscon Advance outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Gaviscon Advance
Type of Application	Article 10a, Well-Established Use
Active Substance	Sodium alginate Potassium carbonate
Form	Oral suspension
Strength	500mg/5ml sodium alginate and 100mg/5ml potassium bicarbonate
MA Holder	Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, East Yorkshire, HU8 7DS, UK
RMS	UK
CMS	Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain and Sweden
Procedure Number	UK/H/0222/001/E02
Timetable	Day 90: 16th June 2008

Module 2
Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Gaviscon Advance Oral suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances	mg/10 ml
Sodium alginate	1000.0
Potassium hydrogen carbonate	200.0

Excipients: methylparahydroxybenzoate (E218) and propylparahydroxybenzoate (E216)

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension
Off-white, viscous suspension.

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

Adults and children 12 years and over: 5-10 ml after meals and at bedtime.

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

Elderly: No dose modification is required for this age group.

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 Special Precautions for Use

Each 10 ml dose has a sodium content of 106 mg.(4.6 mmol) and a potassium content of 78mg (2.0 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 or when taking drugs which can increase plasma potassium levels.

Each 10 ml contains 200mg (2.0 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.

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

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

4.5 Interaction with other Medicinal Products and other Forms of Interaction

None known.

4.6 Pregnancy and lactation

An open, uncontrolled study in 146 pregnant women did not demonstrate any significant adverse effects of this product on the course of pregnancy or on the health of the foetus/new-born child. Based on this and previous experience this 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

None

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 overdosage symptomatic treatment should be given. The patient may notice abdominal distension.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic classification: A02E AO1 Anti-regurgitant

On ingestion the suspension reacts 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 Gaviscon Advance is physical and does not depend on absorption into the systemic circulation.

5.3 Pre-clinical Safety Data

No preclinical findings of relevance to the prescriber have been reported.

6.1 List of excipients

Calcium carbonate, carbomer 974P, methyl hydroxybenzoate, propyl hydroxybenzoate, saccharin sodium, fennel flavour, sodium hydroxide and purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Shelf life: 2 years.
Shelf life after opening: 6 months.

6.4 Special Precautions for Storage

Do not refrigerate.

6.5 Nature and Content of Container

Amber glass bottles with moulded polypropylene cap having a tamper evident strip and lined with an expanded polyethylene wad and containing 80, 100, 125, 140, 150, 180, 200, 250, 300, 400, 500 or 560, 600 ml suspension.
Or
Amber glass bottles with moulded polypropylene cap having a tamper-evident strip and lined with an expanded polyethylene wad with either a measuring device (natural polypropylene) containing 5, 10, 15 and 20 ml graduations, or a measuring spoon (crystal polystyrene) containing 2.5 ml and 5 ml measure and containing 80, 100, 125, 140, 150, 180, 200, 250, 300, 400, 500, 560 or 600 ml suspension.

Not all pack sizes may be marketed. The carton and measuring device and spoon may not be made available in all markets/pack sizes.

6.6 Special precautions for disposal of a used medicinal product and waste material derived from such medicinal product and other handling of the product

To be taken orally. Shake well before use. Check that the cap seal is unbroken before first taking the product.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER(S)

PL 00063/0097

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/09/2006

10. DATE OF REVISION OF THE TEXT

04/04/2007

Module 3/Module 4
Product Information Leaflet/Labelling

GAVISCON ADVANCE
sodium alginate and potassium hydrogen carbonate

PATIENT INFORMATION LEAFLET
PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU TAKE THIS MEDICINE.

IF YOU ARE NOT SURE ABOUT ANYTHING ASK YOUR PHARMACIST OR DOCTOR

What is Gaviscon Advance?
Gaviscon Advance belongs to a group of medicines called "reflux suppressants". Reflux is a process in which the acid stomach juices flow back up into the food pipe. Unlike the stomach the lining of the food pipe is not resistant to acid so that when reflux occurs, it causes the pain and discomfort commonly known as heartburn. This product forms a protective layer that floats on top of the stomach contents. This layer prevents reflux and keeps the stomach contents away from the lining of the food pipe to relieve the symptoms of heartburn and acid indigestion.

What is Gaviscon Advance used for?
Gaviscon Advance is used for the 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.

Before taking Gaviscon Advance:
Do **not** take if you know that you are allergic to any of the ingredients (see further information for a full list). This medicine contains small amounts of sodium (4.6mmol per 10ml), potassium (2.0mmol per 10ml) and calcium. If you have been advised to follow a diet restricted in any of these salts please consult your doctor. Please also talk to your doctor regarding these salt contents if you suffer or have suffered from significant kidney or heart disease or if you regularly take so-called diuretics to treat your high blood pressure, as certain salts could interfere with these diseases or diuretics.
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. This product contains methyl (E218) and propyl (E216) parahydroxy-benzoates which may cause allergic reactions (possibly delayed). This treatment may be less effective if you have decreased amounts of gastric acid produced in your stomach.

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How to take Gaviscon Advance:
Adults, including the elderly and children 12 years and over: 5-10ml (one to two 5ml spoonfuls) after meals and at bedtime, or as directed. Children under 12 years: Should only be taken on medical advice. If you forget a dose it is not necessary to double the dose next time, just carry on taking as before. If you take too much of this product it is unlikely to cause you any harm. However you may feel bloated. Consult your doctor or pharmacist if this does not go away.

After taking Gaviscon Advance:
If symptoms persist after 7 days consult your doctor.

Possible side effects:
Very rarely (less than 1 in 10,000) chance of skin rash or difficulty in breathing due to an allergic reaction from the ingredients. Consult your doctor immediately if you experience these or any other side-effects.

Storing your medicine:
Do not use this product after the expiry date (EXP: month/year) shown • Use within 6 months of opening • Keep out of the reach and sight of children • Do not refrigerate • Shake well before use • Check that the cap seal is unbroken before first using this product.

Further information:
Each 10ml of oral suspension contains 1000mg sodium alginate and 200mg potassium hydrogen carbonate as the active ingredients. The other ingredients are calcium carbonate, carbomer, methyl (E218) and propyl (E216) parahydroxy-benzoates, sodium saccharin, sodium hydroxide, aniseed flavour derived from fennel and purified water. This product does not contain sugar or gluten. Gaviscon Advance is available in bottles of 150ml, 300ml or 500ml only from the pharmacy.

Manufacturer and Product Licence Holder in UK: Reckitt Benckiser Healthcare (UK) Ltd., Hull, HU8 7DS.
Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, HU8 7DS.
Gaviscon Advance and the sword and circle are trade marks.
Text Revised: October 2007

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Gaviscon Advance provides 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. The product belongs to a group of medicines called 'reflux suppressants', which form a protective layer on top of the stomach contents to prevent acid escaping from the stomach where it works into the food pipe where it hurts.
What is this product? Each 10ml of oral suspension contains sodium alginate 1000mg and potassium hydrogen carbonate 200mg as the active ingredients. It also contains calcium carbonate, carbomer, methyl (E218) and propyl (E216) parahydroxybenzoates, sodium saccharin, sodium hydroxide, aniseed flavour derived from fennel and purified water. This product is sugar free and gluten free. You can take Gaviscon Advance if you are pregnant or breast feeding. As with all medicines, the treatment duration should be limited as much as possible.
Before taking this product: Do not take if you know you are allergic to any of the ingredients. This medicine contains small amounts of sodium (4.6mmol per 10ml), potassium (2.0mmol per 10ml) and calcium. If you have been advised to follow a diet restricted in any of these please consult your doctor before taking this product. This product contains methyl (E218) and propyl (E216) parahydroxybenzoates which may cause allergic reactions (possibly delayed). This treatment may be less effective if you have decreased amounts of gastric acid produced in your stomach.
Dosage: Shake well before use. Adults, including the elderly and children 12 years and over: 5-10ml (one to two 5ml spoonfuls) after meals and at bedtime, or as directed. Children under 12 years: Should only be taken on medical advice. If you forget a dose it is not necessary to double the dose next time, just carry on taking as before. If you take too much of this product it is unlikely to cause you any harm. However, you may feel bloated. Consult your doctor or pharmacist if this does not go away.
After taking this product: If symptoms persist after 7 days consult your doctor.
AVAILABLE THROUGH PHARMACIES ONLY
GAVISCON
ADVANCE
Oral suspension
sodium alginate
potassium hydrogen carbonate
FAST POWERFUL RELIEF
Heartburn & Indigestion
Extra Strength Formula
Long Lasting
ANISEED FLAVOUR
Possible side effects: Very rarely (less than 1 in 10,000) chance of skin rash or difficulty in breathing due to an allergic reaction from the ingredients. Consult your doctor immediately if you experience these or any other side-effects.
Storage: Do not refrigerate. Check that the cap seal is unbroken before first using this product. Do not use this product after the expiry date (EXP: month/year) shown. Use within 6 months of opening.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Manufacturer and PL Holder in UK: Reckitt Benckiser Healthcare (UK) Ltd., Hull, HU8 7DS. UK Distributors: Britannia Pharmaceuticals Limited.
Export Distributors: Reckitt & Colman (Overseas) Ltd., Hull, HU8 7DS.
Gaviscon Advance and are trade marks.
Date of preparation: 08/2007
Aniseed flavoured liquid
PL 0063/0097
5 000158 063693
BN
EXP
e500ml
xxxxxxx

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

On 16th June 2008, Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain and Sweden granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Gaviscon Advance (PL 00063/0097; UK/H/0222/001/E02). The product is available on a general sales licence (GSL) for the symptomatic treatment of gastro-oesophageal reflux, such as acid regurgitation, heartburn and indigestion related to reflux, such as following meals, during pregnancy or in patients with symptoms related to reflux oesophogitis.

This application was submitted under Article 10a of 2001/83/EC, a well-established use product containing 500mg/5ml sodium alginate and 100mg/5ml potassium bicarbonate, using the mutual recognition procedure (MRP) with the UK as reference member state (RMS). A licence had previously been granted in the UK on 31st October 1996, and licences had previously been granted in Belgium, Germany, Ireland, Italy and The Netherlands on 10th June 1998 following a first-wave MRP (UK/H/0222/001/MR) and in France on 19th August 2003 following a second-wave MRP (UK/H/0222/001/E01).

The active ingredients in this product are sodium alginate and potassium bicarbonate. Sodium alginate consists of the sodium salt of alginic acid, which is an unbranched block co-polymer composed of residues of D-mannuronic and L-guluronic acid, and is obtained mainly from algae belonging to the *Phaeophyceae*. Its physical properties, viscosity and gel strength are linked directly to the chemical structure. Potassium bicarbonate is a simple salt which acts as a source of carbon dioxide in the presence of stomach acid.

Gaviscon Advance, like the Liquid Gaviscon formulation, has a reflux-suppressant mode of action. The fundamental feature, on which clinical efficacy depends, is the formation of a raft of alginate gel buoyed up by entrapped carbon dioxide which floats on the stomach contents preventing reflux or, in severe cases, being preferentially refluxed into the oesophagus and exerting a demulcent effect. In preventing reflux, Gaviscon Advance provides relief from the symptoms of gastro-oesophageal reflux and also prevents further acid attack on the oesophageal mucosa so allowing healing to take place. Its ATC classification is as an anti-regurgitant, A02E A01. Despite the presence of potassium bicarbonate and calcium carbonate in the formulation, it is not an antacid and does not have the minimum neutralising capacity required set for antacids in the US Federal Register.

No new preclinical studies were conducted, which is acceptable given the extensive use of the two drug substances. Clinical studies on Gaviscon Advance were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Gaviscon Advance provides satisfactory clinical benefits.

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 this product prior to granting its national authorisation.

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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Gaviscon Advance
Name(s) of the active substance(s) (INN)	Sodium alginate Potassium carbonate
Pharmacotherapeutic classification (ATC code)	Other drugs for peptic ulcers and gastro-oesophageal reflux disease (A02BX)
Pharmaceutical form and strength(s)	Oral suspension containing 500mg/5ml sodium alginate and 100mg/5ml potassium bicarbonate
Reference numbers for the Decentralised Procedure	UK/H/0222/001/E02
Reference Member State	United Kingdom
Member States concerned	Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, Greece, Hungary, Iceland, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain and Sweden
Name and address of manufacturer responsible for batch release in the EEA	Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, East Yorkshire, HU8 7DS, UK
Date of first authorisation	31st October 1996
Marketing Authorisation Number(s)	PL 00063/0097
Name and address of the authorisation holder	Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, East Yorkshire, HU8 7DS, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Sodium Alginate

Sodium alginate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Any potential impurities have been identified and characterised.

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

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.

Potassium bicarbonate

Potassium bicarbonate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Any potential impurities have been identified and characterised.

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

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of pharmaceutical excipients calcium carbonate, carbomer 974P, methyl hydroxybenzoate, propyl hydroxybenzoate, saccharin sodium, fennel flavour, sodium hydroxide and purified water. All ingredients comply with their European Pharmacopoeia monograph, with the exception of the fennel flavour (which is controlled to a suitable in-house specification and to EC Directive 88/388 concerning flavourings in food).

None of the excipients contain materials of animal or human origin.

Pharmaceutical Development
The objective of the development programme was to formulate a double concentration product containing 1000mg sodium alginate per 10ml, rather than per 20ml as with Liquid Gaviscon, but which still forms a similar aerated alginate raft and has a lower sodium content.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Container-Closure System
The finished product is packaged in amber glass bottles and moulded polypropylene caps, with tamper-evident strip and lined with an expanded polyethylene wad. Some packs also contain a natural polypropylene measuring device (with 5, 10, 15 and 20ml graduations) or a crystal polystyrene measuring spoon (with 2.5 and 5ml measures). The pack sizes are 80, 100, 125, 140, 150, 180, 200, 250, 300, 400, 500, 560 or 600ml suspension.

Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the Product
Stability studies were performed in accordance with current guidelines, using product manufactured by the proposed finished product manufacturer and in the packaging proposed for marketing. The results support a shelf-life of 2 years (which reduces to 6 months after opening), with the storage instructions “Do not refrigerate”.

Bioequivalence/bioavailability
No bioequivalence studies were conducted, which is acceptable as the mode of action does not depend on any absorption into the systemic circulation.

Summary or Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The marketing authorisation holder has stated that not all pack sizes may be marketed. However, they have committed to providing the regulatory authority with labelling for any pack size before it is marketed.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The tests show that the patients/users are able to act upon the information that it contains.

Pharmaceutical Expert Report
The Pharmaceutical Expert Report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

MAA Form
The MAA form is pharmaceutically satisfactory.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS

No new preclinical data have been provided and, as this application is for a product containing two well-known active substances, no additional preclinical data are required.

The Pre-clinical Expert Report has been written by an appropriately qualified person and is satisfactory.

The Summary of Product Characteristics is satisfactory from a pre-clinical viewpoint.

It is recommended that a marketing authorisation is granted for this licence.

III.3 CLINICAL ASPECTS

PHARMACOKINETICS/PHARMACODYNAMICS
As the mechanism of action of the product is purely physical and absorption is not necessary, no pharmacokinetic or pharmacodynamic data have been provided for this application and none are required.

