COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gaviscon Duo muntsmaak, oral suspension in sachet (sodium alginate, sodium hydrogen carbonate & calcium carbonate)

NL/H/4535/002/DC

Date: 9 February 2026

This module reflects the scientific discussion for the approval of Gaviscon Duo muntsmaak, oral suspension in sachet. The procedure was finalised on 26 July 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CP	Chronic Phase
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gaviscon Duo muntsmaak, oral suspension in sachet, from Reckitt Benckiser Healthcare B.V.

The product is indicated for: the treatment of acid related symptoms of gastro-oesophageal reflux such as acid regurgitation, heartburn and indigestion, for example following meals or during pregnancy.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, which concerns a well-established use application.

For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

This decentralised procedure concerns a line-extension application of the current marketing authorisation for Gaviscon Duo sachets, an oral suspension in sachets, containing 500 mg of sodium alginate, 213 mg of sodium bicarbonate and 325 mg of calcium carbonate per 10 ml, (RVG 109769) marketed by Reckitt Benckiser Healthcare BV and authorized in 2012 by means of decentralised procedure (UK/H/3493/001, later converted into NL/H/4535/001).

Gaviscon DA oral suspension has been authorised for marketing based on a well-established use legal base (Article 10a) in December 2012 by means of decentralised procedure (UK/H/3493/001, later converted into NL/H/4535/001). Current line-extension procedure has the same legal base and aims to add an additional formulation (oral suspension).

The concerned member state (CMS) involved in this procedure was Italy.

II. QUALITY ASPECTS

II.1 Introduction

Gaviscon Duo muntsmaak is an oral suspension. It is an opaque, off white to cream suspension with the odour and flavour of peppermint. Each 10 ml dose contains as active substance 500 mg of sodium alginate, 213 mg of sodium bicarbonate and 325 mg of calcium carbonate.

The excipients are: carbomer 974P, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), saccharin sodium, peppermint flavour (containing propylene glycol (E1520)), sodium hydroxide and purified water.

The oral suspension is packed in amber glass bottles, or pink coated amber glass bottles, with a polypropylene cap with a polyethylene tamper-evident band lined with expanded polyethylene wad.

II.2 Drug Substance

The active substances are sodium alginate, sodium hydrogen carbonate and calcium carbonate. All three active substances are established and described in the European Pharmacopoeia (Ph.Eur.).

Sodium alginate is a white or pale-yellowish-brown powder. It slowly dissolves in water forming a viscous, colloidal solution, practically insoluble in ethanol (96%).

Calcium carbonate is a white or almost white powder. It is practically insoluble in water.

Sodium hydrogen carbonate is a white or almost white, crystalline powder. It is soluble in water and practically insoluble in ethanol (96%).

The CEP procedure is used for all three active substances. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted for each active substance; therefore no details on the manufacturing process have been included.

Quality control of drug substance

All active substance specifications are considered adequate to control the quality and meet the requirements of the respective monographs in the Ph.Eur. and CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches for each active substance.

Stability of drug substance

Sodium alginate

The active substance is stable for 12 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Sodium hydrogen carbonate

The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

Calcium carbonate

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The formulation is identical to that of Gaviscon Double Action Liquid (RVG 109769) marketed by Reckitt Benckiser Healthcare B.V. and authorised on 20 December 2012.

Manufacturing process

The manufacturing process consists of the dissolution and dispersion of the drug substances, mixing and filling operation. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full and three pilot scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph. Eur. requirements or in-house specification. The compositions of the flavours is indicated. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, viscosity, odour, identity of preservatives, alginate, carbonate and calcium, assay of preservatives, sodium alginate, carbon dioxide sodium bicarbonate and calcium, microbiological quality and preservative efficacy. The release and shelf-life requirements/limits differ for pH, preservative assay, carbon dioxide content, sodium bicarbonate content and preservative efficacy. Additionally, a test for uniformity of mass of delivered doses is included in the release specification. The proposed specifications are acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Due to the source of the natural ingredients and manufacturing process of the active ingredients, a number of metallic ions are present as residues in very small amounts. The concentrations of heavy metals are controlled by specifications and are all well within normal dietary intakes and therefore do not present any additional toxicological hazard. The elemental impurities testing has been carried out on the finished formulation as per ICH Q3D guideline, and all the elemental impurities are found to be below the Permitted Daily Exposure (PDE) values.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored up to 52 weeks at 25°C/60%RH, 30°C/75%RH and 6 months at 40°C/75%RH. The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for two years. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are "Do not refrigerate or freeze".

