PART VI: SUMMARY OF RISK MANAGEMENT PLAN

VI.1 Elements for Summary Tables in the EPAR

VI.1.1 Summary Table of Safety Concerns

Summary of safety concerns	
Important identified risk	Hyperkalaemia
Important identified risk	Hypotension
Important identified risk	Foetotoxicity
Important identified risk	Sprue-like enteropathy
Important potential risk	Elevation of liver function values
Important potential risk	Renal impairment
Important potential risk	Hypersensitivity reactions incl. angioedema and serum sickness
Important potential risk	Decrease in haemoglobin and/or haematocrit
Important potential risk	CV risks in patients with type 2 diabetes
Missing information	Exposure in children and adolescents
Missing information	Exposure during breast feeding

VI.1.2 Table of Ongoing and Planned Studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post-authorisation Efficacy Development Plan

Not applicable.

VI.1.4 Summary Table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Hyperkalaemia	SmPC	None
Hypotension	SmPC	None
Foetotoxicity	SmPC	None
Sprue-like enteropathy	SmPC	None
Elevation of liver function values	SmPC	None
Renal impairment	SmPC	None
Hypersensitivity	SmPC	None
Decrease in haemoglobin and/or haematocrit	SmPC	None
CV risk in patients with type 2 diabetes	SmPC	None
Missing information	SmPC	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

It has been estimated that, overall, 26% of the population in 2002 had hypertension. According to an American Heart Association Statistical Fact Sheet (2004), in persons aged over 60 years, as many as one-half in some populations are hypertensive. Worldwide, high blood pressure (BP) is estimated to cause 7.1 million deaths, about 13% of the global fatality total. In clinical trials, antihypertensive therapy has been associated with 35 – 40% less strokes, 20 – 25% less myocardial infarction, and more than 50% less heart failure. Overall control of hypertension is still poor, with only 31 – 46% of patients in EU countries achieving blood pressure goal.

VI.2.2 Summary of Treatment Benefits

In the case of the OM/AML fixed-dose combination tablets, the target population is those patients whose BP is not adequately controlled by monotherapy with OM or AML alone. Monotherapy with any antihypertensive agent achieves goal blood pressure in only a proportion of patients treated, typically about 50%.

The clinical studies and the non-interventional studies that were specifically designed to evaluate the antihypertensive efficacy of OM/AML and reported since first approval in EU in 2008 have been analyzed.

These studies included double-blind and open label studies which were partly performed in special populations, such as patients with type II diabetes mellitus or elderly patients (aged ≥65 years).

All studies confirmed that OM/AML combination remains an effective antihypertensive therapy.

There were no results which suggested any concerns regarding efficacy, even in special groups such as older patients (≥ 65 years), diabetic patients or patients with severe hypertension.

VI.2.3 Unknowns Relating to Treatment Benefits

OM/AML was studied in a large, worldwide population with hypertension, also with patients aged over 65 years. The study population was representative of the target population. There were fewer Black and 'other' race patients than Caucasian or Asian patients were, but the results indicated comparable benefits in these subgroups.

There were no results which suggested any concerns regarding efficacy, even in special groups such as older patients (≥ 65 years), diabetic patients or patients with severe hypertension.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is known	Preventability
High blood potassium	Treatment with OM/AML can lead to an increase in blood potassium. Early symptoms are unspecific and generally include feeling unwell, rapid heartbeat and muscle weakness. More severe increase in blood potassium can lead to complications such as irregular heartbeat or sudden death.	Yes, with proper dose adjustment for patients with renal impairment and periodic monitoring of renal function.

Risk	What is known	Preventability
Low blood pressure	Treatment with OM/AML is supposed to lower blood pressure. However in some circumstances, the blood pressure lowering effect can be too strong. The key symptoms of low blood pressure include light-headedness or dizziness. If the blood pressure is sufficiently low, fainting and convulsions can occur.	Yes, by identification of patients at high risk of low blood pressure and by ensuring careful adherence to dose recommendations for patients that are at higher risk for hypotension.

Risk	What is known	Preventability
Toxicity to the foetus	Treatment with OM/AML during pregnancy can lead to severe side effects for the unborn child that range from kidney insufficiency to fetal death.	Yes, by identification of patients at high risk and by ensuring careful adherence to contraindication during 2nd and 3rd trimester of pregnancy.

Risk	What is known	Preventability
Sprue-like enteropathy	Treatment with OM/AML can lead to sever and chronic diarrhea with substantial weight loss.	Yes, by identification of patients at risk and by considering discontinuation of OM/AML.

Important Potential Risks

Risk	What is known (Including reason why it is considered a potential risk)
Abnormal liver enzyme tests	Data from other ARBs have suggested they might cause liver damage. There have been patients with abnormal liver enzyme test under OM/AML. However, there could also be alternative causes.

Risk	What is known (Including reason why it is considered a potential risk)
Renal impairment	It is known that ARBs can alter kidney function. There have been patients with renal impairment under OM/AML. However, there could also be alternative causes such as old age, diabetes and/or kidney damage through hypertension.

Risk	What is known (Including reason why it is considered a potential risk)
Allergic reaction / Drug intolerance	Allergies reactions can be found with many drugs. There have been patients with allergic reaction under OM/AML, some of them severe. However, there could also be alternative causes such as other drugs or the combination with those.

Risk	What is known (Including reason why it is considered a potential risk)
Decrease in red blood cells	There have been patients with decrease in red blood cells under OM/AML. However, there could also be alternative causes such as old age, diabetes and/or kidney damage through hypertension.

Risk	What is known (Including reason why it is considered a potential risk)
Risk for the heart and blood vessels in patients with type 2 diabetes	There have been patients with heart attacks leading to death under OM in clinical studies. However, there could also be alternative causes such as old age, diabetes, physical and psychological stress and/or heart damage through long-term hypertension.

Missing Information

Risk	What is known
Paediatric use	Safety and efficacy of OM/AML in children and adolescents below 18 years has not been established. No data are available.
Lactation	No information is available regarding the use of OM or AML during breastfeeding.

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a SmPC that provides physicians, pharmacists and other HCP with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the PIL. The measures in these documents are known as routine risk minimization measures.

The SmPC and the PIL for OM/AML can be found in the MAH's EPAR pages [xx-xx].

This medicine has no special conditions and restrictions for its safe and effective use (additional risk minimization measures).

VI.2.6 Planned Post-authorisation Development Plan

List of Studies in Post-authorisation Development Plan

Not applicable.

Studies, which are a condition of the marketing authorisation

None.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
Not applicable, this is the first version of the RMP in the new format			