



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

UKPAR

**Maalox 175mg/200mg Oral Suspension
(aluminium hydroxide & magnesium hydroxide)**

UK Licence No: PL 04425/0697

Aventis Pharma Limited

LAY SUMMARY

Maalox 175mg/200mg Oral Suspension
(aluminium hydroxide & magnesium hydroxide)

This is a summary of the Public Assessment Report (PAR) for Maalox 175mg/200mg Oral Suspension (PL 04425/0697). This medicinal product will be referred to as Maalox Oral Suspension in the remainder of this lay summary for ease of reading.

This summary explains how the application for Maalox Oral Suspension was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Maalox Oral Suspension.

For practical information about using Maalox Oral Suspension, patients should read the package leaflet or contact their doctor or pharmacist.

What is Maalox Oral Suspension and what is it used for?

Maalox Oral Suspension contains two different active ingredients. They are called aluminium hydroxide and magnesium hydroxide. They belong to a group of medicines called antacids.

How does Maalox Oral Suspension work?

This medicine works by lowering the amount of acid in the stomach.

How is Maalox Oral Suspension used?

This medicine is used for the treatment of heartburn or when the stomach has too much acid known as indigestion, inflammation of the stomach known as gastritis, and when prescribed by a doctor it may also be used for lowering the amount of acid in the patient's stomach or gut (intestine) when an ulcer is present.

The medicine should be shaken well before use to ensure it is mixed properly. The medicine should be taken by mouth, if necessary with water or milk.

In adults, the elderly and children aged 14 years or older, the recommended dose is two to four 5ml teaspoonfuls taken 20 minutes to 1 hour after meals and at bedtime. Alternatively, the patient should take the medicine as they have been instructed by their doctor. If the symptoms do not go away the patient should speak to their doctor.

Maalox Oral Suspension is not recommended for children below 14 years of age.

What benefits of Maalox Oral Suspension have been shown in studies?

Maalox Oral Suspension is a few formula of an existing product Maalox Suspension, as such the data to support this application are primarily based on the data submitted for the existing product, Maalox Suspension. No new data were submitted, or are required.

Maalox suspension preparations have been available in the EU for many years and have been shown to be effective for treating the conditions above, and to have acceptable safety. Data have been provided from the published literature on aluminium hydroxide and magnesium hydroxide.

What are the possible side effects of Maalox Oral Suspension?

For information about side effects that may occur when using Maalox Oral Suspension, please refer to Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

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

Why was Maalox Oral Suspension approved?

No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Maalox Oral Suspension outweigh the identified risks, and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Maalox Oral Suspension?

A Risk Management Plan (RMP) has been developed to ensure that Maalox Oral Suspension is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for this product, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Maalox Oral Suspension

A Marketing Authorisation was granted in the UK on 27 January 2017.

The full PAR for Maalox Oral Suspension follows this summary. For more information about treatment with Maalox Oral Suspension read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2017.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 6
III	Non-clinical aspects	Page 7
IV	Clinical aspects	Page 9
V	User consultation	Page 10
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 10
	Annex 1 Table of content of the PAR update	Page 14

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Aventis Pharma Limited a Marketing Authorisation for the medicinal product Maalox 175mg/200mg Oral Suspension (PL 04425/0697) on 27 January 2017. This product is available on the general sales list (legal classification GSL).

Maalox 175mg/200mg Oral Suspension is indicated for antacid therapy in gastric and duodenal ulcer, gastritis, heartburn and gastric hyperacidity. Maalox 175mg/200mg Oral Suspension is to be used in adults and 10-20 mL of the drug product should be taken between 20 minutes and 1 hour after meals, at bedtime or as required.

This application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, as a line extension of an already approved Marketing Authorisation for Maalox Suspension (PL 04425/0378) granted to Aventis Pharma Limited on 23 January 2009. This followed a change of ownership from PL 00050/5002R, which was a reviewed licence granted to Rorer Pharmaceutical Corporation.

