Public Assessment Report

Mutual Recognition Procedure

Gaviscon Advance Tablets

UK/H/222/04

Reckitt Benckiser Healthcare (UK) Limited
Lay Summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Gaviscon Advance Tablets (Product Licence number 00063/0144). This medicine is available without prescription and can be bought in pharmacies and shops that are not pharmacies.

Gaviscon Advance Tablets belongs to a group of medicines called ‘reflux suppressants’ which form a protective layer on top of the stomach preventing stomach acid escaping from the stomach. This helps relieve the pain and discomfort associated with heartburn and indigestion.

Gaviscon Advance Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Gaviscon Advance Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of application (Eudratrack details)</strong></td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>Line extension</td>
</tr>
<tr>
<td>Level 2</td>
<td>Additional strength or form</td>
</tr>
<tr>
<td>Level 3</td>
<td>Fixed combination, Article</td>
</tr>
<tr>
<td>10.1(b)</td>
<td></td>
</tr>
<tr>
<td>Level 4</td>
<td>Chemical substance</td>
</tr>
<tr>
<td>Level 5</td>
<td>Non prescription</td>
</tr>
<tr>
<td><strong>Name(s) of the active substance(s) (INN)</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium alginate</td>
<td></td>
</tr>
<tr>
<td>Potassium bicarbonate</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td></td>
</tr>
<tr>
<td>A02BX 13</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td></td>
</tr>
<tr>
<td>Chewable tablet</td>
<td></td>
</tr>
<tr>
<td>Sodium alginate: 500 mg</td>
<td></td>
</tr>
<tr>
<td>Potassium bicarbonate: 100 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Reference numbers for the Mutual Recognition Procedure</strong></td>
<td>UK/H/222/04</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>Belgium, Ireland, Italy</td>
</tr>
<tr>
<td><strong>Packaging</strong></td>
<td></td>
</tr>
<tr>
<td>uPVC/PE/ PVdC with aluminium foil lidding push-through blisters containing six individually sealed tablets (2 or 4 blister trays in a carton), or in white polypropylene tubes containing 20 tablets with one, two, three or four tubes in a carton.</td>
<td></td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>The fundamental feature of the products is the formation of an alginate raft of near neutral pH which floats on the stomach contents. This raft either physically impedes reflux or, in severe cases, is itself preferentially refluxed into the oesophagus where it exerts a demulcent effect.</td>
</tr>
<tr>
<td></td>
<td>The raft is formed by the reaction of sodium alginate with gastric acid to form an alginic acid gel. This gel floats on top of the stomach contents by virtue of its reduced density resulting from entrapped carbon dioxide formed by the reaction of bicarbonate with gastric acid. Calcium ions in the formulation increase the raft strength by formation of cross-linkages between the alginate chains.</td>
</tr>
<tr>
<td><strong>Approved indications and dosage (see full SPC for details)</strong></td>
<td>This application is for a chewable tablet indicated for use in the symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn, indigestion occurring due to the reflux of stomach contents, for instance, after gastric surgery, as a result of a hiatus hernia, during pregnancy or accompanying reflux oesophagitis. The recommended dose of alginate for adults and children over 12 years of age is 500-1000mg taken four times daily (after meals and at bedtime).</td>
</tr>
<tr>
<td>Special pharmaceutical aspects if any, e.g. novel delivery system</td>
<td>None</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Date of first authorisation</td>
<td>5th January 2005</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00063/0144</td>
</tr>
<tr>
<td>Date of assessment report</td>
<td>23 December 2005</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, United Kingdom.</td>
</tr>
</tbody>
</table>
Module 2

Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Gaviscon Advance Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sodium alginate 500 mg and potassium bicarbonate 100 mg.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

An off-white to cream, circular, flat with bevelled edges tablet 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, 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.

4.2. Posology and method of administration

For oral administration, after being thoroughly chewed.

Adults and children 12 years and over: One to two tablets 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

The sodium content of a two-tablet dose is 103 mg (4.5 mmol) and a potassium content of 78 mg (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 two-tablet dose contains 200 mg (2.0 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 product should not be given to patients with phenylketonuria.

May cause central nervous system depression in the presence of renal insufficiency and should not be used in patients with renal failure.

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.

4.5. Interactions with other medicinal products and other forms of interaction

None known

4.6. Pregnancy and lactation

Open controlled studies in 146 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, Gaviscon Advance Tablets may be used during pregnancy and lactation

4.7. Effects on ability to drive and use machines

None

4.8. Undesirable effects

Very rarely (<1/10,000) patients sensitive to the ingredients 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

Pharmacotherapeutic classification: A02BX 13. Other drugs for peptic ulcer and gastro-oesophageal reflux disease.