In-use stability data have been provided demonstrating that the product remains stable for 6 months following first opening of the container when stored at 30°C/75%RH.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the parabens and Peppermint Flavour have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gaviscon Duo muntsmaak has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made and completed:

- The MAH will submit the test results of the three batches by the appropriate variation, within three months after completion of application procedure no later than 26 October 2023

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

In vitro studies published in the 1970s demonstrated the mode of action of sodium alginate (Washington, 1991). Sodium alginate acts to impede gastro-oesophageal reflux by the formation of an alginate raft that floats on the surface of the stomach contents. The bicarbonate, from the sodium bicarbonate, reacts with gastric acid forming carbon dioxide, which becomes entrapped in the gel and provides it with buoyancy. Early *in vitro* studies also demonstrated that anti-reflux agents containing sodium alginate and bicarbonate do not have a significant neutralising effect on the bulk of the gastric content (Washington, 1991). *In vitro* studies (Richardson et al., 2004, 2005) using isolated pig oesophagus tissue revealed that sodium alginate adheres to the oesophageal mucosa, which suggests that sodium alginate may have a direct mucosal protective effect in addition to reducing reflux. There appears to be no evidence from animal models of the effect of sodium alginate on gastro-oesophageal reflux. However, the human clinical data are substantial.

A series of published animal studies have revealed that oral sodium alginate protects against experimentally-induced intestinal inflammation. Mirshafiey and colleagues demonstrated that, in acetic acid-induced colitis in rats, both pre-treatment and delayed treatment with 0.5% sodium alginate reduced significantly ($p<0.05$) the macroscopic scores of inflammation and ulceration. It also significantly reduced ($p<0.05$) the elevated serum and colonic tissue levels of pro-inflammatory cytokines (Mirshafiey et al., 2005).

In vitro experiments with a fibrosarcoma cell-line (WEHI-164) were also described that indicate that sodium alginate has a cell-stabilising effect, which is associated with reduced activity of the matrix metalloproteinases that are involved in epithelial inflammation and tissue destruction (Mirshafiey et al., 2005).

Sodium bicarbonate is a naturally occurring inorganic compound readily dissociating in water to sodium and bicarbonate ions, both normal constituents of vertebrate physiology; the principal extracellular buffer in the blood and interstitial fluid is the bicarbonate buffer system (OECD, 2002).

In the case of the current orally administered products, sodium bicarbonate acts as an effervescent agent/gas forming agent active in the formation of the alginate raft systems. When given orally both sodium and potassium hydrogen carbonate neutralise hydrochloric acid in gastrointestinal tract secretions with the production of carbon dioxide. They are used in the symptomatic management of gastrointestinal disorders associated with hyperacidity such as dyspepsia, gastro-oesophageal reflux disease and peptic ulcer disease (Martindale, 2017b).

The US FDA in its listing of approved antacid products for over-the-counter (OTC) human use includes sodium bicarbonate/sodium hydrogen carbonate as well as bicarbonate-containing active ingredients in general providing a maximum daily dosage of 200 mEq bicarbonate ion for persons up to 60 years old and 100 mEq for persons 60 years or older (FDA, 2017b). When given orally, sodium bicarbonate neutralises acid secretions in the gastrointestinal tract and is therefore frequently included in antacid preparations; to relieve dyspepsia doses of about 1 to 5 g in water have been taken (Martindale, 2017b).

Therapeutically, sodium bicarbonate as an alkalinising agent, is also used for a variety of other therapeutic purposes including the correction of metabolic acidosis, the management of hyperkalaemia, alkalisation of the urine and as a source of bicarbonate in dialysis fluids. In the treatment of chronic metabolic acidosis, bicarbonate has been given orally and doses providing 57 mmol daily (4.8 g sodium) may be required (Martindale 2017b).

Release of carbon dioxide from bicarbonate containing antacids such as sodium bicarbonate taken orally can cause stomach cramps, belching, nausea, abdominal distension and flatulence (Martindale, 2017b, Brunton, Chabner, and Knollman, 2011). In exceedingly rare cases, acute oral ingestion has been reported to result in a ruptured stomach; the bicarbonate was believed to have resulted in rapid production of sufficient carbon dioxide to rupture a stomach already distended by food, liquid or air. Acute or chronic excessive oral ingestion may cause

metabolic alkalosis, cyanosis and hypernatraemia, conditions that are usually reversible (Martindale, 2017b, OECD 2002).

Excessive doses of sodium salts may also lead to sodium overloading and hyperosmolality, and sodium containing salts must be given cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia or aldosteronism (Martindale, 2017b). These risks are addressed by inclusion of the appropriate posology, recommendations for duration of treatment, precautions and warnings in the prescribing information and labelling of the products.

Calcium carbonate can be used therapeutically as an antacid, a phosphate-binder in the treatment of hyperphosphataemia in patients with chronic renal failure and a calcium supplement in deficiency states and as an adjunct to treatment for osteoporosis (Martindale 2017c). Doses of calcium carbonate administered orally include up to 1.5 g as an antacid (often in combination with other antacids), 3 to 7 g daily in the treatment of hyperphosphataemia, and 1 to 3 g daily as a calcium supplement (Martindale, 2017c).

In humans, calcium carbonate may occasionally cause constipation, whilst flatulence from released carbon dioxide may occur in some patients. High doses or prolonged use may lead to gastric hypersecretion and acid rebound (Martindale, 2017c). However, the clinical relevance of the acid rebound is not established (Hade and Spiro, 1992). Like other calcium salts, calcium carbonate can cause hypercalcaemia, particularly in patients with renal impairment or after high doses. Alkalosis may also occur as a result of the carbonate anion. There have been rare reports of the milk-alkali syndrome and tissue calcification. The possibility of an increased risk of myocardial infarction associated with the use of calcium supplements has been raised. The dose of calcium resulting from administration of a product should be taken into account when treating patients with hypercalcaemia, nephrocalcinosis and recurrent calcium-containing renal calculi (Martindale 2017c, 2014). Appropriate warnings and precautions are included in the prescribing information for the products.

III.2 Pharmacokinetics

A study using ^{14}C-labelled alginate fed as 10% of the diet to ten week-old rats (following 24 hours without food) demonstrated that 85-91% of the radioactivity was recovered in the faeces, 0.11-0.16% in the urine, 0.21-0.42% in respiratory carbon dioxide and 0.002-0.007% in the plasma after 17 hours (Humphreys and Triffitt, 1968). The authors concluded that their data indicated a negligible degree of absorption of alginate following oral intake and assumed that the small amount of unrecovered alginate was due to experimental losses.

On oral administration of bicarbonate salts, such as sodium bicarbonate, any bicarbonate ions not involved in neutralisation of gastrointestinal acid (with the production of carbon dioxide) are absorbed. In the absence of a deficit of bicarbonate in the plasma, bicarbonate ions are readily excreted in the urine which is rendered alkaline (Martindale 2017b). Excess sodium ions are readily excreted in the urine (OECD 2002).

Calcium carbonate is converted to calcium chloride by gastric acid. Some of the calcium is absorbed from the intestines, via active transport or passive diffusion, but a large proportion

(up to 80 %) is reconverted to calcium carbonate and other insoluble calcium salts which are excreted in the faeces. Average absorption of calcium from calcium carbonate over a range of studies has been shown to be in the range of 20 to 40% with any unabsorbed portion excreted in the faeces (EFSA 2011; Martindale 2014). After intestinal absorption, calcium and carbonate/bicarbonate ions enter normal metabolic pathways and body pools; the majority of absorbed calcium is stored in the skeleton. Excess calcium is excreted with water via the kidneys (and also faeces and skin) and excess carbonate is excreted as carbon dioxide via respiration (EFSA 2011).

III.3 Toxicology

Nonclinical data indicates that no toxicity should be expected from the quantities of sodium alginate administered in the recommended doses of the product. In addition, administration of sodium alginate has revealed no evidence of any potential for carcinogenic, mutagenic or reproductive toxicity (Til et al, 1986; Ishidate et al, 1984; Adaniya et al, 1993). There is some evidence of minor nephrotoxicity occurring after prolonged exposure to extremely high concentrations (25% of the diet) of sodium alginate in mice (Til et al, 1986), but this is not relevant to the proposed clinical use. The widespread exposure of the human population to sodium alginate in both pharmaceutical and food products together with long-term post-marketing experience of Gaviscon formulations demonstrate that the products present little or no risk to human safety.