Maalox 175mg/200mg Oral Suspension is a combination of two well-known active substances, aluminium hydroxide and magnesium hydroxide, with extensive clinical use for the relief of acid-related disorders of the upper gastro-intestinal tract. Aluminium hydroxide and magnesium hydroxide are locally-acting basic compounds, which react with gastric acid to form chloride salts of aluminium and magnesium, and water, resulting in acid neutralisation and an increase in the pH of the stomach. The product is presented as white oral suspension, which is homogenous after shaking.

The proposed product differs from Maalox Suspension (PL 04425/0378) as it has a new preservative system without parabens (methyl and propyl parabens have been replaced by domiphen bromide). The proposed product is also stored in a polyethylene terephthalate (PET) bottle.

No new clinical or non-clinical studies were conducted. This is acceptable as Maalox suspension preparations have been available in the EU for many years and their use is well established with recognised efficacy.

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

A summary of the pharmacovigilance system and a detailed Risk Management Plan (RMP) have been provided with this application, and these are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

Maalox 175mg/200mg Oral Suspension contains 175 mg of aluminium hydroxide and 200 mg of magnesium hydroxide.

The following pharmaceutical excipients are also present, hydrochloric acid (10%), citric acid monohydrate, peppermint oil, mannitol (E421), domiphen bromide, saccharin sodium, non-crystallising sorbitol liquid 70% (E420), hydrogen peroxide solution (30%) and purified water.

The finished product is packaged in a 250 ml polyethylene terephthalate (PET) bottle with a polypropylene (PP) closure and polyethylene (PE/LDPE) liner.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

II.2 Drug substance

1. **aluminium hydroxide**

rINN: aluminium hydroxide
Chemical name: aluminium hydroxide

Structural formula:



Molecular formula: Al(OH)_3
Relative molecular mass: 78.00
Appearance: White amorphous suspension
Solubility: Practically insoluble in water, alcohol or other organic solvents. Soluble in diluted acids.

2. **magnesium hydroxide**

rINN: magnesium hydroxide
Chemical name: magnesium hydroxide

Structural formula: $\text{H-O} - \text{Mg} - \text{O-H}$

Molecular formula: Mg(OH)_2
Relative molecular mass: 58.30 g/mol
Appearance: White colour, crystalline structure, aqueous suspension
Solubility: Almost insoluble in water, alcohol or other organic solvents. Soluble in dilute acids.

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

Appropriate proof-of-structure data have been supplied for the active substances. All potential known impurities have been identified and characterised.

Appropriate specifications have been provided for the active substances. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Satisfactory Certificates of Analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, oral suspension. Suitable product development data have been submitted with this application.

All excipients comply with their respective European Pharmacopoeia monographs, except for domiphen bromide which complies with its British Pharmacopoeia monograph.

None of the excipients are of human or animal origin and furthermore, none are sourced from genetically modified organisms.

There were no novel excipients used.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. The manufacturing process has been validated using commercial-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. In-house working standards are used, which have been compared to European Pharmacopoeia references, where available. Certificates of Analysis from commercial-scale batches have been provided that are in line with the finished product specification.

Stability of the product

Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing. The results from these studies support a shelf life of 2 years for suspension stored in an unopened bottle. A 6-months in-use shelf life applies once the bottle is first opened. The special storage condition, "Do not store above 25°C" applies to this product.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Maalox 175mg/200mg Oral Suspension.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substances aluminium hydroxide and magnesium hydroxide are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

The Applicant has provided an exemption from conducting an environmental risk assessment in the form of a waiver, since the active substances aluminium hydroxide and magnesium hydroxide are inorganic metal salts occurring naturally in the environment. The Applicant also claims that marketing of the new formulation of Maalox Oral Suspension will not lead to an increase in overall environmental exposure, since the market for antacids is relatively stable.

The Applicant states that since domiphen bromide is used in the Maalox oral suspension as an excipient, a Phase I ERA is not required.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Maalox 175mg/200mg Oral Suspension.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of Maalox 175mg/200mg Oral Suspension is well-known and no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

The new formula was developed to introduce a new preservative system without parabens and to harmonise the currently approved oral suspension formula in bottles across European countries in response to a manufacturing rationalisation. Methyl and propyl parabens have been replaced by domiphen bromide. Domiphen bromide is a quaternary ammonium that is well established as a fungicide in mouthwashes, antiseptics, cold sterilization and medicines (anti-infective). Quaternary ammonium compound formulations generally have low toxicity and low volatile organic compound emission rates, which may provide an improved performance for various end uses. They have antimicrobial efficacy over a wide pH range (pH 4-10). The antimicrobial properties of domiphen bromide, combined with its low volatility compared with parabens, render it to be a suitable preservative.

Apart from changes related to a new preservative system and formula harmonisation, the therapeutic indication, dosing regimen, and patient population for Maalox 175mg/200mg Oral Suspension are the same as those for the currently approved Maalox Suspension.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant.

IV.2 Pharmacokinetics

Absorption of aluminium and magnesium from antacids is limited. Aluminium hydroxide is slowly converted to aluminium chloride in the stomach. Some absorption of soluble aluminium salts occurs in the gastro-intestinal tract with urinary excretion. Any absorbed magnesium is likewise excreted in the urine. Aluminium containing antacids should not be administered to patients with renal impairment where increased plasma concentration may occur.

IV.3 Pharmacodynamics

Maalox 175mg/200mg Oral Suspension is a balanced mixture of two antacids; aluminium hydroxide is a slow-acting antacid and magnesium hydroxide is quick-acting. The two substances are frequently combined in antacid mixtures. Aluminium hydroxide is an astringent and may cause constipation. This effect is balanced by the effect of magnesium hydroxide, which, in common with other magnesium salts, may cause diarrhoea. Gastro-intestinal side effects are thus rare with Maalox and this makes it especially suitable when long term therapy is necessary.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), 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 Maalox 175mg/200mg Oral Suspension.

A summary of safety concerns, as approved in the RMP, is listed below:

Summary table of safety concerns:

Summary of the safety concerns

Important identified risks	Severe hypersensitivity reactions including angioedema and anaphylactic reactions Intestinal obstruction and ileus in case of large doses in patients with renal impairment and in the elderly Toxic hypermagnesaemia in patient with renal function impairment
Important potential risks	Encephalopathy and dementia in patients with renal impairment in case of hyperaluminaemia following long-term exposure to high doses of aluminium Quinidine overdose in case of concomitant use
Missing information	Use in children Use during pregnancy

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Maalox 175mg/200mg Oral Suspension.

V. USER CONSULTATION

The package leaflet has been evaluated, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. 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 patients/users are able to act upon the information it contains.

VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with Maalox 175mg/200mg Oral Suspension is considered to have demonstrated the therapeutic value of the compounds. The benefit-risk assessment 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 Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for the product granted Marketing Authorisation at a national level, are available on the MHRA website.

The approved labelling for Maalox 175mg/200mg Oral Suspension is presented below:





Maalox[®]
175mg/200mg
Oral Suspension

PL 04425/0697

Each 5 ml contains: 175mg of Aluminium hydroxide and 200mg of Magnesium hydroxide

Fast effective pain relief of
Indigestion + Heartburn + Acidity

Read the enclosed leaflet carefully before use.

Shake well before use to ensure the product is mixed properly

Dosage: Take two to four 5ml teaspoonfuls. Take 20 minutes to 1 hour after meals and at bedtime. If symptoms persist, consult your doctor or pharmacist.

Also contains: Sorbitol (E420)

Consult your doctor: if you have kidney problems or if you are pregnant or breast-feeding.

Storage: Store below 25°C
Keep out of the sight and reach of children.

MA Holder: Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS, UK

417871


 BN:
EXP:

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)