5.1. Pharmacodynamic properties

On ingestion Gaviscon Advance Tablets react 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 Gaviscon Advance Tablets 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

Mannitol
Calcium carbonate
Polyethylene glycol 20,000
Magnesium stearate
Aspartame
Mint flavour no. 3
Acesulfame potassium

6.2. Incompatibilities

Not applicable

6.3. Shelf life

MHRA PAR Gaviscon Advance Tablets PL 00063/0144
Two years

6.4. Special precautions for storage
Do not store above 30°C. Store in the original package.

6.5. Nature and contents of container
White, rigid, injection-moulded, polypropylene cylindrical tube with snap-bead neck finish packed into cartons.

Tube containing 20 tablets. One, two, three or four tubes in a carton.

Unprinted, glass-clear, thermoformable laminate of uPVC/PE/PVdC with aluminium foil lidding blisters packed into cartons.

Blister tray containing six individually sealed tablets. Two or four blister trays in a carton.

Not all pack sizes may be marketed.

6.6. Instruction for Use, Handling and Disposal
No special instructions.

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

8. MARKETING AUTHORISATION NUMBER(S)
PL 00063/0144

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
18/10/2006

Module 3
Product Information Leaflet

The product in question does not have a separate Product Information Leaflet, all of the information is included on the carton.
<table>
<thead>
<tr>
<th>Table</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Row 1</td>
<td>Data 1</td>
</tr>
<tr>
<td>Row 2</td>
<td>Data 2</td>
</tr>
<tr>
<td>Row 3</td>
<td>Data 3</td>
</tr>
</tbody>
</table>

Additional notes or comments:

- Note 1: Additional details.
- Note 2: Further information.
- Note 3: Important remarks.
Module 5

Scientific discussion during initial procedure

1. Introduction

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Gaviscon Advance Tablets, from Reckitt Benckiser Healthcare (UK) Limited for the treatment of symptoms of gastro-oesophageal reflux 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.

This application is a line extension to Gaviscon Advance, UK PL 00063/0097 (UK/H/222/01), an oral suspension for which the first MA was granted in the UK in 1996. The application is submitted under Article 10.1(b) of EEC Directive 2001/83/EC.

The product was granted marketed authorisations on 5 January 2005. With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder (Reckitt Benckiser Healthcare (UK) Limited) applied for marketing authorisations in Belgium, France, Ireland, Italy and The Netherlands.

Gaviscon Advance Tablets are available without prescription.

The UK delegate sought clarification and agreement from the MRFG on the legal basis for line extensions of a combination product, which had been granted authorisation under a fixed combination, Article 10.1 (b) legal basis, and whether a bibliographic application could be made for a combination product where the combination had not had ‘well-established’ use for at least 10 years. A number of member states indicated that the dossier for a fixed combination product was a full independent dossier and that a line extension can be made on any legal basis. A bibliographic application would be acceptable for the single substances but the data on the combination would come from studies carried out by the applicant, so the dossier would be a mixed dossier. A Commission member explained that the legal services opinion on bibliographic applications did not apply to chemical substances and that the Notice to Applicants advice still applied.

The marketing authorisation application can, therefore, be classified as a line extension and the marketing authorisation can be made on a bibliographic basis with a mixture of published data on the individual components and original data on the combination itself.

Problem statement

Gaviscon Advance Tablets were granted marketing authorisations in the United Kingdom on 5th January 2005. With the UK as the reference member state in this mutual recognition procedure (MRP), the Marketing Authorisation Holder, Reckitt Benckiser Healthcare (UK) Limited, is applying for marketing authorisations for Belgium, France, Ireland, Italy and The Netherlands.

About the product

Gaviscon Advance Tablets have been developed as a line extension of Gaviscon Advance, UK PL 00063/0097, an oral suspension for which the first MA was granted in the UK in 1996. Subsequently, marketing authorisations have been granted in Belgium, Germany, Ireland, Italy,
Netherlands, and Spain using MRP (UK/H/222/01), and also in Australia, New Zealand, South Africa and Switzerland.

The fundamental feature of the products is the formation of an alginate raft of near neutral pH which floats on the stomach contents. This raft either physically impedes reflux or, in severe cases, is itself preferentially refluxed into the oesophagus where it exerts a demulcent effect.

The raft is formed by the reaction of sodium alginate with gastric acid to form an alginic acid gel. This gel floats on top of the stomach contents by virtue of its reduced density resulting from entrapped carbon dioxide formed by the reaction of bicarbonate with gastric acid. Calcium ions in the formulation increase the raft strength by formation of cross-linkages between the alginate chains.

