Part VI: Summary of the risk management plan for MultiHance (Gadobenate Dimeglumine)

This is a summary of the risk management plan (RMP) for MultiHance. The RMP details important risks of MultiHance, how these risks can be minimised, and how more information will be obtained about MultiHance risks and uncertainties (missing information).

MultiHance summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how MultiHance should be used.

VI.I The medicine and what it is used for

MultiHance is authorised for use as a contrast agent for magnetic resonance imaging in a number of EEA countries for the following indications (see SmPC for the full indications):

> MultiHance is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) of the liver in adults and children (above the age of 2 years).

In countries outside the EEA, MultiHance is approved for use in MRI of the central nervous system (brain and spine) and whole body in adults and children (from term neonates or over 2 years to 17 years of age depending on indication and country), and for magnetic resonance angiography for the assessment of stenosis, occlusions and collaterals in adults and children above the age of 2 years. Specific applications in the heart include measurement of myocardial perfusion under pharmacological stress conditions and viability diagnostics ("delayed enhancement").

MultiHance contains gadobenate as the active substance and it is given to patients intravenously.

Post-authorisation RMP: Not applicable

Link to product's EPAR summary landing page on the EMA webpage: Not applicable

VI.II Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of MultiHance, together with measures to minimise such risks and the proposed studies for learning more about the risks potentially associated with MultiHance, are outlined below.

Measures to minimise the risks identified for MultiHance are:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging, and the inclusion of tear-off labels to aid in identifying product administered in a patient's chart;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with a prescription, administered by a healthcare professional) helps to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of MultiHance, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of MultiHance is not yet available, it is listed under ‘missing information’ below.

VI.IIA List of important risks and missing information

Important risks of MultiHance are risks that need special risk management activities to further investigate or minimise the risk so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of MultiHance. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term exposure to the medicine).

Part VI IIA: List of important risks and missing information

Important identified risks	• Nephrogenic systemic fibrosis (NSF)
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in the brain • Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues
Missing information	• Safety in children under 2 years of age • Safety in pregnancy and lactation • Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues • Clinical significance of gadolinium retention in the brain

VI.IIB Summary of important risks

Important potential risk: Adverse clinical effects of accumulation and retention of gadolinium in the brain	
Evidence for linking the risk to the medicine	Both experimental animal studies and clinical tissue-sample studies show that retention of Gd complexes in body tissues is observed following exposure to all GdCA and may be dose-dependent. To date, there is insufficient evidence to draw conclusions concerning clinical implications resulting from Gd retention in body organs/tissues.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 and 4.2, as amended based on the conclusions of the Referral Procedure under Article 31 of Directive 2001/83/EC for gadolinium contrast agents (procedure EMEA/H/A-31/1437). Healthcare Professionals are reminded of the following: - GdCA should be used only when diagnostic information is essential and not available with unenhanced MRI. - The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. Additional risk minimisation measures: Joint Direct Healthcare Professional Communication agreed by the MAHs of GdCA with the CHMP to inform healthcare professionals about EMA's opinion on the Article 31 referral procedure for gadolinium contrast agents.
Additional pharmacovigilance activities	None pursuant to an obligation imposed by a competent authority (see Part III.2)
Important potential risk: Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	
Evidence for linking the risk to the medicine	Both experimental animal studies and clinical tissue-sample studies show that retention of Gd complexes in body tissues is observed following exposure to all GdCA and may be dose-dependent. To date, there is insufficient evidence to draw conclusions concerning clinical implications resulting from Gd retention in body organs/tissues.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 and 4.2 as amended based on the conclusions of the Referral Procedure under Article 31 of Directive

	2001/83/EC for gadolinium contrast agents (procedure EMEA/H/A-31/1437). Healthcare Professionals are reminded of the following: - GdCA should be used only when diagnostic information is essential and not available with unenhanced MRI. - The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. Additional risk minimisation measures: Joint Direct Healthcare Professional Communication agreed by the MAHs of GdCA with the CHMP to inform healthcare professionals about EMA's opinion on the Article 31 referral procedure for gadolinium contrast agents
Additional pharmacovigilance activities	None pursuant to an obligation imposed by a competent authority
Missing information: Safety in children under 2 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2 and 4.4 PIL section 2, 3 and 4
Missing information: Safety in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.6 PIL section 2
Missing information: Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 and 4.2 as amended based on the conclusions of the Referral Procedure under Article 31 of Directive 2001/83/EC for gadolinium contrast agents (procedure EMEA/H/A-31/1437). Healthcare Professionals are reminded of the following: - GdCA should be used only when diagnostic information is essential and not available with unenhanced MRI. - The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. Additional risk minimisation measures: Joint Direct Healthcare Professional Communication agreed by the MAHs of GdCA with the CHMP to inform healthcare professionals about EMA's opinion on the Article 31 referral procedure for gadolinium contrast agents

Missing information: Clinical significance of gadolinium retention in the brain	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.1 and 4.2 as amended based on the conclusions of the Referral Procedure under Article 31 of Directive 2001/83/EC for gadolinium contrast agents (procedure EMEA/H/A-31/1437). Healthcare Professionals are reminded of the following: - GdCA should be used only when diagnostic information is essential and not available with unenhanced MRI. - The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. Additional risk minimisation measures: Joint Direct Healthcare Professional Communication agreed by the MAHs of GdCA with the CHMP to inform healthcare professionals about EMA's opinion on the Article 31 referral procedure for gadolinium contrast agents

VI.IIC Post-authorisation development plan

VI.II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation of MultiHance:

GMRA-102: A prospective multicentre cohort study evaluating the long term retention of gadolinium in human bone and skin after the retrospective administration of MultiHance or ProHance in comparison with a control group receiving no exposure to gadolinium.

No MultiHance is administered to patients as part of this trial; in fact the study design is retrospective in terms of GdCA administration but prospective in terms of bone and skin sampling. As amended the protocol calls for enrolment of a minimum total of 36 subjects (minimum of 26 subjects, who are scheduled to orthopedic surgical procedures and have completed one or more retrospective administrations of ProHance or MultiHance at least 1 month before their scheduled surgery as part of his/her clinical management, as well as a control group of 10 subjects with no exposure to Gd).

Purpose of the study: To evaluate the long term retention of gadolinium in human bone and skin after the retrospective administration of MultiHance or ProHance

VI.II.C.2 Other studies in post-authorisation development plan

GMRA-104. A retrospective, multicentre study evaluation autopsy tissue specimens for levels of gadolinium and other metals after the single agent administration of one of four gadolinium-based contrast agents in comparison with a control group having no exposure to gadolinium.

No MultiHance is administered to patients as part of this trial. All gadolinium-containing contrast agents (GdCA) have been shown to result in retention of trace amounts gadolinium in brain and body tissues. This retrospective, multicentre autopsy study aims to quantify levels of gadolinium

and other metals in the brain and other organs after the single agent administration of one of four gadolinium-containing contrast agents (including MultiHance, ProHance, Gadavist, or Dotarem) and in deceased subjects never exposed to a GdCA.