Sodium bicarbonate is generally regarded as a relatively non-toxic and non-irritant material when used at an appropriate dose. As with sodium salts in general adverse effects are attributable to electrolyte imbalances from excessive sodium (Martindale, 2017b). This risk is addressed by inclusion of the appropriate precautions and warnings in the prescribing information and labelling of the products. Although the few available non-clinical studies are not 'state of the art', a review of the published non-clinical data indicates that no toxicity should be expected from the quantities of sodium bicarbonate administered in the recommended dose of the products (OECD 2002). In addition, administration of sodium bicarbonate has revealed no evidence of any potential for carcinogenic, mutagenic or reproductive toxicity.

In the absence of any formal programme of non-clinical studies, the status of sodium bicarbonate, and sodium and bicarbonate ions, as naturally occurring inorganic constituents of vertebrate physiology together with the widespread exposure of the human population to sodium bicarbonate in both pharmaceutical and food products and the long-term post-marketing experience of Gaviscon formulations demonstrate that the product presents little or no risk to human safety.

Calcium carbonate is generally regarded as a relatively non-toxic and non-irritant material when used at an appropriate dose. The available toxicological database on calcium carbonate is limited, but does not give rise to concern, including the results of recent OECD and GLP compliant studies on nanoparticulate material. The few effects seen in studies in animals and humans are associated with high calcium carbonate intakes, and are also seen with other calcium salts (EFSA, 2011). In the absence of any evidence of major toxicity in non-clinical studies, the status of calcium and carbonate ions, as naturally occurring inorganic constituents

of vertebrate physiology together with the widespread exposure of the human population to calcium carbonate in both pharmaceutical and food products and the long-term post-marketing experience of calcium carbonate containing formulations demonstrate that the product presents little or no risk to human safety.

The excipients in the Gaviscon sachet products are well-established pharmaceutical excipients and food additives and should present little risk to the general patient population. Appropriate precautions and warnings regarding patient groups more likely to experience adverse events are provided in the prescribing information and labelling of the products. In addition, no toxicological hazard is anticipated from the presence of trace levels of formaldehyde and metallic ions present in the sodium alginate used in the products.

During the production of the grade of sodium alginate used in Gaviscon products, formaldehyde is added as a preservative. Formaldehyde is a natural component present in all mammalian cells, humans have detectable quantities of natural formaldehyde in their circulation (about 2.5 mg/ml of blood), and it is rapidly detoxified by active enzymatic pathways. Use in man has been long-term and widespread with medical, industrial and food processing applications. According to the EFSA formaldehyde is toxic. For the Gaviscon products, no toxicological hazard would be expected from the presence of formaldehyde residues as formaldehyde is present in the finished product at a concentration significantly below (over 100-fold lower) the tolerable intake of 5.2 mg/day established by the WHO for formaldehyde in drinking water (WHO, 2011).

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Gaviscon Duo is another formulation and intended for substitution of other forms, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium alginate, sodium hydrogen carbonate and calcium carbonate are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate

additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The mode of action of alginate products is physicochemical in nature, sodium alginate is not absorbed systemically, but forms a raft within the stomach. Therefore, pharmacokinetic studies are not appropriate to indicate bioequivalence.

IV.3 Pharmacodynamics

The mode of action of medicinal products containing sodium alginate, sodium hydrogen carbonate and calcium carbonate is physical and does not depend on absorption into the systemic circulation.

In the acidic environment of the stomach alginate salts and alginic acids precipitate to form a low density, viscous gel (Knight et al, 1988; May et al, 1984). Sodium alginate is not absorbed systemically but forms a raft within the stomach.

The sodium hydrogen carbonate 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). Hence, the mode of action of sodium hydrogen carbonate in acid neutralization is essential for effective raft formation. Sodium hydrogen carbonate relieves heartburn and acid indigestion.

Calcium salts increase raft strength by formation of calcium ion cross-linkages between the alginate chains (Grant et al, 1973; Davies et al, 1994; Malmud et al, 1979). Calcium carbonate is an antacid that provides relief for heartburn, acid indigestion, and upset stomach. Calcium carbonate is also a dietary supplement that helps to provide calcium to support healthy bones, muscles, nervous system, and heart. Sodium hydrogen carbonate is an effective antacid that neutralizes gastric acid.

Taking things together, the combination of active substances provides a protective and neutralising effect: The protective effective is that on ingestion, the medicinal product reacts rapidly with gastric acid to form a protective barrier (raft) of alginic acid gel having a near neutral pH and which floats on the stomach contents. Effective impediment of gastro-oesophageal reflux may last for up to 4 hours. This means that acid regurgitation is mechanically prevented and the oesophagus is thus protected. In severe cases the raft itself may be refluxed into the oesophagus, in preference to the stomach contents, and exert a demulcent effect (Mandel et al, 2000).

The neutralising effect is that calcium carbonate and sodium hydrogen carbonate react immediately following ingestion to neutralise gastric acid and provide fast relief from indigestion and heartburn. The total neutralising capacity of the product at the lowest dose of one sachet is approximately 10 mEqH+. This effect has also been demonstrated *in vivo* via

intragastric pH monitoring using a multi-electrode catheter in fasted healthy male and female participants to remove variability caused by postprandial buffering (Wilkinson, 2018). In the study the primary endpoint was the percentage of time that intragastric pH ≥ 4 during the 30 minutes post-treatment period and the results recorded 50.8% of the time with Gaviscon Double Action versus 3.5% with placebo (p = 0.0051).

The medicinal product also neutralizes the postprandial acid pocket.

Gaviscon Double Action Peppermint flavour, Oral Suspension in Sachet concern a fixed combination product with sodium alginate, sodium hydrogen carbonate, and calcium carbonate as active substances. According to literature, a fixed combination product with these active substances exerts both raft-forming (sodium alginate) and acid-neutralizing pharmacodynamic effects (sodium hydrogen carbonate, calcium carbonate).

In the submitted documentation on quality aspects of the proposed product and other alginate-antacid medicinal products registered in the European Union for more than 10 years, the MAH appropriately justified that the physicochemical, raft-forming, and acid-neutralizing properties of these products are similar. Based on this and minimal systemic availability of alginate-antacid it is concluded that pharmacodynamic effects of Gaviscon Double Action Peppermint flavour, Oral Suspension in Sachet are similar to those of other Gaviscon alginate-antacid formulations registered in the European Union for more than 10 years.

IV.4 Clinical efficacy

The clinical efficacy of Gaviscon Double Action (DA) tablets at dosages of four times daily, two or four tablets during 7 days for symptomatic treatment of gastroesophageal reflux disease (GERD), was demonstrated in submitted publications (Thomas et al, 2014; Wilkinson et al, 2018). Referenced systematic review and meta-analysis by Leiman et al. (2016) and Tran et al. (2007), and the meta-analyses conducted by the MAH also support the efficacy of alginate-based treatments with respect to decreasing and resolving GERD symptoms. These meta-analyses included different alginate medicinal products and different formulations (e.g. tablets and liquid).

The posology for Gaviscon DA mixed berries tablets for gastro-oesophageal reflux of up to four times daily two to four tablets up to 7 days is in line with the posology of the decentralised registered Gaviscon DA chewable tablets (NL/H/4534/001) (2010) for a similar indication. Respective tablets were registered on a well-established use legal basis.

The MAH did not discuss to what extent literature on the clinical effects of Gaviscon DA tablets registered within the European Union for more than 10 years can be extrapolated to its proposed Gaviscon DA mixed berries chewable tablets. However, in submitted documentation on quality aspects the MAH appropriately justified that the physicochemical, raft-forming, and acid-neutralizing properties of these products are similar. Because of this, the RMS is of the opinion that bridging of clinical effects reported for Gaviscon DA tablets in literature and proposed Gaviscon DA mixed berries chewable tablets is appropriate.

Aforementioned data support the clinical efficacy of Gaviscon DA mixed berries tablets for the treatment of acid related symptoms of gastro-oesophageal reflux such as heartburn, acid regurgitation and indigestion, for example following meals or during pregnancy in patients aged 12 years and above.

IV.5 Clinical safety

Fixed dose combination products of sodium alginate, sodium hydrogen carbonate, and calcium carbonate with varying amounts of active substances and in different formulations (tablets, suspensions) are used frequently in European clinical practice for more than a decade. Submitted publications and PSUR data show that the risk of adverse events is overall low, i.e. <1% per year (Hampson et al, 2010; Thomas et al, 2014; Coyle et al, 2017; Wilkinson et al, 2018). Most of the reported adverse events were non-serious. Reported adverse events can be treated if necessary. Hence, fixed dose combination products of sodium alginate, sodium hydrogen carbonate, and calcium carbonate are well-tolerated by the majority of patients.

Since the efficacy of Gaviscon DA tablets with respect to the treatment of acid related symptoms of gastro-oesophageal reflux such as heartburn, acid regurgitation and indigestion can be extrapolated to proposed Gaviscon Double Action Peppermint flavour, Oral Suspension in Sachet, this will also apply to the clinical safety of these medicinal products.

There is no evidence to suggest that the usual adult dosage needs to be modified for use in elderly patients.

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

Very rarely (less than one in 10,000) patients may develop allergic manifestations such as urticaria, anaphylactic and anaphylactoid reactions. The only proposed contraindication to use of Gaviscon DA is known or suspected hypersensitivity to any of the active substances or to any of the excipients (e.g. carmoisine lake).

Gaviscon DA liquid and tablets contain sodium ions, but the levels present are not considered sufficient to require contraindication of its use in any patient group, although this should be taken into account when a highly restricted salt diet is recommended such as in some cases of congestive cardiac failure and renal impairment.

Due to the presence of calcium, care needs to be taken in treating patients with hypercalcaemia, nephrocalcinosis and recurrent calcium containing renal calculi.

The tablets contain aspartame and should not be taken by patients with phenylketonuria.

Due to the physical mode of action of Gaviscon DA tablets and liquid formulations, these formulations may be used during pregnancy and lactation.

Patients should seek medical advice if symptoms do not improve after seven days. Since in rare cases the symptoms associated with gastric reflux may result from a more serious underlying condition such as gastric carcinoma, this is a sensible measure to guard against prolonged self-medication resulting in such conditions going undiagnosed.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan,, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Gaviscon Duo muntsmaak. At the time of approval, the most recent version of the RMP was version 0.1 dated 10 February 2022.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Fixed dose combination products of sodium alginate, sodium hydrogen carbonate, and calcium carbonate with varying amounts of active substances and in different formulations (tablets, suspensions) have been authorised within the European Union for decades. The clinical effects of these alginate-antacid medicinal products are well-known.

For this authorisation, reference is made to the clinical studies and experience with fixed dose combinations of sodium alginate, sodium hydrogen carbonate, and calcium carbonate. No new clinical studies were conducted. The MAH demonstrated that the use of fixed dose combinations is well-established within the European Union.

The submitted clinical studies support the clinical efficacy at the recommended posology of liquid alginate-antacid medicinal products at an acceptable safety level with respect to the treatment of acid related symptoms of gastro-oesophageal reflux such as heartburn, acid regurgitation and indigestion in patients aged 12 years and above.

Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Gaviscon Double Action Mint Oral Suspension 150ml, PL 00063/0552. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gaviscon Duo muntsmaak, oral suspension in sachet has a proven chemical-pharmaceutical quality and is considered to be a line-extension of Gaviscon Duo sachets, an oral suspension in sachets. Gaviscon Duo sachets is a well-known medicinal product with an established favourable efficacy and safety profile.

Sufficient non-clinical and clinical data relevant to the extension have been submitted. The efficacy and safety results were satisfactory, and in line with the known efficacy and safety of the existing sodium hydrogen carbonate, sodium alginate and calcium carbonate oral suspension formulations.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gaviscon Duo muntsmaak with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 July 2023.

LITERATURE REFERENCES

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4535/002 /IB/001	Change in control of the Finished Product • During assessment of the initial MAA, the applicant was requested to submit, by means of a variation, the test results of 3 batches to demonstrate uniformity of mass testing has taken place. Analytical results of three drug product batches demonstrating compliance with the complete set of release specification (thus including uniformity of mass of delivered doses) were requested to be included in section 3.2.P.5.4.	No	15-11-2023	Approved	-