The development programme

The rationale for Gaviscon Advance Tablets was to develop a solid dosage format for delivery of 500mg sodium alginate that would have similar raft-forming capabilities to that of Gaviscon Advance and Liquid Gaviscon containing the same quantity of sodium alginate.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

No new preclinical studies were conducted, which is acceptable given that the application was made as a fixed combination under Article 10.1(b).

No clinical studies in patients have been carried out using Gaviscon Advance Tablets. The pharmacodynamic equivalence of Gaviscon Advance Tablets and Gaviscon Advance has been demonstrated in the findings of PD studies included in the marketing authorisation application. These data have been considered adequate to support the clinical efficacy and safety for Gaviscon Advance in the treatment of symptoms of GOR at comparable doses (in terms of sodium alginate content) to those proposed for Gaviscon Advance Tablets.

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. 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.

2. Quality aspects

GMP inspection

A copy of the Manufacturing Authorisation (ML/63/1, dated 24th August 2000, valid until 23rd August 2005) for the manufacturing, assembly and release site has been provided. Reckitt Benckiser Healthcare (UK) Limited, Dansom Lane, Hull, HU8 7DS, East Yorkshire, United Kingdom is responsible for the manufacture, assembly and release of the product. Pharmapac UK limited, Unit 20, Valley Road Business Park, Bidston, Merseyside, CH41 7EL, are an additional assembler of the product. These are the sites used for existing, licensed Gaviscon products. Manufacture is in accordance with the principles of Good Manufacturing Practice.

Introduction

This application is for a chewable tablet indicated for use in the symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn, indigestion occurring due to the reflux of stomach contents, for instance, after gastric surgery, as a result of a hiatus hernia, during pregnancy or
accompanying reflux oesophagitis. The application has been made under Article 10.1(b) of EEC Directive 2001/83/EC.

The application is considered a line extension, specifically the change or addition of a new pharmaceutical form. The drug substance ingredients (sodium alginate and potassium bicarbonate) in the proposed product, Gaviscon Advance Tablets, are the same qualitatively and quantitatively as those in Gaviscon Advance (oral suspension, PL 00063/0097). The excipients in the proposed product are qualitatively the same as those in Gaviscon Peppermint 500 Tablets (PL 00063/0136), apart from the proposed addition of Acesulfame K, an additional sweetener.

**Drug substance**

Sodium alginate is the subject of a Ph Eur Monograph.

A satisfactory specification for sodium alginate has been provided. The drug substance complies with the requirements of the Ph Eur monograph.

Batch analysis data has been provided for three batches, confirming compliance with the proposed specification.

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. Degradation of alginates results in depolymerisation of the chains to give shorter fragments. Physical properties of alginates are directly linked to the chemical structure of the biopolymer. As with all polymers there is a relationship between molecular weight and physical strength of the polymer. In the case of sodium alginate, physical properties are more dependent on the ratio and sequence of the D-mannuronate (M) and L-glucuronate (G) units than on the overall molecular weight. The likely consequence of depolymerisation would be changes in physical characteristics such as viscosity, gel strength and pH which are all controlled in the proposed specification for sodium alginate.

**Potassium bicarbonate**

Potassium bicarbonate complies with the Ph Eur monograph. The information provided is in compliance with the requirements for inorganic pharmacopoeial active ingredients given in the CPMP guideline ‘Requirements in Relation to Active Substances’ and is considered acceptable.

**Drug product**

**Composition**

The composition of the proposed product is given in the table below. Each tablet contains sodium alginate (500 mg) and potassium bicarbonate (100 mg).

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active constituents</td>
<td></td>
<td>Ph Eur</td>
</tr>
</tbody>
</table>
### Sodium alginate
- Raft forming agent
- Ph Eur

### Potassium bicarbonate
- Raft aerating agent
- Ph Eur

### Calcium carbonate
- Raft strengthening agent
- Ph Eur

### Mannitol
- Filler
- Ph Eur

### Polyethylene glycol 20,000
- Binder/ taste modifier
- Ph Eur

### Magnesium stearate
- Lubricant
- Ph Eur

### Mint flavour no.3
- Flavour
- RB

### Aspartame
- Sweetener
- Ph Eur

### Acesulfame K
- Sweetener
- Ph Eur

Processing aid: Purified water Ph Eur

RB = Reckitt Benckiser

The excipients selected were qualitatively the same as those used in Gaviscon Peppermint 500 Tablets (PL 00063/0136). Acesulfame K was added as an additional sweetener and Mint flavour No. 3 as a different flavouring agent than those used in other Gaviscon brands. Calcium carbonate is listed as an excipient (as in Gaviscon Advance oral suspension) rather than an active ingredient (as in Gaviscon 500 Peppermint Tablets).

### Pharmaceutical Development

The aim of development of Gaviscon Advance Tablets was to produce a solid dosage form of Gaviscon Advance oral suspension (PL 00063/0097), providing 500mg sodium alginate and 100mg potassium bicarbonate, so that two Gaviscon Advance Tablets give the same active concentration as a 10ml dose of Gaviscon Advance oral suspension.

As the tablets contain the same amount of active ingredients per dose as Gaviscon Advance suspension for which raft formation optimisation has already been established (through studies showing that it has non-inferior pharmacodynamic properties (raft forming and reflux suppressing abilities) to the suspension in healthy volunteers), further formulation development studies were not considered necessary. This is acceptable.

Tabletting was carried out during conventional rotary presses at pilot and production scale. The data obtained was then used to determine the in-process control parameters and FPS.

No further studies were performed on the product compatibility with the container closure system. However, data from stability studies support compatibility.

### Manufacture

**Outline of manufacture of bulk product**

All the raw materials are sieved.

**Tabletting blend**

The processing of the tabletting blend involves conventional wet granulation and blending.
**Tablets**
The powder mix is compressed into tablets on a suitable press.

**Prime Packaging**
The tablets are packed into either blisters or polypropylene packs.

**Outline of in-process controls**

**Mixed Powder**
(i) Materials are dispensed and checked for weight, material identity information and batch number information.
(ii) Mixing time is automatically monitored.

**Bulk Tablets**
(i) The tablets are tested for compliance with the regulatory specification.
(ii) At regular intervals during compression samples of the tablets are tested for weight variation and hardness variation.

**Prime Packaging**
At regular intervals during packaging, the packs are checked for fill weight and seal efficiency.

**Validation**
The process was appropriately validated. The data generated were generally consistent and complied with the proposed control specification. The process appears to be under control and provides a reproducible bulk product equivalent to the clinical study batch.

**Control of excipients**
Two representative Certificates of Analysis for each of the excipients have been provided, which are compliant with Ph Eur monographs, with the exception of mint flavour, which is controlled to in-house specifications.

A statement is provided that the mint flavour conforms to the requirements of Directive 88/388/EC relating to flavourings in foodstuffs. The composition has been provided.

An assurance has been provided that none of the ingredients of the product were prepared from materials of animal origin. The applicant states that the magnesium is vegetable grade.

**Control of Drug Product**
Satisfactory control tests are applied at time of release. Current batches of drug substance exhibit impurity limits generally below the limits of detection of their respective assays.

According to the Ph Eur general monograph on tablets, chewable tablets are not required to comply with the Ph Eur disintegration test.

Impurity testing is not performed. Degradation of sodium alginate results in depolymerisation of the chains to give shorter fragments, and consequently changes in the physical characteristics such as viscosity, gel strength and pH which are controlled in the specification for sodium alginate. Stability studies on products in the Gaviscon range have shown that hydrolysis of potassium bicarbonate is the most likely degradation reaction occurring in the drug product. Hydrolysis only
takes place in conditions of high humidity. Total carbon dioxide degradation is measured indirectly by the gasometric method and is required to be within the limits. This rationale has been applied and approved for Gaviscon Advance (PL 00063/0097) and Gaviscon Peppermint Tablets, and Gaviscon Peppermint Tablets 500 (PL 00063/0134, 0136).

The applicant does not propose to test for microbial contamination. This is satisfactory since the product is a dry tablet with low water activity (Aw). With the exception of sodium alginate all raw materials are chemically synthesised and pose no biological risk. Sodium alginate is supplied to a microbiological specification (total viable aerobic count, absence of E coli and salmonellae).

Microbial testing is not performed at release for existing Gaviscon products on the market [Gaviscon Peppermint Tablets, Gaviscon Peppermint Tablets 500 (PL 00063/0134, 0136)], this is acceptable.

The applicant states that a specification with a test method for raft formation as a product performance indicator is not relevant for the product, as all three active ingredients contribute to the formation of the raft and are all tested for in the Drug Product Specification. Sodium alginate forms an alginic acid in the stomach, potassium bicarbonate is used as the source of carbon dioxide to provide buoyancy for the alginate raft, and calcium carbonate is included as the source of calcium ions that cross-link the alginate molecules and increase raft strength. As this has been accepted for the existing products Gaviscon Peppermint Tablets, Gaviscon Peppermint Tablets 500 (PL 00063/0134, 0136) and Gaviscon Advance suspension (PL 00063/0097), this is acceptable.

The limits set for sodium alginate are the same as those set in existing Gaviscon products, this is acceptable.

