# RISK MANAGEMENT PLAN - PART VI

## SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN

| | |
|---|---|
| **Active substance(s) (INN or common name)** | **Aluminium hydroxide and magnesium hydroxide** |
| **Product's concerned (Brand name(s))** | **MAALOX** |
| **Name of Marketing Authorization Holder or Applicant** | Sanofi and licensees |
| | |
| **Data lock point (DLP) for this module** | **31-Jan-2013** |
| **Version number of RMP when this module was last updated** | **Version 1.0** |

# TABLE OF CONTENTS

## LIST OF TABLES

## ABBREVIATIONS

| | |
|---|---|
| CCSI: | Company Core Safety Information |
| DLP: | Data Lock Point |
| EU: | European Union |
| GI: | gastrointestinal |
| PIL: | Patient Information Leaflet |
| RMP: | Risk Management Plan |
| SmPC: | Summary of Product Characteristics |

## VI.1. ELEMENTS FOR SUMMARY TABLES IN THE EPAR

### VI.1.1. Summary table of safety concerns

**Table 1 - Summary table of safety concerns**

| | |
|---|---|
| **Important identified risks** | Severe hypersensitivity reactions including angioedema and anaphylactic reactions<br>Intestinal obstruction and ileus in case of large doses in patients with renal impairment and in the elderly |
| **Important potential risks** | Encephalopathy and dementia in patients with renal impairment in case of long-term exposure to high doses.<br>Quinidine overdose in case of concomitant use |
| **Important missing information** | Use in children aged less than 2 years |

### VI.1.2. Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Not applicable as there are no ongoing or planned additional pharmacovigilance activities in the pharmacovigilance plan.

### VI.1.3. Summary of post-authorisation efficacy development plan

Not applicable.

## VI.1.4. Summary table of risk minimisation measures of post-authorisation efficacy development plan

**Table 2 - Summary table of risk minimisation measures of post-authorisation efficacy development plan**

| Safety concern | Routine risk minimisation activities | Additional risk minimisation activities |
|---|---|---|
| **Important identified risks** | | |
| Severe hypersensitivity reactions including angioedema and anaphylactic reactions | Communication of the risk in the Company Core Safety Information (CCSI; see *ANNEX 2*)<br><br>Section 11 (Adverse Reactions) of the CCSI states that hypersensitivity reactions, such as pruritis, urticaria, angioedma, and anaphalactic reactions are a risk of aluminium hydroxide and magnesium combinations although the frequency of this risk is listed as unhknown.<br><br>Section 4 (Contraindications) of the CCSI states that the use of Maalox is contraindicated in case of hypersensitivity to the active ingredients or to any of the excipients.<br><br>Local Summary of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) have been developed to be consistent with the CCSI and to deliver the same information to health care professionals and patients. | None |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation activities |
|---|---|---|
| Intestinal obstruction and ileus in case of large doses in patients with renal impairment and in the elderly | Communication of the risk in the CCSI (*ANNEX 2*)<br><br>Section 5 (Warnings) of the CCSI warns that aluminium hydroxide may cause constipation and magnesium salts overdose may cause hypomotility of the bowel; and that large doses of the product may trigger or aggravate intestinal obstruction and ileus in patients at higher risk such as those with renal impairment, and the elderly.<br><br>Section 12 (Overdose) of the CCSI warns that signs and symptoms of an overdose may include intestinal obstruction and ileus in patients at risk.<br><br>Severe renal failure is listed under “Contraindications” in Section 4 of the CCSI , as it is a risk factor for ileus and intestinal obstruction.<br><br>Constipation induced by aluminium hydroxide is listed under “Adverse reactions” in Section 11 of the CCSI.<br><br>Local SmPCs and PILs have been developed to be consistent with the CCSI and to deliver the same information to health care professionals and patients. | None |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation activities |
|---|---|---|
| **Important potential risks** | | |
| Encephalopathy and dementia in patients with renal impairment in case of long-term exposure to high doses | Communication of the risk in the CCSI (*ANNEX 2*)<br>Section 5 (Warnings) of the CCSI warns that, in patients with renal impairment, plasma levels of both aluminium and magnesium may increase and that in these patients, a long term exposure to high doses of aluminium and magnesium salts may lead to encephalopathy or dementia.<br>Section 4 (Contraindications) of the CCSI states that the use of Maalox is contraindicated in case of severe renal failure.<br>Hyperaluminemia is listed under "Adverse reactions" in Section 11 of the CCSI, and is also listed under "Interactions" in Section 7 (aluminium hydroxide and citrates may result in increased aluminium levels, especially in patients with renal impairment).<br>Local SmPCs and PILs have been developed to be consistent with the CCSI and to deliver the same information to health care professionals and patients. | None |
| Quinidine overdose in case of concomitant use | Communication of the risk in the CCSI (*ANNEX 2*)<br>Section 7 (interactions) of the CCSI warns that concomitant use with quinidines may increase serum levels of quinidine and lead to overdose.<br>Local SmPCs and PILs have been developed to be consistent with the CCSI and to deliver the same information to health care professionals and patients. | None |

| Safety concern | Routine risk minimisation activities | Additional risk minimisation activities |
|---|---|---|
| **Important missing information** | | |
| Missing information for children aged less than 2 years | Communication of the risk in the CCSI (*ANNEX 2*)<br>The use of Maalox in infants less than 2 years has been warned in the CCSI section 5 (Warnings).<br>Pediatric age range may vary depending on nationally authorized medicinal product. Maalox is not recommended in children under 15 years of age in Europe. | None |

