Public Assessment Report

UKPAR

Gaviscon Double Action Aniseed
(sodium alginate, sodium bicarbonate and calcium carbonate)

UK Licence No: PL 00063/0543

Reckitt Benckiser Healthcare (UK) Limited
LAY SUMMARY
Gaviscon Double Action Aniseed
(sodium alginate, sodium bicarbonate and calcium carbonate)

This is a summary of the Public Assessment Report (PAR) for Gaviscon Double Action Aniseed (PL 00063/0543). It explains how Gaviscon Double Action Aniseed was assessed and its authorisation recommended, as well as the condition of use. It is not intended to provide practical advice on how to use Gaviscon Double Action Aniseed.

For practical information about using Gaviscon Double Action Aniseed, patients should read the package leaflet or contact their doctor or pharmacist.

What is Gaviscon Double Action Aniseed and what is it used for?
This medicine is the same as Gaviscon Double Action Liquid, which is already authorised. The company (Reckitt Benckiser Healthcare (UK) Limited) referred to its own data provided for the grant of the licence for Gaviscon Double Action Liquid (PL 00063/0156) as a basis for the grant of the identical licence for Gaviscon Double Action Aniseed (PL 00063/0543).

Gaviscon Double Action Aniseed is used for the treatment of symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion which may occur, for example following meals or during pregnancy and for symptoms of excess stomach acid (hyperacidity).

How does Gaviscon Double Action Aniseed work?
Gaviscon Double Action Aniseed contains the active ingredients sodium alginate, sodium bicarbonate and calcium carbonate. These act to neutralise excess stomach acid to relieve pain and discomfort, and form a protective barrier over the stomach contents to soothe the burning pain in the chest.

How is Gaviscon Double Action Aniseed used?
Gaviscon Double Action Aniseed is taken orally. Patients should check that the cap seal is not broken before using this product.

Adults, elderly and children 12 years and over should take 10-20 ml (two to four 5ml spoonfuls) after meals and at bedtime, up to four times a day.

Children under 12 years old should only take this medicine on medical advice.

This product is available on a general sales licence (GSL).

For further information on how Gaviscon Double Action Aniseed is used, refer to the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Gaviscon Double Action Aniseed have been shown in studies?
Gaviscon Double Action Aniseed (PL 00063/0543) is considered to be identical to the previously authorised product, Gaviscon Double Action Liquid (PL 00063/0156), with the same benefits and risks, so, no new studies have been provided for Gaviscon Double Action Aniseed but reference is made to the studies for Gaviscon Double Action Liquid (PL 00063/0156).

What are the possible side effects of Gaviscon Double Action Aniseed?
Like all medicines, this medicine can cause side effects, although not everybody gets them.
For the full list of all side effects reported with Gaviscon Double Action Aniseed, see section 4 of the package leaflet.

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

**Why was Gaviscon Double Action Aniseed approved?**
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Gaviscon Double Action Aniseed outweigh its risks; and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Gaviscon Double Action Aniseed?**
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

**Other information about Gaviscon Double Action Aniseed**
A Marketing Authorisation was granted in the UK on 24 June 2008.

The full PAR for Gaviscon Double Action Aniseed follows this summary.

For more information about treatment with Gaviscon Double Action Aniseed, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation for the medicinal product Gaviscon Double Action Aniseed (PL 00063/0543) on 24 June 2008. This product is available on a general sales licence (GSL) for the treatment of symptoms resulting from the reflux of acid, bile and pepsin into the oesophagus such as acid regurgitation, heartburn and indigestion, for example following meals or during pregnancy, and for symptoms of excess stomach acid (hyperacidity).

It can also be used to treat the symptoms of gastro-oesophageal reflux during concomitant treatment with or following withdrawal of acid suppressing therapy.

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Gaviscon Double Action Liquid, authorised to Reckitt Benckiser Healthcare (UK) Limited (PL 00063/0156) on 26 January 2006.

The medicinal product is a combination of two antacids (calcium carbonate and sodium bicarbonate) and an alginate. Calcium carbonate neutralises gastric acid to provide fast relief from indigestion and heartburn. This effect is increased by the addition of sodium bicarbonate which also has a neutralising action.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product.

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

A detailed description of the pharmacovigilance system has been provided with this application and this is satisfactory.
II QUALITY ASPECTS

II.1 Introduction

This is a simple, informed consent application for Gaviscon Double Action Aniseed submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Gaviscon Double Action Liquid, which was originally approved to Reckitt Benckiser Healthcare (UK) Limited (PL 00063/0156) on 26 January 2006. The application is considered valid.

II.2. Drug Substance

Drug substance specification

The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3. Medicinal Product

Name

The proposed product name for this application is Gaviscon Double Action Aniseed. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size

The product contains sodium alginate, sodium bicarbonate and calcium carbonate. The finished product is packaged in amber glass bottles, sealed with a polypropylene cap and a tamper-evident polyethylene band (lined with expanded polyethylene wad). Pack sizes are 150 ml, 200 ml, 300 ml and 600 ml. The proposed shelf-life (2 years unopened and 6 months after opening) and storage conditions (“Do not freeze” and “Do not store above 30°C”) are consistent with the details registered for the cross-reference product.

Legal status

On approval, the product will be available on a general sales licence (GSL).

Marketing Authorisation Holder/Contact Persons/Company

Reckitt Benckiser Healthcare (UK) Limited, 1 Dansom Lane, Hull, HU8 7DS, United Kingdom.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturer

The proposed manufacturing site is consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

Qualitative and quantitative composition

The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification

The proposed finished product specification is in-line with the details registered for the cross-reference product.

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

This information is consistent with the cross-reference product.

Expert Report
The applicant has included detailed expert reports in Module 2 of the dossier. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Environmental Risk Assessment (ERA)
A suitable justification has been provided for not submitting an environmental risk assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Pharmacovigilance System
A satisfactory pharmacovigilance system has been provided to monitor the safety of this product.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In-line with current legislation, the applicant has also included the
name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
QUALITY
The data for this application are consistent with that previously assessed for the cross-reference product and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
This application is identical to a previously granted application for Gaviscon Double Action Liquid, which was originally approved to Reckitt Benckiser Healthcare (UK) Limited (PL 00063/0156) on 26 January 2006.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

BENEFIT /RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with sodium alginate, sodium bicarbonate and calcium carbonate is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

The approved labelling for Gaviscon Double Action Aniseed is presented below:
The following table lists non-safety variations of clinical significance to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>17/08/2015</td>
<td>Type II</td>
<td>To update sections 4.1 (Therapeutic indications) and 5.1 (Pharmacodynamic properties) of the SmPC in line with the Gaviscon Advance licences by including updates in three areas; Capping the acid pocket, Action of the product against bile and pepsin and Co-prescribing with Proton Pump Inhibitors.</td>
<td>Approved 18 April 2016</td>
</tr>
</tbody>
</table>
ANNEX 1

Our Reference: PL 00063/0543 – 0026
Product: Gaviscon Double Action Aniseed
Marketing Authorisation Holder: Reckitt Benckiser Healthcare (UK) Limited
Active Ingredient(s): Sodium alginate, sodium bicarbonate and calcium carbonate
Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To update sections 4.1 (Therapeutic indications) and 5.1 (Pharmacodynamic properties) of the SmPC in line with the Gaviscon Advance licences by including updates in three areas; Capping the acid pocket, Action of the product against bile and pepsin and Co-prescribing with Proton Pump Inhibitors.

Supporting Evidence
The applicant has provided updated sections of 4.1 and 5.1 of the SmPC. In addition, updates to capping the acid pocket, action of the product against bile and pepsin and co-prescribing with Proton Pump Inhibitors have been provided.

Evaluation
The amended sections of the SmPC are satisfactory.
1. Capping the Acid Pocket

An increase in postprandial acid reflux is a common feature of gastro-oesophageal reflux disease (GORD). Following a meal, the intra-gastric acidity is buffered by food. Throughout the different regions of the stomach, the pH increases to various levels, however this buffering effect is more evident in the centre of the gastric lumen than at the outer edge (Caparello et al. 2012; Fisher et al. 1997). An unbuffered pool of acid that floats on top of digested food is known as the "acid pocket" (Fletcher et al. 2001) forming as a consequence of inadequate mixing of newly secreted acid. The volume of the acid pocket is approximately 50-70 ml and has a pH of 1.7-2.5 (Beaumont et al. 2010). The region of acidity extends for 2-3 cm in the cardia across the squamocolumnar junction, a region that does not experience strong peristaltic contractions and thus mixing is less (Goetze et al. 2009). This acidified pool has a greater extension in GORD patients compared to healthy subjects; the acid pocket extends higher into the lower oesophageal sphincter (LOS) and distal oesophagus, particularly in patients with large hiatal hernias (Beaumont et al. 2010; Boeckxstaens and Rohof 2014; Clarke et al. 2008; Mittal et al. 1987; Pandolfino et al. 2007; Sloan and Kahnilas 1991). A large hiatal hernia can capture the acid pocket in the hiatal sac which increases reflux (Beaumont et al. 2010). The position of the acid pocket is known to be most relevant to the prevalence of GORD than the length. Supradiaphragmatic localisation of the acid pocket resulted in an increase in Transient Lower Oesophageal Sphincter Relaxations by 74-85% compared to 7-20% in the infradiaphragmatic location and increased acid reflux by 91% compared to 11% in the infradiaphragmatic location (Beaumont et al. 2010; Rohof et al. 2012).