Combined with the total carbon dioxide assay, the amount of calcium (as calcium carbonate) present in the product is also tested on release as a means of assuring the accuracy of potassium bicarbonate content.

Limits for water content at release and shelf life are acceptable.

Batch data for two production scale batches and one pilot scale batch demonstrate conformance to the proposed drug product specification.

All non-pharmacopoeial testing methods have been described and validated. The information provided is acceptable.

**Reference standards or materials**
A sodium alginate reference standard is used in the identification and content of sodium alginate, a Certificate of Analysis has been provided. Potassium bicarbonate and calcium carbonate reference standards are used in the total carbon dioxide test. Certificates of Analysis have been provided.

**Container closure system**
The chewable tablets are presented in uPVC/PE/PVdC plastic laminate with aluminium foil lidding push-through blisters containing six individually sealed tablets (2 or 4 blister trays in a carton), or in white polypropylene tubes containing 20 tablets with one, two, three or four tubes in a carton.
Assurance has been provided from the suppliers of the packaging materials that both packaging materials specified in the application are in compliance with Directive 90/128/EEC, with respect to their suitability for contact with food.

Specifications have been provided for all packaging materials, supported by Certificates of Analysis.

No compatibility studies with the primary packaging have been conducted, however results of stability studies under long term and accelerated conditions demonstrate the adequacy of the packaging.

**Stability**

Stability data were generated on full scale production and pilot size batches of product manufactured and stored in the intended packaging.

All stability results for all sub-batches, packaged in both blister and plastic tubes and over the three stability conditions are within specification limits and support a 2-year shelf-life.

The applicant justifies not performing any in-use stability studies on the product for the blister packed product, as the packs are ‘single dose units’ and the tablet will only be exposed to the environment immediately prior to consumption. For the product packaged in a tube, the product is a dry tablet with a low Aw and with the exception of sodium alginate, all raw materials are chemically synthesised and pose no microbiological risk. The sodium alginate is supplied to a microbiological specification. Data have been presented that support the view that contamination with environmental organisms throughout the in-use shelf-life of a multi-use container (e.g. tube) will not present spoilage problems due to lack of moisture. The tubes are not hygroscopic and will not actively absorb any moisture introduced throughout the product use, and the water is unlikely to increase significantly to a level where bacterial and fungal growth will be supported. Exposure to the environment each time the product is used will be very brief with the maximum number of doses in each tube being 20-24 tablets, thus restricting the length of time that the product will be exposed to any potential contamination.

**Summary of product characteristics**

Sections 1, 2, 3, 6, 7 of the SPC are similar in format as those for approved Gaviscon tablets, this is acceptable. Both 4.1 and 4.6 of the proposed SPC contain appropriate references to use of the product in pregnancy in line with other products in the Gaviscon range.

**Information about the experts**

The pharmaceutical expert report is of sufficient quality with regard to current European regulatory requirements.

**TSE Compliance**

Magnesium stearate is stated to be of vegetable grade.

**Quality overall summary**

The quality overall summary is an accurate reflection of the data provided.

**Pharmaceutical conclusions**

Marketing authorisation is recommended for this product.
3. **Pre-clinical aspects**

In view of the experience of use of the individual ingredients of the Gaviscon Advance Tablets and of the similarities to currently marketed Gaviscon products, it was not considered necessary for the applicant to perform any toxicological investigations with the Gaviscon Advance Tablet formulation. A comprehensive review of the published literature concerning sodium alginate was included in the Toxico-Pharmacological Expert Report submitted as part of the marketing authorisation application for Gaviscon Advance, UK PL 00063/0097, which has been reproduced in a slightly different format for the Non-Clinical Overview submitted for this application. The safety of the additional active ingredient, potassium bicarbonate, and of the excipients, has also been considered.

4. **Clinical aspects**

1. **INTRODUCTION**

This application is a line extension to Gaviscon Advance, UK PL 00063/0097. The application is submitted under Article 10.1(b) of EEC Directive 2001/83/EC.

2. **BACKGROUND**

Gaviscon Advance Tablets have been developed as a line extension of Gaviscon Advance, an oral suspension for which the first MA was granted in the UK in 1996. Subsequently, MAs have been granted in Belgium, Germany, Ireland, Italy, Netherlands, and Spain using MRP, and also in Australia, New Zealand, South Africa and Switzerland.

The rationale for Gaviscon Advance Tablets was to develop a solid dosage format for delivery of 500mg sodium alginate that would have similar raft-forming capabilities to that of Gaviscon Advance and Liquid Gaviscon containing the same quantity of sodium alginate.

Gaviscon Advance and Gaviscon Advance Tablets contain sodium alginate (500mg per 5ml per tablet), which forms an alginic acid gel in the stomach. Potassium bicarbonate is used in Gaviscon Advance Tablets as the source of carbon dioxide to provide buoyancy for the alginate raft. Calcium carbonate is also included in both products as the source of calcium ions, which cross-link the alginate molecules and increase the raft strength.

3. **INDICATIONS**

The proposed indications for Gaviscon Advance Tablets are those currently approved for Gaviscon Advance:

*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.*
4. **DOSE & DOSE SCHEDULE**

For both products, the recommended dose of alginate for adults and children over 12 years of age is 500-1000mg taken four times daily (after meals and at bedtime). This dose is provided by one to two Gaviscon Advance Tablets. It is recommended that both Gaviscon Advance and Gaviscon Advance Tablets should only be given to children under twelve years of age on medical advice. No limit is placed on the duration of treatment, although it is recommended that if symptoms of GOR do not improve within seven days, the clinical situation should be reviewed.

5. **TOXICOLOGY**

Not assessed.

6. **CLINICAL PHARMACOLOGY**

Gaviscon Advance Tablets are intended for use in the relief of symptoms of GOR at the same dosage (in terms of sodium alginate content) as Gaviscon Advance and Liquid Gaviscon. Since the mode of action of these products is physicochemical in nature, sodium alginate not being absorbed systemically but forming a raft within the stomach, pharmacokinetic bioequivalence studies are not considered appropriate to indicate clinical equivalence.

The aim of the clinical programme for Gaviscon Advance Tablets was to demonstrate that it has non-inferior pharmacodynamic properties (raft-forming and reflux suppressant abilities) to Gaviscon Advance and, hence, similar clinical efficacy to Gaviscon Advance when doses containing the same amount of sodium alginate are considered.

Two raft formation studies were performed covering the dosage range proposed for Gaviscon Advance Tablets; the first compared doses of Gaviscon Advance Tablets and Gaviscon Advance containing 500mg sodium alginate and the second compared doses containing 1000mg sodium alginate. A third study compared the reflux suppression capability of doses of Gaviscon Advance Tablets and Gaviscon Advance containing 1000mg sodium alginate. All three studies were performed in healthy subjects.

**Pharmacodynamics**

The fundamental feature of the products is the formation of an alginate raft of near neutral pH which floats on the stomach contents. This raft either physically impedes reflux or, in severe cases, is itself preferentially refluxed into the oesophagus where it exerts a demulcent effect.

In the Gaviscon Advance, Liquid Gaviscon and Gaviscon Advance Tablets formulations, the raft is formed by the reaction of sodium alginate with gastric acid to form an alginic acid gel. This gel floats on top of the stomach contents by virtue of its reduced density resulting from entrapped carbon dioxide formed by the reaction of bicarbonate with gastric acid. Calcium ions in the formulation increase the raft strength by formation of cross-linkages between the alginate chains.

**RAFT FORMATION**

Two studies (0106501 and 0106502) to investigate raft formation and duration were performed using Gaviscon Advance Tablets with the aim of demonstrating non-inferiority in comparison to Gaviscon Advance containing the same quantities of sodium alginate.
Study Methods

Both studies were open label, single dose, two-period crossover design and performed in healthy male adult subjects aged between 18 and 45 years. Study 0106501 compared doses of one Gaviscon Advance Tablet and 5ml Gaviscon Advance (500mg sodium alginate) and Study 0106502 compared two Gaviscon Advance Tablets and 10ml Gaviscon Advance (1000 mg sodium alginate).

An established gamma scientific technique was used to observe both a standard $^{99}$m-Tc labelled test meal and the $^{111}$In labelled study drugs during their residence in the stomach. Data was collected at 15 minute intervals over a 4-hour period following administration of the study drug and after correction for duration, background radiation and isotope decay was used to derive various parameters relating to the gastric retention, emptying times and distribution in the stomach of both the study drugs and corresponding test meals.

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 Gaviscon Advance Tablets in comparison to Gaviscon Advance was to be demonstrated by a de-transformed 95% Confidence Interval (CI) entirely above the non-inferiority limit of 0.8.

An open label design was employed since a tablet and liquid formulation were to be compared. It was not considered that this would adversely affect the outcome of the 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.

Power calculations determined that in order for the study to have 85% power to demonstrate non-inferiority of Gaviscon Advance Tablets in comparison to Gaviscon Advance, ten subjects would be required. Twelve subjects were to be recruited into each study to ensure that sufficient subjects completed both study days according to the protocol and were eligible for inclusion in the efficacy evaluable (EE) population. A total of 12 subjects were recruited into each study. All 12 subjects in study 0106502 completed both dosing days and 11 subjects in study 0106501 completed both dosing days.

