COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gaviscon Duo kauwtabletten, chewable tablets (sodium alginate, sodium bicarbonate, calcium carbonate)

NL/H/4534/001/DC

Date: 27 February 2023

This module reflects the scientific discussion for the approval of Gaviscon Duo kauwtabletten, chewable tablets. The procedure was finalised in the United Kingdom (UK/H/1143/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

GAVISCON DOUBLE ACTION TABLETS
PL 00063/0157

UKPAR

TABLE OF CONTENTS

GAVISCON DOUBLE ACTION TABLETS
PL 00063/0157

LAY SUMMARY

The MHRA today granted Reckitt Benckiser Healthcare (UK) Limited a Marketing Authorisation (licence) for the medicinal product Gaviscon Double Action Tablets (PL 00063/0157). This is a medicine for general sale to the public for the treatment of gastro-oesophageal reflux, such as acid regurgitation, heartburn and indigestion, and for symptoms of excess stomach acid (hyperacidity).

Gaviscon Double Action Tablets contains the active ingredients sodium alginate, sodium bicarbonate and calcium carbonate.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Gaviscon Double Action Tablets outweighed the risks, hence a Marketing Authorisation has been granted.

GAVISCON DOUBLE ACTION TABLETS
PL 00063/0157

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Gaviscon Double Action Tablets to Reckitt Benckiser Healthcare (UK) Limited (PL 00063/0157) on 26th January 2006. The products are available for general sales.

The application was submitted as a standard abridged application according to Article 10.a of Directive 2001/83/EC, a bibliographic application.

These mint flavoured, chewable tablets contain the active ingredients sodium alginate, sodium bicarbonate and calcium carbonate and is indicated for the treatment of gastro-oesophageal reflux, such as acid regurgitation, heartburn and indigestion, and for symptoms of excess stomach acid (hyperacidity). The mode of action is physical and does not depend on absorption.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Sodium Alginate

Sodium alginate is the subject of a Ph Eur Monograph and the same grade of material has been used in other formulations of Gaviscon.

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

A satisfactory specification for sodium alginate has been provided. The drug substance complies with the requirements of the Ph Eur monograph. The specification tests have been adequately justified and are the same for other Gaviscon products.

Batch analysis data have been provided and comply with the proposed specification.

Stability of sodium alginate is acceptable.

Sodium bicarbonate

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

Sodium bicarbonate is adequately controlled by the Ph Eur monograph.

Batch analysis data have been provided and comply with the proposed specification.

Calcium carbonate

Calcium carbonate is the subject of a Ph Eur Monograph.

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

A satisfactory specification for calcium carbonate has been provided. The drug substance complies with the requirements of the Ph Eur monograph and is the same as other licensed Gaviscon preparations.

Batch analysis data have been provided and comply with the proposed specification.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely mannitol, polyethylene glycol, magnesium stearate, mint flavouring, acesulfame K, aspartame, carmoisine lake 11012 and copovidonum.

With the exception of peppermint flavour and the colouring agent carmoisine lake 11012, all excipients comply with their respective Ph Eur monograph. Mint flavour is satisfactorily controlled by an in-house specification and conforms to the requirements of Directive 88/388/EC relating to flavourings in foodstuffs. Carmoisine lake 11012 complies with foodstuffs directive 94/36/EC.

Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

The finished product is presented in glass-clear uPVC/ PE/ PVdC with aluminium foil lidding push-through blisters containing 4, 6 or 8 sealed tablets. Larger packs (16, 24, 32, 48, 60, 62, 64 and 80) will be made up of multiples of the above units. The packaging components are said to comply with Directive 90/128/EEC with respect to their suitability for contact with food. Adequate specifications for all packaging have been provided and certificates of analysis have been provided showing compliance with these specifications.

Manufacture
A copy of the relevant manufacturing authorisation from the finished product manufacturer has been supplied. A satisfactory batch formula for the manufacture of the maximum batch size has been provided.