The formulation contains sodium alginate and potassium bicarbonate, which have antacid properties. However, the sum of the two only amounts to 3.01 mEq per 5 ml dose, which is less than the 5.0 mEq per 5 ml designated by the US Federal Register as Antacid. This means that, technically, these two salts do not constitute an antacid, even though it is their ability to react with this that produces CO_2 to form the raft.

EFFICACY

Four efficacy studies have been performed:

1. Gaviscon Advance versus Placebo

The efficacy of the two treatments was assessed at 2 and 4 weeks by the investigator. The results, in an intention-to-treat analysis were as follows:

	Placebo		Gaviscon Advance	
	wk 2	wk 4	wk 2	wk 4
Very good/good	12 (26%)	11 (24%)	26 (61%)	24 (54%)
Acceptable	13 (28%)	8 (17%)	8 (19%)	14 (32 %)
Poor/very poor	22 (47%)	28 (60%)	9 (21%)	6 (13%)

The difference between the groups was statistically significant ($p<0.0001$). An efficacy analysis of the same patients involved smaller numbers: it showed a significant difference in favour of Gaviscon at Week 2 ($p<0.001$), but only borderline significance at Week 4 ($p=0.087$). This was a consequence of patient withdrawals, particularly in the placebo group.

Similar results were obtained from patients' own evaluation of their response to the treatments.

Assessment of the patients' individual symptoms showed less striking results. The only significant differences between treatment groups were in mean severity of daytime acid regurgitation, which favoured Gaviscon Advance at Week 2 ($p=0.047$) and Week 4 ($p=0.029$) for the efficacy population. But the frequency of daytime flatulence/wind favoured placebo at Week 2 ($p=0.012$). In general, however, the trends favoured Gaviscon Advance.

Diary card evaluation of symptoms by the patients showed significant differences for 'morning heartburn' and bedtime 'acid coming up into your mouth', both in frequency and severity. But significant differences between 'bedtime heartburn' and morning 'acid coming up into your mouth' were not seen.

Withdrawals due to 'lack of effect' was 20% in the placebo group. In the Gaviscon Advance group withdrawals were 6%, including both 'lack of effect' and 'lost to follow-up'.

The palatability of placebo and Gaviscon Advance (as estimated from how much the patients liked or disliked the preparations) showed no significant differences between the two. This is an important observation, since a difference here might explain the efficacy findings.

Adverse events (a wide range of symptoms) were commoner in the placebo patients (38%) than in the patients taking Gaviscon Advance (27%). The placebo group showed three severe adverse events: rash and itching in one patient, and exacerbation of obstructive airway disease in another. The Gaviscon Advance group showed four severe events: diarrhoea and stomach pain each in one patient, and nausea in two patients. These findings do not suggest any safety issues with Gaviscon Advance.

2. Gaviscon Advance versus Liquid Gaviscon in treating oesophageal reflux

This was a randomised, single-blind, multicentre study to demonstrate the equivalent efficacy of 10ml *qid* Gaviscon Advance versus 20ml *qid* Liquid Gaviscon in patients who had all experienced reflux oesophagitis in the 24 hours before their first trial visit.

At weeks 0, 2 and 4, the investigators assessed the reflux oesophagitis symptoms (heartburn/retrosternal pain, acid regurgitation, wind/flatulence and nausea) over the previous 24 hours, and also the overall efficacy of the preparations. The results, in an intention-to-treat and an efficacy analysis were as follows:

	Investigators (% 'good' or 'very good')		**Patients' assessment: (% 'slightly' or 'much better')**	
Efficacy population	**Week 2**	**Week 4**	**Week 2**	**Week 4**
Gav. Advance	73	70	82	79
Liqu. Gaviscon	66	74	80	85

	Investigators impression (% 'good' or 'very good')		**Patients' assessment of symptoms: (slightly or much better)**	
Intent to Treat population	**Week 2**	**Week 4**	**Week 2**	**Week 4**
Gav. Advance	66	65	80	75
Liqu. Gaviscon	61	67	78	82

Seven out of these eight pairs of numbers had confidence intervals of between –0.2 + 0.2, and so were indicative of equivalence.