Results

In both studies (0106501 and 0106502) gastric residence of both study drugs was significantly greater than that of the corresponding test meal in both the whole and upper 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.

It was considered that single doses of both one or two Gaviscon Advance Tablets and 5 or 10ml Gaviscon Advance formed a robust alginate raft which floated on top of the stomach contents and emptied after the test meal.

The gastric retention of Gaviscon Advance Tablets was not significantly different to that of Gaviscon Advance in either study.
In study 0106501 the 95% CI was 0.90-1.18 and in study 0106502 the 95% CI was 0.86-1.05. As both 95% CIs lie entirely above the pre-defined non-inferiority limit of 0.80, it was concluded that gastric retention of Gaviscon Advance Tablets is non-inferior to that of Gaviscon Advance at doses containing 500 mg and 1000 mg sodium alginate.

**REFLUX SUPPRESSION**

Study 0106503 to investigate reflux suppression was performed using Gaviscon Advance Tablets with the aim of demonstrating that a single dose of Gaviscon Advance Tablets was not inferior to a single dose of Gaviscon Advance containing the same quantity of sodium alginate in the suppression of GOR provoked by a standard meal.

**Study Methods**

The study was an open, single dose, three-period crossover design and performed in healthy male and female subjects aged between 18 and 65 years. The active doses compared were two Gaviscon Advance Tablets and 10 ml Gaviscon Advance (1000 mg sodium alginate). A non-active control (10 ml water) was also included.

Subjects ate a standard meal designed to provoke reflux and then received one of the study drugs. Ambulatory oesophageal pH monitoring, an established technique for assessing acid reflux, was used to record oesophageal pH at six second intervals over the 4-hour period following dosing. The data recorded were used to derive various parameters relating to oesophageal pH.

The primary efficacy parameter was the percentage of time for which the oesophageal pH was less than pH 4. Gaviscon Advance Tablets was to be deemed to be non-inferior to Gaviscon Advance if the upper 95% CI for the least squares adjusted mean difference in angular transformed percentage of time for which the oesophageal pH fell below pH 4 lay entirely below the non-inferiority limit of 0.056. To demonstrate the sensitivity of the method, a comparison of Gaviscon Advance with control was performed using a 5% significance test.

An open label design was employed since a tablet and liquid formulation were to be compared. It was not considered that this would adversely affect the outcome of the studies since the criteria for evaluation of reflux suppression were assessed objectively and could not be biased by either investigator or subject. A washout period of approximately 24 hours between study drugs was included to ensure that there was no likelihood of carryover effects.

Power calculations determined that in order for the study to have 80% power to determine non-inferiority of Gaviscon Advance Tablets versus Gaviscon Advance, 30 subjects would be required. A maximum of 36 subjects were to be randomised to ensure 30 would complete all three dosing days and be eligible for inclusion in the EE population. Subjects were to be eligible for randomisation if following an initial test meal their oesophageal pH was below pH 4 for at least 2% of the 4-hour measurement period. A total of 89 subjects attended for reflux screening of whom 36 were randomised and 35 completed the study. Data collected following dosing with all 3 study treatments for one completed subject and following dosing with Gaviscon Advance Tablets for a second completing subject were considered to be not evaluable and so were not included in the EE analysis.
Results

The least squares adjusted mean difference in angular transformed percentage of time for which the oesophageal pH fell below pH 4 was 0.019 with the 95% CI, at -0.0121- 0.0501, entirely below the non-inferiority limit of 0.056.

A single dose of two Gaviscon Advance Tablets was considered to be non-inferior to a single dose of 10ml Gaviscon Advance. This conclusion was supported by analysis of the secondary efficacy parameters; time for which the oesophageal pH was below pH 5 and the number of occasions on which oesophageal pH fell below pH 4 and pH 5.

The sensitivity of the method to differences between active treatment and control was demonstrated by a statistically significant difference between Gaviscon Advance and water in the mean angular transformed percentage of time for which the oesophageal pH fell below pH 4 and pH 5 and the number of occasions on which oesophageal pH fell below pH 4 and pH 5.

7. EFFICACY

No clinical studies in patients have been carried out using Gaviscon Advance Tablets. The pharmacodynamic equivalence of Gaviscon Advance Tablets and Gaviscon Advance has been demonstrated in the findings of PD studies included in the MAA. These data have been considered adequate to support the clinical efficacy and safety for Gaviscon Advance in the treatment of symptoms of GOR at comparable doses (in terms of sodium alginate content) to those proposed for Gaviscon Advance Tablets.

Two raft formation studies 0106501 and 0106502 were carried out using Gaviscon Advance Tablets with the aim of demonstrating non-inferior raft formation and duration for doses of Gaviscon Advance Tablets in comparison to Gaviscon Advance. The lower and higher doses of Gaviscon Advance Tablets, containing 500 mg and 1000 mg of sodium alginate respectively, were each compared with a dose of Gaviscon Advance containing the same amount of sodium alginate.

Both doses of Gaviscon Advance Tablets were shown to produce a robust raft which floated on top of, and emptied after, the stomach contents. In both cases retention in the stomach for Gaviscon Advance Tablets was shown to be non-inferior to that of Gaviscon Advance.

A reflux suppression study 0106503 was carried out with the aim of demonstrating that the higher dose of Gaviscon Advance Tablets, containing 1000 mg sodium alginate, was non-inferior to a dose of Gaviscon Advance containing the same quantity of sodium alginate in its ability to suppress GOR. Assessment of the frequency and severity of acid reflux by measurement of oesophageal pH confirmed that this was indeed the case.

The results of the raft formation study 0106502 indicated that a dose of Advance Tablets containing 1000 mg sodium alginate produces an alginate raft with non-inferior gastric retention compared to a 1000 mg dose of Gaviscon Advance, i.e., the same amount of sodium alginate.

The reflux suppression study 0106503 showed that, when the same doses were compared, Gaviscon Advance Tablets was non-inferior to Gaviscon Advance in ability to suppress GOR.
From these studies it is concluded that a single dose of two Gaviscon Advance Tablets (1000 mg sodium alginate) will be non-inferior to a single dose of 10 ml Gaviscon Advance in terms of clinical efficacy.

**OTHER EFFICACY DATA**

Clinical data provided in the MAA for Gaviscon Advance included two studies (0104601 and 0100901) which demonstrated the superiority compared to placebo of 5 ml (equivalent to one Gaviscon Advance Tablet) and 10 ml (equivalent to two Gaviscon Advance Tablets) doses of Gaviscon Advance taken four times daily. The 5 ml dose was taken for up to a fortnight and the 10 ml dose for up to four weeks.

**Assessor's Comment**

This is considered satisfactory. Studies in healthy volunteers have demonstrated that a dose of two Gaviscon Advance Tablets has pharmacodynamic properties that are non-inferior to 10 ml Gaviscon Advance. A one-tablet dose of Gaviscon Advance Tablets has pharmacodynamic properties that are non-inferior to 5 ml Gaviscon Advance.

The efficacy of 5-10ml doses of Gaviscon Advance 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.

In view of the PD and previous efficacy data, similar efficacy is probable from doses of one to two Gaviscon Advance Tablets.

**8. SAFETY**

No new or unexpected safety concerns are considered to arise from this marketing authorisation application.

**9. EXPERT REPORT**

A satisfactory clinical expert report has been provided with appropriate CV.

**10. SUMMARY OF PRODUCT CHARACTERISTICS**

The SPC is satisfactory and is consistent with Gaviscon Advance.

**11. DISCUSSION**

There is no clinical objection to the grant of a marketing authorisation. Adequate clinical pharmacology evidence to support efficacy. No new or unexpected safety concerns are foreseen.
5. **Overall conclusions**

This application is a line extension to Gaviscon Advance, UK PL 00063/0097 (UK/H/222/01), an oral suspension for which the first MA was granted in the UK in 1996. The application is submitted under Article 10.1(b) of EEC Directive 2001/83/EC.

No new efficacy or safety data have been included in the dossier, which is acceptable given that the application was made as a fixed combination under Article 10.1(b).

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SmPC includes all relevant warnings.

There are no pre-clinical concerns with this application or with the clinical use of Gaviscon Advance Tablets.
## Module 6

### Steps take after initial procedure

<table>
<thead>
<tr>
<th>Type of step</th>
<th>Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic safety update</td>
<td>PSUR 6 month</td>
<td>19/10/05</td>
</tr>
<tr>
<td>Pharmaceutical variation type IB</td>
<td>Change in name of the medicinal product in the UK.</td>
<td>18/05/2006</td>
</tr>
<tr>
<td>Pharmaceutical variation type II</td>
<td>Change to formulation excipients, macrogol 2000 and coolmint powder flavour trusil 131412 added, polyethylene glycol 20,000 and mint flavour no. 3 removed. Change to the shape and size of the polypropylene container, changing from a cylindrical tube to a cylinder container (tub). Only changes consequential to this application are approved on the livery.</td>
<td>27/08/2006</td>
</tr>
<tr>
<td>Medical variation type II</td>
<td>To bring the SPC in line with the SPC approved during the Mutual Recognition Procedure completed in Belgium, Italy and Ireland on 1st November 2005.</td>
<td>18/10/2006</td>
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