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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 internal organs or other body parts in people in whom certain diseases are known or suspected. MRI is a painless procedure that does not use X-rays (radiation). Dotagraf is a contrast agent that is injected into a vein just before starting the MRI procedure to produce better images. Such imaging procedures are 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 intra-operative ultrasound is performed during surgery and therefore has no value for planning of surgery.

2.2 Summary of treatment benefits

Dotagraf is a generic product. A generic product contains the same active ingredients as a product that has already been authorized (the 'reference product'). The reference product of Dotagraf is Dotarem. Gadoteric acid is the active ingredient of both products. Clinical trials with Dotarem have shown that gadoteric acid helps to produce better images than MRI without contrast. This means that in many cases, using a product containing gadoteric acid helps doctors to better detect certain diseases in the MR images and to distinguish between different kinds of diseases than when the MRI procedure is done without this contrast agent. With the improved 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

From experience with the reference product, there is no evidence to suggest that imaging results would be any different in certain patient groups.

2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Thickening and hardening of the skin and connective tissues in patients with underlying kidney problems (Nephrogenic systemic fibrosis)	Nephrogenic systemic fibrosis (NSF) is a rare 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. Administration of gadolinium containing contrast agents such as gadoteric acid may play a role in the development of NSF. Most	Patients should tell their doctor about any known kidney problems. The doctor might order a blood test to check kidney function before using gadoteric acid and will consider the need to use gadoteric acid very carefully in patients with severe underlying kidney problems.

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	patients who developed NSF had severe underlying kidney problems or received high and/or repeated doses of the contrast agent.	
Convulsions/seizures ("fits") (Convulsions)	Seizure-like events have been reported to occur rarely after intravenous use of MRI contrast agents, including products containing gadoteric acid. It is not entirely certain whether they are caused by the contrast agent, because most patients in whom such events were reported were suffering from underlying brain disease or had a known seizure disorder.	It is not possible to predict or prevent these rare reactions. Patients should tell their doctor about any known brain disease or seizure history. Patients who are known to be at increased risk for seizures are closely observed during the procedure so that they can be treated immediately in case a seizure should occur.
Allergy-like reactions, which may be severe (Anaphylaxis)	Severe allergy-like reactions may occur with all contrast agents, including gadoteric acid. Such reactions usually happen within a few minutes after injection of the contrast agent. Patients with asthma, allergies, or previous reactions to contrast media might be at increased risk. In rare cases, such reactions might be life-threatening or even fatal.	It is not possible to predict or entirely prevent these rare reactions. Patients should tell their doctor about any known allergies or previous reactions to contrast agents. All 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)
Gadolinium deposits in other organs and tissues than the brain (Gadolinium presence or accumulation/ retention in organs and tissues other than brain tissues)	There have been reports of unexpectedly prolonged retention of gadolinium in other organs and tissues than the brain (for example, in skin or bones) after repeated use of MRI contrast agents. No risk factors for this phenomenon other than frequent, repeated use of gadolinium containing contrast agents have been identified. To date, no adverse health effects (with the possible exception of NSF, thought to be associated with deposition of gadolinium in the skin) have been confirmed to be related to these findings.
Gadolinium presence/deposits in the brain (Presence or accumulation/ retention of gadolinium in the	There have been reports of unexpectedly prolonged retention of gadolinium in the brain after repeated use of MRI contrast agents. No risk factors for this phenomenon other than frequent, repeated use of gadolinium containing contrast agents have been identified. To date, no adverse health effects have been confirmed to be related to this finding.

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brain)	

Important missing information

Risk	What is known
Safety of Dotagraf in pregnant women (Use of Dotagraf during pregnancy)	Pregnant women are generally excluded from clinical trials, and therefore the safety of gadoteric acid in pregnant women has not been established. It is known that gadolinium can cross the placenta. Therefore, Dotagraf should be avoided in pregnant women unless the clinical condition requires its use. An article published after the data lock point for this RMP (1) suggested that women who received gadolinium-based contrast agents at any point during pregnancy had an increased risk of abortions, stillbirths, and adverse pediatric outcomes than women who did not undergo MRIs during pregnancy. However, this article failed to adjust for the effects of the underlying conditions of the mother that would necessitate a contrast-enhanced MRI during pregnancy. It is known that small amounts of gadolinium-containing contrast agents may appear in the breast milk of nursing women. However, there is no suspicion from animal studies or everyday clinical practice that gadoteric acid may be harmful to breastfed children.
Possibility of undesirable effects of gadolinium deposits in other organs and tissues than the brain (Clinical significance of gadolinium presence or accumulation/retention in organs and tissues other than brain tissues)	It is currently not known whether the deposition of gadolinium in other organs and tissues than the brain (for example, in bones) after repeated use of MRI contrast agents might be associated with any undesirable effects. In patients with severe underlying kidney problems, NSF has rarely occurred after treatment with gadolinium containing contrast agents (see above); and deposition of gadolinium in the skin and other tissues might play a role in the development of this rare disease. Otherwise, no other adverse health effects have been confirmed to be possibly related to gadolinium deposition/accumulation in the body of patients.
Possibility of undesirable effects of gadolinium presence/deposits in the brain (Clinical significance of gadolinium presence or accumulation/retention in the brain)	It is currently not known whether the deposition of gadolinium in the brain after repeated use of MRI contrast agents might be associated with any undesirable effects. To date, no adverse health effects have been confirmed to be related to this finding.

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2.5 Summary of risk minimisation measures by safety concern

All medicines have nationally approved labelling documents which provide physicians, pharmacists and other health care professionals as well as patients with details on how to use the medicine, the risks and recommendations for minimizing them. The measures in these documents are known as routine risk minimisation measures.

This medicine additionally has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities. These additional risk minimisation measures are for the following risk:

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 and which products and practices are more likely to trigger NSF.
Main additional risk minimisation measures: • Education and outreach efforts towards healthcare providers (website, informational sessions and speeches at conferences)

Presence or accumulation/retention of gadolinium in the brain

Risk minimisation measure(s)
Objective and rationale: • Healthcare providers and patients should be aware that small amounts of gadolinium may be retained in their bodies, including the brain, for unknown periods of time and that the risk of this gadolinium presence is unknown. It should be understood which products and practices are more likely to result in this presence and which patients groups are more vulnerable.
Main additional risk minimisation measures: • CCDS and SmPC changes • Dear Healthcare Professional Communuications as needed • Customer letters • Education and outreach efforts (via website, trainings, and seminars; informational brochure)

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2.6 Planned post authorisation development plan

List of studies in post authorisation development plan				
Study/activity	**Objectives**	**Safety concerns/efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
NSF Annual safety reports to be submitted to EMA	To ensure communication of any new information to regulatory authorities	Nephrogenic systemic fibrosis	Ongoing	DLP 01 May
Interventional study of long-term gadolinium retention in bone (Study No.: ALS Gd 64/001) (CHMP follow-up measure EMA/HA/A-31/1097/FUM001) Note that study uses Guerbet's Dotarem and not generic Dotagraf. Bayer expects that the results for Dotarem will also be applicable to Dotagraf.	To explore the potential for the long-term presence or retention of gadolinium in the bones of patients with moderate or severe renal impairment or stable renal function who have received a single dose of a GBCA or multiple doses of the same GBCA.	Gadolinium presence or accumulation/ retention in organs and tissues other than brain tissues; Clinical significance of gadolinium presence or accumulation/ retention in organs and tissues other than brain tissues	Ongoing	Final report expected: Q2/2018
Exploratory non-clinical studies to investigate increased signal intensity and presence or accumulation/ retention of gadolinium in the brain	Investigation of the phenomenon of presence or accumulation/ retention of gadolinium in the brain and any potential clinical relevance (including tests of neurological and motor function in rats administered GBCAs)	Presence or accumulation/ retention of gadolinium in the brain; Clinical significance of gadolinium presence or accumulation/ retention in the brain	Partially completed, some studies ongoing.	Study results will be published upon completion (some have already been published)

Studies which are a condition of the marketing authorisation

Not applicable.

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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
1.0	Dec 2016	Identified Risks: • Nephrogenic systemic fibrosis • Convulsions • Anaphylaxis Potential Risks: • Gadolinium presence or accumulation/retention in organs and tissues other than brain tissues • Presence or accumulation/retention of gadolinium in the brain Missing information: • Use of Dotagraf during pregnancy • Clinical significance of gadolinium presence or accumulation/retention in organs and tissues other than brain tissues • Clinical significance of gadolinium presence or accumulation/retention in the brain	EU RMP in 'Generic' format issued to support an EU marketing authorisation application.

3. References

1. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. Jama. 2016;316(9):952-61.