A satisfactory method of manufacture has been provided, with adequate in-process controls and limits set. The manufacturing process is straightforward using standard techniques.

Results of pilot scale validation studies have been provided and are satisfactory.

Control of drug product
The finished product specifications at both release and shelf-life are satisfactory. Analytical methods used are satisfactory and have been suitably validated. Satisfactory batch analysis data have been provided, showing compliance with the proposed release specification.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, which is satisfactory. The precautions ‘Store in the original packaging’ and ‘do not store above 30°C’ have been included.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

The application was submitted as a standard abridged application according to Article 10.a of Directive 2001/83/EC, a bibliographic application. Therefore, no new preclinical data have been submitted and none are required for this type of application.

CLINICAL ASSESSMENT

INDICATIONS

These are for the treatment of the symptoms of gastrooesophageal reflex such as acid regurgitation, heartburn and indigestion following meals or during pregnancy and for symptoms of excess stomach acid (hyperacidity).

DOSE AND DOSE SCHEDULE

The tablets should be thoroughly chewed. In anyone over the age of 12 years two to four tablets may be taken after meals and at bedtime. The tablets should only be given to children under 12 years on medical advice.

TOXICOLOGY

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

CLINICA L PHARMACOLOGY

On ingestion, the tablets react rapidly with gastric acid to form a raft of alginic acid gel which has a nearly neutral pH. This floats on the stomach contents, impeding gastrooesophageal reflux. In severe cases, the raft itself may reflux into the oesophagus, having a demulcent effect. At the same time, calcium carbonate neutralises the gastric acid, this effect being enhanced by the sodium bicarbonate also present. The total neutralising capacity of the product at the lowest dose is approximately 10m Eq H+.

The mode of action of Gaviscon Double Action tablets is physical and does not depend on absorption into the systemic circulation.

As the preclinical expert (also the clinical expert) states in his overview, the mode of action of Gaviscon products is to impede reflux by the formation of an alginate raft which floats on the surface of the stomach contents. The other ingredient vital for formation of the raft is sodium bicarbonate, which acts as a source of carbon dioxide to provide buoyancy. Calcium carbonate provides a source of calcium ions which cross-link the alginate molecules and increase the raft strength. In addition, calcium carbonate and sodium bicarbonate have a neutralising effect on gastric acid. The level of calcium carbonate is increased in these tablets compared with other Gaviscon formulations in order to provide increased acid neutralising capacity.

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

The action of alginate in preventing reflux, or in severe cases being itself refluxed into the oesophagus and exerting a demulcent effect, results in relief of symptoms of gastric reflux and additionally may prevent further attack of the oesophageal mucosa, allowing healing to take

place. Efficacy of alginate treatment has been shown both in clinical trials and long-term experience of everyday use.

The aim of the development of these tablets and liquid was to produce an effective alginate-containing product which also delivers levels of acid neutralising capacity equivalent to other marketed antacid products.

Pharmacodunamics

Raft formation

A randomised, open, three-way crossover study was performed to investigate the formulation and retention of alginate rafts assessed by gamma scintigraphy, in healthy volunteers (males, aged 18-45 years), following administration of single doses of the test liquid (10ml, 500mg sodium alginate) and tablets (2x250mg) and liquid Gaviscon (10ml, 500g sodium alginate) An established gamma scintigraphic technique was used. Data was collected at 15 minute intervals over 4 hours and used to derive parameters relating to gastric emptying, etc.

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

From the results, it was deemed that both the test liquid and tablets (x2) had non -inferior gastric retention to Gaviscon liquid 10ml.

Pharmacokinetics

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

EFFICACY

The raft formulation study already referred to showed that both the test liquid and tablets produced robust rafts which floated on top of, and emptied after, the stomach contents. Retention in the stomach was shown to be non-inferior to liquid Gaviscon. Based on previous studies detailed by the Company, a 1000mg sodium alginate dose would be at least equally effective. Thus, in terms of clinical efficacy, a single dose of 2 or 4 of the test tablets, or 10ml or 20ml of the test liquid (500mg or 1000mg sodium alginate) can be expected to be non-inferior to a single dose of 10ml or 20ml Gaviscon Liquid.

However, the tablets and liquid are indicated, apart from the treatment of symptoms of gastro-oesophaged reflux, for symptoms of excess stomach acid (hyperacidity). This is addressed in the expert report with the brief statement that 'In addition, calcium carbonate and sodium bicarbonate have a neutralising capacity, but remains within acceptable daily limits'. In fact the amount of calcium carbonate is at least doubled (from 160mg to 325mg in the liquid or 375mg with 2x250mg tablets)

SAFETY

Calcium-containing antacids can induce rebound acid secretion, while prolonged high doses cause hypercalcaemia and alkalosis and may precipitate the milk-alkali syndrome. This whole subject would benefit from being addressed more fully by the clinical expert, despite the claim

that 'appropriate precautions and warnings regarding patient groups more likely to experience adverse events are provided in the SmPC'. The brief paragraphs provided would benefit from an in-depth expansion to provide adequate reassurance in these areas of concern.

The safety of sodium alginate has been discussed in detail -and is not really in doubt.

EXPERT REPORTS

The clinical expert report outlines most of the issues adequately. However far greater attention will need to be given to the higher calcium carbonate content. The author of the expert report is appropriately qualified.

SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory.

PATIENT INFORMATION LEAFLET AND LABEL

This is satisfactory.

MAA

The Marketing Authorisation Application is satisfactory.

DISCUSSION

The data presented are satisfactory for the granting of a product licence.

RECOMMENDATION

A product licence may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Gaviscon Double Action Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

No new or unexpected safety concerns arise from this application.

The SPC and PIL are satisfactory and consistent with that for the reference products.

RISK BENEFIT ASSESSMENT

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

GAVISCON DOUBLE ACTION TABLETS
PL 00063/0157

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 12th July 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 4th August 2004
3	Additional pharmaceutical information was requested from the applicant on 18th February 2005 and 27th July 2005
4	Additional clinical information was requested on 29th March 2005
5	Additional clinical information was provided on 27th April 2005
6.	Additional pharmaceutical information was provided on 14th July 2005 and 12th December 2005
7.	The applications were determined on 26th January 2006

GAVISCON DOUBLE ACTION TABLETS
PL 00063/0157

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gaviscon Double Action Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sodium alginate 250 mg, sodium bicarbonate 106.5 mg and calcium carbonate 187.5 mg.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

A flat, circular, bi-layer tablet with bevelled edges. One layer of the tablet is pink and slightly mottled, and the other white.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion, for example following meals or during pregnancy, and for symptoms of excess stomach acid (hyperacidity).

4.2. Posology and method of administration

For oral administration, after being thoroughly chewed.

Adults and children 12 years and over: Two to four tablets after meals and at bedtime, up to four times per day.

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 four-tablet dose is 221.5 mg (9.64 mmol). This should be taken into account when a highly restricted salt diet is recommended, e.g. in some cases of congestive cardiac failure and renal impairment.

Each four-tablet dose contains 300 mg (7.5 mmol) of calcium. 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.

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. Interaction with other medicinal products and other forms of interaction
None known.

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

4.7. Effect on ability to drive and use machines
Not relevant.

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.

Ingestion of large quantities of calcium carbonate may cause alkalosis, hypercalcaemia, acid rebound, milk alkali syndrome or constipation. These usually occur following larger than recommended dosages

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: A02BX, Other drugs for peptic ulcer and gastro-oesophageal reflux disease.

The medicinal product is a combination of two antacids (calcium carbonate and sodium bicarbonate) and an alginate.

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

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. The total neutralising capacity of the product at the lowest dose of two tablets is approximately 10 $mEqH^+$.

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

5.3. Pre-clinical safety data
No pre-clinical findings of any relevance to the prescriber have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Macrogol 20,000
Mannitol (E421)
Copovidone
Acesulfame K
Aspartame (E951)
Mint Flavour
Carmoisine Lake (E122)

6.2. Incompatibilities
Not applicable.

6.3. Shelf-life
2 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
Unprinted, glass, clear, thermoformable laminate of uPVC/PE/PVdC with aluminium foil lidding blisters packed into cartons.

Blister tray containing two, four, six or eight sealed tablets. Pack sizes: 4, 6, 8, 16, 24, 32, 48, 60, 62, 64 and 80 chewable tablets.

Not all pack sizes may be marketed.

6.6. Instructions for use and handling
No special instructions.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 00063/0157

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/01/2006

10 DATE OF REVISION OF THE TEXT

26/01/2006

⠠⠝⠁⠍⠑ ⠠⠁⠝⠙ ⠠⠎⠞⠗⠑⠝⠛⠞⠓ ⠠⠕⠋ ⠠⠍⠁⠞⠑⠗⠊⠁⠇

Gaviscon Double Action Tablets


GAVISCON
DOUBLE ACTION TABLETS
16 CHEWABLE TABLETS
NEW
GAVISCON
DOUBLE ACTION
TABLETS
FAST POWERFUL RELIEF
Heartburn AND Indigestion
Long Lasting
16
GAVISCON
DOUBLE ACTION TABLETS
16 CHEWABLE TABLETS
RB000745
BN
EXP
Do not use after expiry date shown.
Gaviscon Double Action peppermint tablets bring fast soothing and long lasting relief from the pain and discomfort of heartburn and acid indigestion. They get to work in two different ways:
1) neutralising excess stomach acid to relieve discomfort.
2) forming a protective barrier over the stomach contents to soothe that burning pain in your chest.
So whatever your symptoms of heartburn or indigestion Gaviscon Double Action can provide fast soothing relief.
What are these tablets? Each chewable tablet contains 250 mg sodium alginate, 106.5mg sodium bicarbonate and 187.5mg calcium carbonate as the active ingredients. It also contains mannitol (E421), copovidone, acesulfame-K, aspartame (E951), mint flavour and carmoisine lake (E122). These tablets are sugar and gluten free. You can take this product if you are pregnant or breast feeding.
Dosage: For oral administration. Adults and children over 12 years: When symptoms occur take two to four tablets after meals and at bedtime, up to four times a day. Chew thoroughly before swallowing. Children under 12 years: Not to be given unless recommended by your doctor.
Before taking this product: Each four tablet dose contains 9.64 mmol sodium and 7.5 mmol calcium. If you have been advised a diet restricted in any of these please ask your doctor before taking this product. If you have phenylketonuria, note that the product is sweetened with aspartame, a source of phenylalanine. Do not take this product if you know you are allergic to any of the ingredients as very rarely difficulty in breathing and skin rashes have occurred. Contains carmoisine lake (E122) which may cause allergic reactions. Consult your doctor if you experience these or any other side effects.
After taking this product: If symptoms persist after 7 days consult your doctor. If you take too many tablets you may feel bloated. It is unlikely to cause you any harm, but please consult your doctor or pharmacist. If you forget a dose, it is not necessary to double the dose next time. Just carry on taking as before. Do not store above 30°C. Store in the original package.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN. Do not use this medicine after the expiry date (EXP: month/year) shown. Date of preparation MM/YYYY.
Manufacturer and Product Licence Holder in UK:
Reckitt Benckiser Healthcare (UK) Limited, Hull, HU8 7DS.
Export Distributors: Reckitt & Colman (Overseas) Ltd.,
Hull HU8 7DS, U.K.
PL 00063/157
Gaviscon and are trademarks