## VI.2. ELEMENTS FOR A PUBLIC SUMMARY

### VI.2.1. Overview of disease epidemiology

Upper gastrointestinal symptoms due to acid related disorders of the upper gastro intestinal (GI) tract are common complaints affecting 25-40% of the general population (1, 2). Symptoms mainly consist of heartburn, reported to affect 7.7% to 15% of the general population (3), and dyspepsia, reported to affect 20-40% of the general population (4). All age groups are affected (5) and upper gastrointestinal symptoms from acid related disorders are reported in many races and ethnicities (6, 5, 7, 8, 9). Acid related disorders of the upper GI tract are common in both sexes but some studies report that they may be slightly more prevalent in women than in men (57.7% vs 42.3%; 5, **9**).

Acid related disorders of the upper GI tract are usually not associated with severe problems in the intestine and are not associated with an increased mortality. Nevertheless, the symptoms of these disorders significantly impact the quality of life of affected patients.

### VI.2.2. Summary of treatment benefits

Maalox belongs to a group of medicines called “antacids”. Maalox contains a combination of 2 different medicinal ingredients, ie, aluminium hydroxide and magnesium hydroxide, which works by lowering the excessive stomach acid.

Aluminium hydroxide has relatively slow but long acting acid neutralization effect over the entire stomach wall, whereas magnesium hydroxide has a rapid acting acid neutralization effect. This combined action allows Maalox to achieve a rapid acid neutralization within a few minutes as well as a more prolonged acid neutralization effect.

Antacids remain a standard therapeutic treatment of epigastric pain due to acid related disorders of the upper gastrointestinal tract.

### VI.2.3. Unknowns relating to treatment benefits

Maalox has been on the market for over 45 years and no unknown benefits related to treatment are expected.

### VI.2.4. Summary of safety concerns

**Table 3 - Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Allergic reactions which cause difficulty in breathing or dizziness | The formulation of Maalox for oral suspension containing parabens as excipients, is known to induce allergic reactions. This is likely due to an immunological reaction. | Liimit the exposure of the sensitive population. This risk is listed in the Company Core Safety Information (CCSI; see *ANNEX 2*), in Section 4 “Contraindications” and in Section 11 “Adverse reactions”. |

| Risk | What is known | Preventability |
|---|---|---|
| Inhibition of bowel mobility (ileus) and obstruction of the intestines in case of large doses in elderly patients or in patients with renal impairment | Aluminium hydroxide, like other aluminium compounds, is astringent and may cause constipation; large doses can cause intestinal obstruction. Magnesium salts are linked to hypomotility of the bowel with ileus or paralytic ileus in more severe cases. Hypermagnesiumia blocks neuromuscular transmission and inhibits acetylcholine release. | Limit the exposure of the sensitive population. Section 5 (Warnings) of the CCSI warns that aluminium hydroxide may cause constipation and magnesium salts overdose may cause hypomotility of the bowel; and that large doses of the product may trigger or aggravate intestinal obstruction and ileus in patients at higher risk such as those with renal impairment, and the elderly. Section 12 (Overdose) of the CCSI warns that signs and symptoms of an overdose may include intestinal obstruction and ileus in patients at risk.<br>Severe renal failure is listed under “Contraindications” in Section 4, of the CCSI as it is a risk factor for ileus and intestinal obstruction. Constipation induced by aluminium hydroxide is listed under “Adverse reactions” in Section 11 of the CCSI. |

**Table 4 - Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Degenerative disease of the brain (encephalopathy and dementia) | Enhanced gastrointestinal absorption of aluminium when complexed with citrate in patients with renal failure can lead to toxic hyperaluminemia. Hyperaluminemia has been described in premature infants receiving prolonged intravenous alimentation, and in recipients of plasmapheresis receiving large volumes of replacement albumin solutions, which contain high concentrations of aluminium. |

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Quinidine overdose in case of concomitant use | Quinidine is excreted unchanged in the urine. In acid urine much of the quinidine is unable to diffuse freely back into the cells and so is lost in the urine. In alkaline urine more of the quinidine diffuses back into the cells and is retained. In this way the pH of the urine determines how much quinidine is lost or retained and thereby governs the serum levels. In vitro data suggest that changes in pH and adsorption effects within the gut due to antacids could also affect the absorption of quinidine. Urinary excretion of quinidine is dependent on urinary pH; drugs that increase urinary pH such as some antacids, tend to increase the concentration of quinidine in blood. |

**Table 5 - Important missing information**

| Risk | What is known |
|---|---|
| Missing information for children aged less than 2 years | Pediatric age range may vary depending on nationally authorized medicinal product. The use of Maalox is not recommended in children under 15 years of age in the EU. The CCSI (*ANNEX 2*) warns against the use of Maalox in children aged less than 2 years (source: CCSI) |

### VI.2.5. Summary of additional risk minimisation measures by safety concern

Not applicable since no additional risk minimization measures are required.

### VI.2.7. Summary of changes to the RMP over time

Not applicable since this is the first RMP for Maalox.

### VI.2.6. Planned post authorisation development plan

There is no post authorization development plan for Maalox.

### VI.2.7. Summary of changes to the RMP over time

Not applicable as this is the first RMP for Maalox.