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HEALTH PRODUCTS REGULATORY AUTHORITY

PUBLIC ASSESSMENT REPORT FOR A
MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Maalox Sachets 460 mg/400 mg Oral Suspension
ALUMINIUM HYDROXIDE/ MAGNESIUM HYDROXIDE
PA0540/110/006

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Maalox Sachets 460 mg/ 400 mg Oral Suspension from Sanofi Aventis Ireland Ltd. on <DATE of authorisation>for the relief of the symptoms of dyspepsia

This application for a marketing authorisation was submitted in accordance with Article 8(3) of Directive 2001/83/EC, a line extension of the existing PA 540/110/4 Maalox 400 mg/400 mg Chewable tablets. It is a full national application relating to known active substances.

The method of sale and supply is for supply through pharmacies as non prescription product with promotion to the public.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Maalox Sachets 460 mg/400 mg Oral Suspension
Name(s) of the active substance(s) (INN)	Aluminium oxide hydrated (aluminium hydroxide)/ Magnesium hydroxide
Pharmacotherapeutic classification (ATC code)	A02AB10
Pharmaceutical form and strength(s)	460 mg/400 mg Oral Suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA540/110/006
Marketing Authorisation Holder	Sanofi-Aventis Ireland Limited

II QUALITY ASPECTS

II.1. Introduction

This application is for Maalox Sachets 460 mg/400 mg Oral Suspension

II.2 Drug substance

The active substances are Aluminium oxide hydrated (Aluminium hydroxide) and Magnesium hydroxide, established active substances described in the European Pharmacopoeia, and manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided

II.3 Medicinal product

P.1 Composition

Maalox Sachets contain a white to faintly yellow homogenous oral suspension. Each sachet contains 460 mg of Aluminium oxide hydrated (Aluminium hydroxide) and 400 mg of Magnesium hydroxide. The other ingredients include sucrose solution, sorbitol liquid (non-crystallising), xanthan gum, guar, sodium chloride, hydrogen peroxide solution and natural lemon lime flavour.

P.2 Pharmaceutical Development

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

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for liquid preparations for oral use, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as polypropylene-aluminium sachets each containing 4.3ml of oral suspension. Each carton contains 20 sachets.

Evidence has been provided that packaging type complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years. This medicinal product does not require any special storage conditions. After first opening the sachet, the contents should be used immediately.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Maalox Sachets 460 mg/ 400 mg Oral Suspension

III NON-CLINICAL ASPECTS

III.1 Introduction

This application for Maalox Sachets 460 mg/400 mg Oral Suspension is a line extension to the already approved reference product Maalox chewable tablets containing 400 mg aluminium hydroxide and 400 mg magnesium hydroxide.

III.2 Pharmacology

The pharmacodynamic properties of aluminium hydroxide and magnesium hydroxide are considered well known. As aluminium hydroxide and magnesium hydroxide is a widely used, well-known active substance, the applicant has not provided additional pharmacodynamic studies and further studies are not required. A non clinical expert statement has been provided and is considered acceptable.

III.3 Pharmacokinetics

The pharmacokinetic properties of aluminium hydroxide and magnesium hydroxide are considered well known. As aluminium hydroxide and magnesium hydroxide is a widely used, well-known active substance, the applicant has not provided additional pharmacokinetic studies and further studies are not required. A non clinical expert statement has been provided and is considered acceptable.

III.4 Toxicology

The toxicological properties of aluminium hydroxide and magnesium hydroxide are considered well known. As aluminium hydroxide and magnesium hydroxide is a widely used, well-known active substance, the applicant has not provided additional toxicity studies and further studies are not required. A non clinical expert statement has been provided and is considered acceptable.

III.5 Ecotoxicity/environmental risk assessment

Since this application amounts to a new line extension to existing marketing authorizations, the overall increase in exposure is not thought to significantly impact on the environment through approval of this national line extension. Additionally, the active ingredients of Maalox, aluminium hydroxide and magnesium hydroxide, are naturally occurring and are considered exempted from an Environmental Risk Assessment.

III.6 Discussion on the non-clinical aspects

The application for the line extension for Maalox Sachets 460 mg/400 mg Oral Suspension based on the existing marketing authorization dossier approved for Maalox 400 mg/400 mg Chewable tablets (PA 540/110/4) is considered adequate and is therefore considered approvable.

IV CLINICAL ASPECTS

IV.1 Introduction

This application for a marketing authorisation was submitted in accordance with Article 8(3) of Directive 2001/83/EC, a line extension of the existing PA 540/110/4 Maalox 400 mg/400 mg Chewable tablets. It is a full national application relating to known active substances.

Aluminium oxide hydrated (Aluminium hydroxide) and Magnesium hydroxide are well known active substances with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product marketed by Marketing Authorisation Holder.

The clinical equivalence of Maalox Sachets 460 mg/ 400 mg Oral Suspension and Maalox chewable tablets has been demonstrated by means of a comparative in vitro study of antacid capacity.
This *in vitro* method is one of several available methods for simulating *in vivo* behaviour (kinetics and buffer property) of an antacid product in the human stomach.

The method has been filed in numerous European countries and have been already approved by several Health Authorities so far, thus accepting the “modified Rosset-Rice” method as basis of their assessment.

The results of the method support conclusions that the antacid efficacy of Maalox® 4.3 ml sachet or Maalox® sugar free chewable tablet is equivalent to that of the Maalox® chewable tablet.

Based on the European Note for Guidance on locally acting products (CPMP/EWP/239/95) are deemed sufficient without further clinical evaluation on the *in vivo* benefit or pharmacodynamic modelisation of the already proved local antacid properties of Maalox®, to support the national line extension nationally for Maalox® 4.3ml sachets and Maalox® sugar free chewable tablets.

The tolerability of the Maalox Sachets 460 mg/ 400 mg Oral Suspension has been ascertained in an open label phase 3 study consisting of 40treated for 1-6 sachets per day for 10 days. 88% of patients considered the taste of the product as completely acceptable or acceptable.

In conclusion similar antacid capacity was demonstrated between Maalox Sachets 460 mg/ 400 mg Oral Suspension and Maalox chewable tablets. Both products have the same dose regimen. The active constituents aluminium hydroxide/magnesium hydroxide combinations are well established and are widely used.

The MAH has stated that Good Clinical Practice standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The pharmacokinetic properties of aluminium hydroxide and magnesium hydroxide are considered well known. As aluminium hydroxide and magnesium hydroxide is a widely used, well-known active substance, the applicant has not provided additional pharmacokinetic studies and further studies are not required. The clinical overview provided is considered acceptable.

IV.3 Pharmacodynamics

The pharmacodynamic properties of aluminium hydroxide and magnesium hydroxide are considered well known. As aluminium hydroxide and magnesium hydroxide is a widely used, well-known active substance, the applicant has not provided additional pharmacodynamic studies and further studies are not required. The clinical overview provided is considered acceptable.

IV.4 Clinical Efficacy

Maalox was first approved in the EU in 1966 (Spain) and since then has been registered in most European countries and in many more worldwide.

The long experience of Maalox use has demonstrated its favourable efficacy profile in the approved indications and the recommended doses.
The composition of active ingredients is similar as Maalox chewable tablets (PA 540/110/4), however the aluminium oxide hydrated component is higher.

Also some of the excipients have been replaced. The excipients are well established and no interaction with the active substances are expected, this was confirmed by the comparative invitro study. As the effects are locally acting and the well known efficacy and safety profile no additional efficacy studies have been conducted and are not warranted for this application.

Maalox Sachets 460 mg/ 400 mg Oral Suspension have been approved in a number of EU states France (04/07/2000), Belgium (02/02/2012), Cyprus (14/03/2012), Czech Republic (27/04/2011), Estonia (03/03/2010) , Greece (11/07/2011), Hungary (10/06/2010), Italy (03/01/2011), Latvia (22/10/2010), Lithuania (15/06/2010), Luxembourg (01/07/2012), Poland (13/12/2012) and Slovakia (25/05/2010) post marketing data does not highlight any new safety concerns.

There are no objections to granting a marketing authorisation from an efficacy perspective.

IV.5 Clinical Safety

The safety profile of Maalox is well known and described. No new safety issues are expected as this formulation has the same active ingredients as Maalox chewable tablets (PA 540/110/4).

No new safety studies have been conducted or are warranted for this line extension application.

There are no objections to granting a marketing authorisation from a safety perspective.

IV.6 Discussion on the clinical aspects

The efficacy and safety of Maalox preparations are well established, as in vitro comparability has been demonstrated to the authorised Maalox chewable tablets and both have the same active substances, the efficacy and safety profile is considered to similar.

Therefore the benefit/risk profile is considered positive and there are no objections to granting a marketing authorisation for Maalox Sachets 460 mg/ 400 mg Oral Suspension

V OVERALL CONCLUSIONS

The overall assessment outcome of Maalox Sachets 460 mg/ 400mg Oral Suspension is positive.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Maalox Sachets 460 mg/ 400 mg Oral Suspension demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation