PRIMOVIST®
(Gadoxetate disodium)
EU Risk Management Plan

Part VI – Summary of activities in the risk management plan by product

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	patient group cannot be recommended.	

2. Elements for a Public Summary

2.1 Overview of disease epidemiology

Magnetic resonance imaging (MRI) is one of several choices to create images of the liver in people in whom certain liver diseases are known or suspected. MRI is a painless procedure that does not use X-rays (radiation). Primovist is a contrast agent that is injected into a vein just before starting the MRI procedure to produce better images of the liver.

Because there are many different kinds of liver diseases, an imaging procedure is often useful to see what kind of disease a person has, and to decide about the most suitable treatment. There are also other kinds of imaging procedures. Each kind of imaging procedure has different benefits and risks. For example, computed tomography ("CT scan") uses X-rays, and and intra-operative ultrasound is performed during surgery and therefore has no value for planning of surgery.

2.2 Summary of treatment benefits

MRI with Primovist has shown that this contrast agent helps to produce better images of the liver than MRI without Primovist. This means that when Primovist is used, doctors are better able to detect certain liver diseases in the MR images and to distinguish between different kinds of liver lesions (e.g., benign vs. malignant), than when the MRI procedure is done without Primovist. With the improved liver images, doctors and patients are then in a better position to decide about the best treatment options for the disease.

2.3 Unknowns relating to treatment benefits

Primovist has been studied in more than 2000 patients in clinical trials. In the main and supporting studies, Primovist was tested in men and women who were between 18 and more than 80 years old, including patients of different races. Worldwide, Primovist has been used in more than 1.7 million patients. There is no evidence to suggest that results would be any different in patients from other ethnic groups or in younger patients. Primovist is currently being evaluated in children > 2 months and < 18 years of age to obtain further information. In addition, a Phase 3 multi-centre study is planned in children 0 – 2 months of age.

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2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergy-like reactions, which may be severe	Severe allergy-like reactions may occur with all contrast agents, including Primovist. It is not known how often severe reactions may occur, because none of the patients involved in the tests with Primovist experienced a severe reaction. From everyday clinical practice, it appears that life-threatening allergy-like reactions are rare.	It is not possible to rule out that such a reaction may occur if a patient is treated with Primovist. Patients are observed for a period of time after the injection so that they can be treated immediately in case a severe allergy-like reaction should occur.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Nephrogenic Systemic Fibrosis (NSF), a disease involving thickening and hardening of the skin and connective tissues	Nephrogenic Systemic Fibrosis (NSF) is a disease involving thickening and hardening of the skin and connective tissues. NSF may result in debilitating joint immobility, muscle weakness or impairment of the function of internal organs which may potentially be life threatening. Through 25 Mar 2013, no cases of NSF have been reported in association with Primovist from any country or source, and it is uncertain whether Primovist may cause NSF. However, the use of some other gadolinium-containing contrast agents in patients with poor kidney function has been associated with NSF. Therefore, it cannot be ruled out that Primovist may also cause NSF to occur in patients with this condition. To help decide whether a patient is at possible risk for NSF, it is recommended to take a blood test to check how well the kidneys are working before making the decision to use Primovist, especially in older patients.

Important missing information

Missing information	What is known
Possible long-term effects of gadolinium deposits in bones or tissues	In patients with poor kidney function, it is possible that use of gadolinium-containing contrast agents might result in gadolinium deposits in bones or tissues. With Primovist, as of 25 Mar 2013, there have been no reports describing unfavourable long-term effects of such deposits.
Safety of Primovist in children or adolescents (persons under 18 years)	The safety of Primovist in persons under 18 years has not yet been tested. Therefore, use of Primovist in this patient group cannot be recommended. However, there is no suspicion from animal studies, ongoing clinical trials or post-marketing experience to suggest that Primovist may be harmful in children or adolescents.
Safety of Primovist in	Pregnant women are generally excluded from clinical trials with Primovist,

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pregnant or breastfeeding women	and therefore the safety of Primovist in pregnant women has not been established. Therefore, Primovist should not be used during pregnancy unless strictly necessary. However, there is no suspicion from animal studies or everyday clinical practice that Primovist may be harmful to these women or their unborn children. It is known that small amounts of gadolinium-containing contrast agents may appear in breast milk of nursing women. However, there is no suspicion from animal studies or everyday clinical practice that Primovist may be harmful to breastfed children.

2.5 Summary of additional risk minimisation measures by safety concern

These additional risk minimisation measures are for the following risks:

Nephrogenic Systemic Fibrosis (NSF), a disease involving hardening and thickening of the skin and connective tissues

Risk minimisation measure(s)
Objective and rationale: Healthcare providers should understand the risk of NSF and know which patients groups are at highest risk
Main additional risk minimisation measures • Education and outreach efforts towards healthcare providers (website, informational sessions and speeches at conferences) • Peel-off tracking labels (“sticky labels”) which can be attached to the patient record

2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
NSF Observational Study (“PERI Study“, Study No. 13701)	To assess the magnitude of potential risk for the development of NSF with Gd-based contrast agents	NSF	Enrolment terminated, follow-up of enrolled patients ongoing	Annual reviews and reports. Submission date of final study report mid-2014.
Interventional study of long-term Gd-retention in bone (Study No.:	To explore the potential for the long-term retention of Gd in	Gd-retention in bone, NSF	Ongoing	LPLV planned for Oct 2014. Submission date of final study

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Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
ALS-Gd64/001)	the bones of patients with moderate or severe renal impairment or stable renal function who have received a single dose of a Gd-based contrast agent or multiple doses of the same Gd-based contrast agent.			report Q2/2015 (planned)
Phase 4 non-interventional Primovist Paediatric Study (Study No. 13729) Category: 2 (US PMR, MRP follow-up measure SE/H/429/01-02/FU/02)	To obtain safety information and additional diagnostic information from a paediatric population (>2 months - <18 yrs).	Safety and efficacy in paediatric patients > 2 months to < 18 years	Ongoing	Enrolment completed. Final study report planned for October 2013
Study No. 16078: Open-label multi-centre Phase 3 clinical trial in paediatric subjects 0 to 2 months of age (Study no. 16078) Category: 2 (US PMR)	To gain experience and obtain information about the safety, efficacy, and plasma Gd concentrations after administration of Primovist in paediatric subjects 0 to 2 months of age who are referred for enhanced liver MRI for any indication.	Safety, efficacy and Gd plasma levels in paediatric subjects 0 -2 months of age	Planned	Submission date of final study report Q3/2015 (planned)

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Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation in the EU.

2.7 Summary of changes to the Risk Management Plan over time

Table 2-1: Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	25 Mar 2013	No additional safety concerns beyond those described in previous version of this RMP. No safety concerns were omitted.	Routine update, including transfer into new EU-RMP format. The topic “Potential risk for the development of NSF with the administration of Primovist injection in patients with moderate renal impairment” was listed separately as important missing information in the previous RMP version. This topic is now subsumed under the important potential risk “Nephrogenic systemic fibrosis (NSF)”, as the risk minimization measures included patients with both moderate and severe renal impairment, and no reports of NSF have been associated with Primovist even in severely renally impaired patients.