Eight patients in each group withdrew because of adverse events. There were three serious adverse events; two in the Liquid Gaviscon group (false labour and dimished fetal movements), which were not thought to be related to treatment. One in the Gaviscon Advance group (chest pain) had an unknown relationship to treatment.

In conclusion, the two formulations were equivalent in efficacy; both were well-tolerated, having no safety problems.

3. Raft formation: Advance Liquid Gaviscon v two formulations of Gaviscon Advance
This was an open-label crossover study of alginate rafts (Liquid Gaviscon v Gaviscon Advance 312 v Gaviscon Advance 340: Gavison 312 is the subject of this application) in fasted volunteers given products labelled with ^{111}In.

The gastric residence of Gaviscon Advance was statistically significantly greater than that of Liquid Gaviscon: the ratio of AUC's was 1.1777 with 95% confidence limits of 1.050 and 1.278. After correction for gastric residence of the test meal, the ratio became slightly less – 1.197 (95% CI limits: 1.082 and 1.327). Although the difference between the two formulations was significantly different, they were within ± 20% of each other, and were concluded to have equivalent raft-forming properties. The gastric retention of Gaviscon Advance was consistently greater than Liquid Gaviscon, which would probably increase its clinical efficacy.

The gastric residence time of both the rafts was significantly longer than the test meals. Furthermore, for each treatment a significantly higher proportion of the alginate resided in the upper region of the stomach. (The proportion of Gaviscon Advance was slightly – but non-significantly – higher than that of Liquid Gaviscon. This is consistent with the formulation's longer residence time).

Two adverse events were reported: mild abdominal discomfort after Liquid Gaviscon (the investigator felt that this was unrelated to treatment) and whitish loose stools after Gaviscon Advance (the investigator thought that this was related to the medication).

In conclusion, Gaviscon Advance has been shown to form a raft that is very similar in its properties to Liquid Gaviscon, but lasts slightly longer in the stomach. No safety issues arose in this volunteer study.

4. A study of gastro-oesophageal reflux in healthy volunteers

This was a four-period crossover study, comparing two formulas (312 and 340) of Gaviscon Advance versus Liquid Gaviscon and versus tap water. Acid reflux was assessed by oesophageal pH monitoring and food reflux by gamma scintigraphy (following a refluxogenic test meal).

Criteria for assessing the treatment effect included the number of episodes of reflux that were below pH 4, 5 and 6 and the time for which the pH was below these units.

The Gaviscon preparations all reduced the number and time of the pH swings when compared with water. However, the effects were not significantly different, even though the trends were consistent.

The scintigraphy data was unsatisfactory. These data were expressed as area under scintigraphy count (AUC) versus time for each of the three products, and was very similar (about 1200 counts per minute) for each. The investigators felt that something was wrong with the methodology, as in previous studies the counts has been very much higher.

Three adverse events were reported: stomach pain, injured shoulder following a fall and an inflamed right nostril. These events were considered mild and unrelated to treatment.

Both formulations of Gaviscon reduced acid reflux when compared with tap water, though these effects were not statistically significant. The investigation of the effect of Gaviscon on food reflux was technically flawed, so that no conclusions could be drawn.

SAFETY

See individual efficacy studies above.

EXPERT REPORTS

The Clinical Expert Report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC), PATIENT INFORMATION LEAFLET (PIL), LABELLING & APPLICATION FORM (MAA)

These are all medically satisfactory.

MEDICAL CONCLUSION

The grant of a marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Gaviscon Advance 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 new preclinical data were submitted and none are required for applications of this type.

EFFICACY

The studies submitted do provide convincing evidence of efficacy, and the choice of actives and their respective doses in the proposed fixed combination have been adequately justified.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for similar products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with sodium alginate and potassium bicarbonate is considered to have demonstrated the therapeutic value of the product. The risk-benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome