Part VI: Summary of the risk management plan for ProHance (Gadoteridol)

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

ProHance SmPC and its package leaflet give essential information to healthcare professionals and patients on how ProHance should be used.

VI.I The medicine and what it is used for

ProHance 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):

- Adults: MRI of the central nervous system (CNS), whole body including head, neck, liver, breast, musculoskeletal system and soft tissue;
- Children: MRI of CNS with no age limitation;
- Children: MRI of whole body with no age limitation (country-specific).

ProHance contains gadoteridol as the active substance and it is given 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 ProHance, together with measures to minimise such risks and the proposed studies for learning more about the risks potentially associated with ProHance, are outlined below.

Measures to minimise the risks identified for ProHance 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 ProHance, 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 ProHance is not yet available, it is listed under 'missing information' below.

VI.II.A List of important risks and missing information

Important risks of ProHance 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 ProHance. 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).

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 gadolinium accumulation in organs and tissues other than brain tissues
Missing information	• Safety in pregnancy and lactation • Clinical significance of gadolinium retention in brain • Clinical significance of gadolinium retention in organs and tissues other than brain tissues

VI.II.B 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 GBCA 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: - GBCA 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: None
Additional pharmacovigilance activities	8403760: Gadolinium based Contrast Agents (GBCAs) 29-Week Intravenous Repeat-dose Toxicity in the Juvenile Cynomolgus Monkey, with a 52-Week Recovery Phase 8468661: Gadolinium based Contrast Agents (GBCAs): Sensory Nerve Toxicity and intraepidermal Nerve Fibers Density Quantification in Cynomolgus Monkeys after single intravenous Administration with a 52-Week Recovery Phase GMRA-105: Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group—ODYSSEY

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 GBCA 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: - GBCA 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: None
Additional pharmacovigilance activities	None pursuant to an obligation imposed by a competent authority

VI.II.C Post-authorisation development plan

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

There are no planned or ongoing studies which are conditions of the marketing authorisation or specific obligation of ProHance.

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

8403760: Gadolinium based Contrast Agents (GBCAs) 29-Week Intravenous Repeat-dose Toxicity in the Juvenile Cynomolgus Monkey, with a 52-Week Recovery Phase.

Purpose of the study: Preclinical study to evaluate the toxicity of Omniscan, MultiHance and Gadavist (as representatives of linear and macrocyclic GBCAs), following repeated intravenous

administration to juvenile cynomolgus monkeys and to assess the reversibility of effects observed, if any, during a 52-week recovery phase.

8468661: Gadolinium based Contrast Agents (GBCAs): Sensory Nerve Toxicity and intraepidermal Nerve Fibers Density Quantification in Cynomolgus Monkeys after single intravenous Administration with a 52-Week Recovery Phase.

Purpose of the study: Preclinical study to evaluate the possible effects on the peripheral nervous system and determine the toxicokinetics of MultiHance or ProHance when intravenously administered once (0.3 mmol/kg) to cynomolgus monkeys and to assess the reversibility of effects observed, if any, during a 52-week recovery phase.

GMRA-105: A prospective evaluation of potential effects of repeated gadolinium-based contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.

This study will be conducted as a prospective, multinational, multicentre, longitudinal cohort study in two groups of participants exposed to GBCA (either macrocyclic or linear) and a matched control group of participants not exposed to any GBCA. Each GBCA-exposed participant should be likely to undergo at least 5 GBCA-enhanced MR examinations with the same GBCA throughout the 5-year study duration. This study will compare the results from the Control group of participants who have never been exposed to a GBCA to the results of each group (macrocyclic and linear) of GBCA-exposed participants.

Purpose of the study: To prospectively assess the potential effect of repeated exposure to either a linear or a macrocyclic GBCA on change from baseline to Year 5 in motor and cognitive function among neurologically normal adults in comparison to a matched non-GBCA exposed control group.