Since recent evidence suggests the importance of the acid pocket in the pathogenesis of postprandial reflux and reflux symptoms, alginates, which raft forms in the proximal stomach, are an appropriate therapy for targeting postprandial acid reflux (Rohof et al. 2013; Sifrim and Penagini 2013). Alginates are natural polysaccharide polymers extracted from brown seaweed (Phacophycæae). Alginates are block co-polymers of L-guluronic and D-mannuronic acid residues which are connected by 1:4 glycosidic linkages. The relative proportions of D-mannuronic and L-guluronic acids are species-dependent and are dependent on growth conditions (Mandel et al. 2000).
Alginate preparations do not have a pharmacological action since their mode of action in the prevention of reflux is physical. Depending on the formulation, in the acidic environment of the stomach alginate salts and alginic acids precipitate to form a low density but viscous gel (Knight et al. 1988; May et al. 1984). The bicarbonate in the formulation reacts with the gastric acid to produce carbon dioxide, which becomes entrapped in the raft, increasing its buoyancy, so that the alginate gel floats on top of the stomach contents (Johnson et al. 1997; Johnson et al. 1998). Calcium salts are included in some products to increase raft strength by formation of calcium ion cross-linkages between the alginate chains (Davies et al. 1994; Grant et al. 1973; Malmud et al. 1979). The alginate raft prevents reflux due to its strength and cohesiveness; however it may also be refluxed, in place of gastric contents, into the oesophagus where it can form a barrier to protect the oesophageal mucosa from corrosive attack (McHardy and Balart 1972; Richardson et al. 2004; Richardson et al. 2005; Woodland et al. 2014).

A series of stepwise postprandial pH pull-thorugh studies using concurrent high resolution manometry, fluoroscopy and a symptom questionnaire assessed the ability of the alginate (Gaviscon Double Action Liquid) to neutralize and/or displace the acid pocket in 10 GORD patients (Kwiatek et al. 2011). Patients consumed a refluxogenic (high fat content) meal and 20 min postprandial, a pH pull through was completed. Patients swallowed a 20 ml dose of Gaviscon Double Action Liquid and the pull through protocol was repeated. The presence of GORD related symptoms were assessed by the Reflux Disease Questionnaire (RDQ) items in the fasted state, 20 min after consuming a high-fat meal and 20 min later after the ingestion of Gaviscon.

Overall, eight out of ten patients exhibited an acidified segment extending from the proximal stomach into the gastro-oesophageal junction (GOJ) when fasted that persisted post prandially. Gaviscon Double Action Liquid neutralised the acidified segment (area of pH<4) located in the proximal stomach in six out of eight patients in the study, and shifted the pH transition point away from the GOJ. The length and pressure of the GOJ high-pressure zone were minimally affected, suggesting the raft displaces the gastric contents away from the GOJ. In summary these data suggests Gaviscon Double Action Liquid forms a raft that caps the acid pocket which may reduce postprandial acid reflux.
A randomised parallel scintigraphy imaging study observed the alginate raft \textit{in vivo} in 16 patients (8 Gaviscon Double Action Liquid, 8 Antagel) with proven GORD (Rohof \textit{et al.} 2013). All patients had large hiatal hernia (greater than 3 cm). A 10 ml dose of Gaviscon Double Action has a neutralising capacity of approximately 10 mEq H\(^+\) and a 10 ml dose of Antagel has a neutralising capacity of 30 mEq H\(^+\). High resolution manometry and pH-impedance monitoring were placed \textit{in situ} to monitor reflux event frequency. A \(^{99m}\)Tc-pertechnetate solution enabled the acid distribution in the stomach to be visualised scintigraphically. Participants consumed a standardised meal and a 10 ml dose of either Gaviscon Double Action Liquid or Antagel (antacid containing 200 mg magnesium hydroxide and 400 mg aluminium oxide per 10 ml) (labelled with \(^{111}\)In). Patients received the meal (510 kcal) 10 min following positioning of the catheters, and administration of Gaviscon Double Action Liquid or Antagel 30 min following initial positioning of the catheter. Monitoring continued for 2 hours after meal commencement.

Localisation of the acid pocket and alginate raft are demonstrated in Figure 1. The radiolabeled acid pocket was scintigraphically visible in all patients within 15 min of meal ingestion. The \(^{111}\)In labelled Gaviscon Double Action Liquid formed a raft that was scintigraphically detected immediately after administration. The superimposed image of the Gaviscon Double Action Liquid and acid pocket demonstrated the co-localisation. The acid pocket and Gaviscon Double Action Liquid were visible for the duration of the 2 hour study.
Figure 1 Scintigraphic images of $^{99m}$Tc-pertechnetate–labelled acid pocket (A) and $^{111}$In-labeled alginate-antacid (B) and the two scintigraphic superimposed (recordings C).

The total number of reflux episodes was reduced with alginate-antacid ingestion compared to the antacid (median, 21 [15–27] vs. 14 [8.5–17], respectively; $P = 0.05$). The number of acid reflux episodes and the rate of acid reflux were also significantly lower after treatment with Gaviscon Double Action Liquid compared with antacid (15 [5.5–20] vs. 3.5 [0–6.5], $P = 0.03$ and 68 % [40 %–79 %] vs. 21 % [0 %–44 %], $P = 0.02$), and there was a trend toward reduced oesophageal acid exposure (7.4 [2.1–22] vs. 0.2 [0–4.1], $P = 0.08$). However, the number of weakly acid reflux episodes was not significantly different between Gaviscon Double Action Liquid and antacid (antacid 6 [6.0–7.5] vs. alginate-antacid 8 [6.0–13.0], $P = 0.38$). The time to acid reflux (antacid 14 min [9–23] vs. alginate-antacid 63 min [23–92], $P = 0.01$) and the mean pH of reflux episodes were significantly increased with Gaviscon Double Action Liquid compared to antacid (antacid 3.5 [2.0–5.0] vs. alginate-antacid 5.0 [4.1–6.2], $P < 0.05$). There was a trend that the acid pocket position was located below the diaphragm in 71 % of patients given Gaviscon Double Action Liquid compared to 21 % of those given antacid ($P = 0.08$). There was an inverse correlation between a subdiaphragm position of the acid pocket and acid reflux ($r = -0.76$, $P < .001$) suggesting the acid pocket positioning corresponded with a lower rate of acid reflux.
A randomised double-blind crossover study evaluated the effectiveness of Gaviscon Double Action Liquid compared to an antacid, with equivalent acid neutralising capacity (~18 mmol/L), in controlling post-prandial acid reflux in 14 GORD patients (De Ruigh et al. 2014). High-resolution manometry/ pH-impedance was conducted whilst a standardised meal (970kcal) was consumed. Gaviscon Double Action Liquid was dosed at 20 ml dose and Antacid Liquid Supreme CSV at 7.5 ml. The primary outcome was distal oesophageal acid exposure; secondary outcomes were number of reflux events, proximal extent of reflux, nadir pH of the refluxate, mechanism of reflux and reflux symptoms scored using a validated GerdQ instrument. Ten patients completed the study and results are outlined in Table 1. Gaviscon Double Action Liquid had significantly less distal oesophageal acid exposure and greater nadir refluxate pH in the 30-150 min post-prandial period than the antacid (P = 0.001). There was a trend in the number of acid reflux events, however this failed to reach statistical significance (P = 0.06). No differences in the total number of reflux events or the number of proximal reflux events were observed with either study medication.
Table 1 Post-prandial acid exposure and reflux data for Gaviscon Double Action Liquid and antacid.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Post-prandial acid exposure and reflux</th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Gaviscon</td>
<td>Antacid</td>
<td>P</td>
</tr>
<tr>
<td>Distal acid exposure: median % (IQR)</td>
<td>0.7 (0–28.2)</td>
<td>8.0 (0–7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of acid reflux events: mean ± S.E.M.</td>
<td>8.7 ± 3.0</td>
<td>12.4 ± 2.7</td>
<td>0.06</td>
</tr>
<tr>
<td>Total reflux events: mean ± S.E.M.</td>
<td>22.6 ± 4.9</td>
<td>25.1 ± 7.3</td>
<td>0.54</td>
</tr>
<tr>
<td>Proximal reflux events: mean ± S.E.M.</td>
<td>8.4 ± 4.4</td>
<td>6.4 ± 3.7</td>
<td>0.29</td>
</tr>
</tbody>
</table>

The mean nadir pH for each 30 min postprandial study period is demonstrated in Figure 2. At 60 min postprandial, the nadir pH was significantly greater in the Gaviscon Double Action Liquid group which was present until 150 min postprandially. Thus the oesophageal acid exposure was significantly reduced compared to antacid, which sinks to the distal stomach.

Figure 2 Mean nadir pH of refluxate during each 30-min post-prandial period during Gaviscon Double Action Liquid and antacid.
Gaviscon Advance has also been shown to act directly in the proximal stomach and form a mass at the gastro-oesophageal junction after a solid meal (Sweis et al. 2013). In summary, Gaviscon Double Action Liquid forms a raft that interacts with and caps the acid pocket displacing it distally (Rohof et al. 2013), and is consistent with the previous findings (Kwiatek et al. 2011). Additionally Gaviscon Double Action Liquid reduced the total number of acid reflux events. Gaviscon Double Action Liquid was more effective than antacid in controlling post-prandial oesophageal acid exposure. Data suggests Gaviscon Double Action Liquid co-localised with the acid pocket to displace and neutralise, and reduce oesophageal acid exposure (De Ruigh et al. 2014). Capping and displacement of the acid pocket distally, below the diaphragm, into a position similar to that of healthy subjects selectively decreased the number of acidic reflux episodes. Thus, alginates create a protective cover on top of the secreted acid which can be described as 'capping the acid pocket'.
2. Action of the Products against Bile and Pepsin

The refluxate that enters the oesophagus during GOR is composed of the contents of the stomach and also the duodenal contents that are refluxed into the stomach. These include gastric juice components (Acid (HCl), pepsins, mucus, bicarbonate, intrinsic factor, prostaglandins, histamine, gastrin, food and drink.) and duodenal reflux components (Bile acids and pancreatic enzymes).

Pepsin is the major enzyme in gastric juice. It is the active enzyme derived from the precursor pepsinogen, in acidic conditions (pH<5.5) autocatalysis of pepsinogen occurs to remove 44 amino acids and form the active enzyme pepsin. The concentration of pepsin in the stomach can reach 1 mg/ml (Ten Kate et al. 1988) and pepsin is frequently detected in oesophageal aspirates (Gotley et al. 1991).

The most damaging component of the gastric refluxate is pepsin, not acid. Acid alone (pH > 1.3) is unable to produce experimental damage to the oesophagus but the addition of pepsin to acidic solutions will result in significant damage equivalent to oesophagitis (Goldberg et al. 1969; Johnson and Harmon 1986; Salo et al. 1983; Tobey et al. 2001). Pepsin is maximally active at pH 2 but it remains active up to a pH of 5.5 and it is not irreversibly denatured until pH 8.0, therefore acid suppression is not the solution to overcome the proteolytic damage to the oesophagus (Johnson et al. 1997).

A postprandial increase in bile acid content within the proximal stomach has been recorded. One study observed the formation of a postprandial bile acid pocket in 50% of cases after 50 minutes (Boecxstaens 2011). Evidence shows that even if pepsin is exposed to pH 7 for 24 hours it retains 79% of its activity when it is returned to pH 3 (Johnston et al. 2007). There is therefore the potential for repetitive damage to tissues by pepsin as a result of multiple reflux events.

Alginates (Gaviscon Advance) have been shown to bind and trap pepsin and bile, potentially removing them from the refluxate. Alginates bind to oesophageal mucosa, interact with mucin (Batchelor et al. 2000; Richardson et al. 2004) and inhibit diffusion and activity of pepsin (Strugala et al. 2005; Tang et al. 2005).
Alginate (Gaviscon Advance) can inhibit pepsin activity as demonstrated in vitro using two distinct colorimetric assays (Strugala et al. 2009). The studies indicated that dilute solutions of Gaviscon Advance were able to inhibit pepsin activity completely in the Azocoll assay and by about three-quarters in the N-terminal assay. There was a strong dose-dependency exhibited. Alginate, the active ingredient in Gaviscon Advance has previously been shown to inhibit pepsin activity (Strugala et al. 2005) as has Carbopol (Foster et al. 1994), a non-active component. It appears that the superior pepsin inhibition of the Alginate product may be a consequence of having dual pepsin inhibiting roles perhaps through a synergistic interaction. Alginites therefore help to reduce the causticity of the refluxate and protect the oesophagus from damage whilst also reducing the enzymatic activity of pepsin.

It is clear that a reduction in the damaging capacity of pepsin in the refluxate is going to have a profound protective effect on the oesophagus. Alginites have a clear advantage over other treatments for GORD by abrogating the effect of the main damaging component of the refluxate, pepsin.

Gaviscon Advance, in the form of a small layer of formulation was shown to exhibit a considerable ability to retard the diffusion of pepsin (Strugala et al. 2009). Using a Franz cell model Gaviscon Advance reduced the amount of pepsin from the refluxate reaching the 'oesophageal cellular compartment' by approximately half. It could be concluded that an in vivo raft of substantial dimensions could have a greater ability to reduce pepsin diffusion.

It was shown that all of the pepsin in a 5 ml reflux event could be removed by the Gaviscon Advance raft thus preventing the enzyme reaching the oesophagus. Even after repeated reflux events a single Gaviscon Advance raft was capable of removing a large proportion of the pepsin in the reflux event (Strugala et al. 2009).

Importantly, Gaviscon Advance does not have any influence on normal physiology. Both pepsin and acid are essential components of the digestive process being essential for the initial digestion of food and also bactericidal action. The mode of action of Gaviscon Advance is such that it only affects pathological exposure of pepsin (and acid) to the oesophagus giving a distinct mode of action to all other therapeutic options for GORD which alter the gastric conditions.

Bile acids are another damaging agent in the refluxate as a consequence of gastro-oesophageal reflux. There have been several studies to investigate the damaging potential of bile acids at different pH levels. Bile acids are particularly implicated in the progression to Barrett's oesophagus and oesophageal adenocarcinoma. Suggested mechanisms by which bile acids cause damage to the oesophagus includes alteration to membrane permeability (Johnson and Hamon 1986), changes in cell proliferation and differentiation (Boni et al. 2006; Zhang et al. 2007), initiation of oxygen-derived free radicals, induction of DNA damage (Dvorak et al. 2007; Fein et al. 2007; Jenkins et al. 2008), and up-regulation of oncogenes (Jenkins et al. 2008; Tselepis et al. 2003).
It was shown that all of the bile acid in a 5 ml reflux event could be removed by the Gaviscon Advance (Aniseed Flavour) raft regardless of the bile acid investigated. Even after repeated reflux events a single Gaviscon Advance raft was capable of removing a large proportion of the bile acid in the reflux event. The Gaviscon Advance raft was therefore able to reduce the exposure of the oesophagus to bile acids and thus reduce the damage caused (Strugala et al. 2009).

In a Franz cell model a layer of Gaviscon Advance was able to completely block the passage of some bile acids from the refluxate and into an oesophageal cellular compartment. The product was efficient against conjugated bile acids such as taurocholic and glycocholic acids but not against unconjugated bile acids (cholic and deoxycholic acids). This suggests that the different physicochemical properties of the bile acids may influence their interaction with Gaviscon Advance. The conjugated bile acids are the predominant form found in the refluxate (Kauer et al. 1997, Nehra et al. 1999) and therefore Gaviscon Advance may be a specific inhibitor of this species (Strugala et al. 2009).

The experimental data indicates that Gaviscon Advance can specifically remove both pepsin and bile acids from the refluxate and limit the diffusion of these damaging agents. This gives Gaviscon Advance a clear role to play in reducing the causticity of the refluxate and protecting the oesophagus from damage. In addition, Gaviscon Advance has a strong ability to inhibit the enzymatic activity of pepsin thus giving a second mode of action to combat damage to the oesophagus in GORD.

Ex-vivo analysis of esophageal biopsies from patients with heartburn symptomist were used to evaluate the feasibility of an alginate-based topical mucosal protection In mini-Ussing chambers, the change in transepithelial electrical resistance (TER) of biopsies when exposed to neutral, weakly acidic, and acidic solutions was measured. Topical pretreatment with alginate (Gaviscon Advance) but not with control solutions prevented the acid-induced decrease in TER thus alginites provide a topical protection to acid (Woodland et al. 2013).

In summary, the anti-reflux product Gaviscon Double Action acts to suppress reflux in general and combats not only acid, but also pepsin and bile acids that are responsible for much of the damage to the oesophageal mucosa during GORD.
3. Co-prescribing with Proton Pump Inhibitors

The efficacy of proton pump inhibitors (PPIs) in healing oesophagitis is well established, however it is evident that PPI relief form symptomatic heartburn, regurgitation, chest pain, cough and laryngitis is less efficacious (Kahriias and Boeckxstaens 2012). It has been estimated that up to 45% of patients continue to experience symptoms whilst taking PPIs (El-Serag et al. 2010).

Patients with symptoms of gastro-oesophageal reflux disease or dyspepsia generally receive initial treatment with acid suppressing drugs, in particular PPIs, and it is common practice to treat patients with a higher dose of a PPI for an initial period of four to eight weeks. Patients then either continue to be maintained on lower doses of PPIs or stepped-off PPI therapy altogether, depending upon severity and frequency of symptoms. Alginaotes can also be applied as a rescue therapy during PPI step down/ step off therapy (Evans et al. 2007; Murie et al. 2012). Alginaotes can be successfully used to maintain satisfactory symptom control. Gaviscon Advance provided satisfactory symptom control for at least 10 months in up to 59% of patients who were stepped-off maintenance doses of PPIs (Cawston and Wood 2003). In a prospective study carried out in GP practices in England, 82.6% of patients were able to reduce or stop their PPI one year after alginate intervention (Connolly et al. 2009). A recent survey of Spanish Primary Care Practitioners (PCP) indicates that they believe treatment with a PPI alone is not sufficient for the control of GORD symptoms (de Argila et al. 2014). The combination treatment of PPI and alginate-antacids was recommended by 37% for treating heartburn, and by 21% for regurgitation. A better control of symptoms, an increase in the onset of action, and reduction of nocturnal acid breakthrough were the most frequent reasons for combination treatment.

During treatment with PPIs, a significant proportion of patients, possibly up to 70% depending upon the PPI used, will experience "acid breakthrough", particularly at night (Fouda et al. 1999; Katz et al. 1998; Katz et al. 2000; Nathoo 2001; Robinson 2000; TYTGAT 2001). Of these, a significant proportion will experience recurrence of painful symptoms such as heartburn and indigestion (Nzeako and Murray 2002) which may require treatment with additional medication such as alginate-based reflux suppressants such as Gaviscon Double Action.

Alginaotes (Gaviscon Advance) do not have an effect of the bioavailability of omeprazole (Dettmar et al. 2006a). Although alginaotes rely on an acidic environment for their mode of action, studies have shown that concomitant use of acid suppressing drugs, either PPIs or H2-receptor antagonists, do not prevent alginate products from forming the "raft" essential for its therapeutic activity (Dettmar et al. 2005; Washington et al. 1993).
A measure of oesophageal and gastric pH showed alginates (Liquid Gaviscon) are significantly superior to control, ranitidine and omeprazole in immediately reducing gastro-oesophageal reflux into the oesophagus and gastric acidity during the first hour (Dettmar et al. 2006b). Ranitidine showed a superior effect from 2 h, consistent with its pharmacological mode of action (Dettmar et al. 2006b). Alginate (Liquid Gaviscon) was non-inferior to omeprazole in achieving a 24 h heartburn-free period in moderate episodic heartburn (Pouchain et al. 2012). Seventeen (12.6%) of the 135 patients in the alginate group experienced at least one AE during the study. Sodium alginate suspension (50 mg/ml) was as effective as omeprazole for symptomatic relief in a four-week study of patients with non-erosive reflux disease (Chiu et al. 2013). The severity of all adverse events was mild or moderate, no severe adverse events were reported during the study period. Sodium alginate combined with omeprazole was better than omeprazole alone in complete resolution of heartburn for at least seven consecutive days, in a study of Japanese patients with non-erosive reflux disease (Manabe et al. 2012). Treatment with omeprazole and sodium alginate was well tolerated.

Pilot Study GA1214 evaluated the efficacy of Gaviscon Double Action Mint compared with matched placebo liquid in the suppression of GORD symptoms in 52 patients whose symptoms were inadequately controlled by once-daily PPI therapy alone (GA1214 2013). Efficacy assessments were based on the HRDQ and ReQuest patient questionnaires. The primary efficacy variable was the change in HRDQ score (heartburn and regurgitation combined; mean over the 7 days of treatment, hereafter referred to as post-baseline) from baseline (mean over the 7 days of run-in) and was compared between the two treatment groups (placebo vs. Gaviscon Double Action Mint). A decrease in the HRDQ scores (heartburn and regurgitation combined) from baseline to post-baseline was observed in both the placebo and the Gaviscon Double Action Mint groups. The mean (SD) change in the HRDQ score was -3.70 (4.22) for patients in the placebo group and -5.72 (3.52) for patients in the Gaviscon Double Action Mint group. Results of an ANCOVA model revealed significant least square (LS) Mean reductions in the respective scores from baseline in both treatment groups with p-values each < 0.0001. This reduction in the HRDQ score was significantly greater for patients in the Gaviscon Double Action Mint group than for patients in the placebo group (LS Mean difference = -2.10 in favour of Gaviscon Double Action Mint, p = 0.0120). The study patients receive a greater benefit from a 4 times daily treatment regimen with Gaviscon Double Action Mint than with placebo in terms of suppressing GORD symptoms over and above the benefits from taking their PPI. However, there was also a significant relief from the core GORD symptoms in response to placebo treatment. None of the patients withdrew from the study, and patient compliance was high. No unexpected or new safety signals for Gaviscon Double Action Mint were observed in this pilot study.
Conclusion

The changes are acceptable, given that the evidence above supports them with published literature and studies conducted by the marketing authorisation holder (MAH). These data use a mixture of combinations with different active substances, however enough studies are conducted with the combination relevant to this licence that the changes are acceptable. It would also be expected that the likely efficacy would be similar across the combinations given the mode of action.

Pilot Study GA1102 was a multi-centre, randomised, placebo-controlled, double-blind trial with a pre-study treatment run-in period (GA1102 2013). The study evaluated Gaviscon Advance and matched placebo as add on treatments in GORD patients with persistent symptoms of GORD, despite taking a PPI once daily for at least 4 weeks. Symptoms of GORD were assessed using patient self-assessment questionnaires. Efficacy data were obtained from the heartburn regurgitation and dyspepsia questionnaire (HRDQ) and ReQuest questionnaires as well as from the visual analogue scale (VAS) for patient’s satisfaction recorded in the case report form (CRF). In total 138 patients were evaluated for safety, 134 for ITT and 106 for PP. The primary endpoint was the change in HRDQ [heartburn and regurgitation only] score (mean over the 7 days of treatment) from baseline (mean over the 7 days of run-in) which was analysed using an analysis of covariance (ANCOVA). The mean change in HRDQ score (heartburn and regurgitation combined) from baseline to post-dose was statistically significantly greater for Gaviscon Advance (-4.95, SD 4.89) than for placebo (-3.48, SD 5.51) in the ITT population (LS Mean difference -1.64 [95% CI -3.13, -0.14], p = 0.0321). When the ANCOVA was performed (i) without centre as effect and (ii) with the centre by treatment interaction added, p-values of p = 0.0143 and 0.0084, respectively, were obtained, confirming the robustness of the primary analysis. In addition, there was no evidence of a treatment-by-centre interaction (p = 0.5316). For the PP population, the mean change in HRDQ score (heartburn and regurgitation combined) from baseline to post-dose was greater for Gaviscon Advance (-5.45, SD 4.96) than for placebo (-3.81, SD 5.32) but the LS Mean difference (-1.57 [95% CI -3.27, 0.13]) was not statistically significant (p = 0.0696). When the ANCOVA was performed (i) without centre as effect and (ii) with the centre by treatment interaction added, p-values of 0.0343 and 0.0899, respectively, were obtained. Again, there was no evidence of a treatment-by-centre interaction (p = 0.8965). The incidence of adverse events in GA1102 was similar for Gaviscon Advance and placebo and, as with GA1214, no safety concerns were raised. In summary, the study demonstrated that Gaviscon Advance is more efficacious than placebo in suppressing the GORD symptoms of heartburn and regurgitation, when given as add-on therapy in patients with inadequate response to once daily PPI.

In conclusion, Gaviscon Double Action is suitable for the treatment of acid breakthrough symptoms in patients currently being treated with PPIs or patients involved in PPI step-down or step-off programmes.
The variation was approved on 18 April 2016 and the updated SmPC fragments have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

Following approval of the variation on 18 April 2016 the SmPC was updated. In accordance with Directive 2010/84/EU, the current granted UK SmPC and PIL are available on the MHRA website.