VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Clariscan (gadoteric acid) a gadolinium-based contrast agent (GBCA), is a diagnostic medicinal product used in patients undergoing a magnetic resonance imaging (MRI) scan.

GBCAs are used as a contrast enhancer to help make the inside of the body more visible on the scan and thus helps diagnose various diseases. GBCAs are only used by specialists.

Patients receive an intravenous injection of a gadolinium-based contrast agent just before or during the scan. Products containing Gadoteric acid are approved as MRI contrast agents and are used for the evaluation of head, brain and spine magnetic resonance imaging, whole body examination and imaging of blood vessels.

Gadolinium-based contrast agents can cause side effects, the majority are mild and transient. However, serious, life threatening anaphylaxis has been reported. In addition, there have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal disease. NSF is a serious condition which leads to hardened skin and decreased joint mobility, it may affect soft tissue and internal organs. Patients undergoing liver transplantation are at particular high risk since the incidence of acute renal failure is high in this group. Also to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age are at risk.

VI.2.2 Summary of treatment benefits

Gadoteric acid, the active substance of Clariscan, has shown in clinical trials its ability to increase the number of detected lesions in the brain and to improve the visualization of lesions, compared with non-contrasted images.

VI.2.3 Unknowns relating to treatment benefits

Use in pregnancy

There are no data from the use of gadoteric acid in pregnant women. Studies in animals did indicate direct or indirect harmful effects with respect to reproductive toxicity. Gadoteric acid containing medicines should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

VI.2.4 Summary of safety concerns

VI.2.4.1 Important identified risks

Table 26 Summary of important identified risks

Risk	What is known	Preventability
Allergic reactions (Hypersensitivity including anaphylaxis)	Hypersensitivity reactions may occur immediately (less than 60 minutes), while some of them may start within 7 days. Rarely an immediate reaction can be life-threatening and then requires emergency treatment. The staff at the MR centre is prepared if immediate intervention becomes necessary. Typical symptoms include swelling of face, mouth, hands, feet or throat which may cause difficulty in swallowing or breathing, in addition fainting, breathing difficulties, coughing, wheezing, sneezing, runny nose, eye irritation, eye swelling, urticaria (hives), itching, reddening of the skin, and skin rash. Hypersensitivity reactions may be independent of the dose, may occur after even the first dose of the product. They are generally unpredictable. The risk of occurrence is increased if you experienced an allergic reaction after previous administration of an MRI contrast agent.	Tell your doctor if you are allergic to Clariscan or if you reacted on contrast agents for magnetic resonance imaging. In case of allergy Clariscan must not be used.
Nephrogenic Systemic fibrosis (NSF)	NSF, which causes hardening of the skin and may affect also soft tissue and internal organs, is associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment. There have been cases of NFS most of which were in patients who received gadoteric acid containing medicines together with other gadolinium-containing contrast agents.	The risk of NSF is higher in patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) and in patients in the perioperative liver transplantation period. Therefore Clariscan (gadoteric acid) should only be used in after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. It is recommended that prior to administration of Clariscan all patients are screened for renal dysfunction by obtaining laboratory tests. If it is necessary to use the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan.

Table 26 Summary of important identified risks

Risk	What is known	Preventability
Convulsions (fits)	Gadolinium containing contrast agents are known to causes seizures (fits), especially in patients with a low threshold for seizures. Patients with a history of seizures or with brain lesions may have a low threshold for seizures.	Precaution measures include close monitoring after administration of the medicine. All equipment and drugs necessary to counter any convulsions, which may occur, must be made ready for use beforehand

VI.2.4.2 Important potential risks

Table 27 Summary of important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Gadolinium accumulation in organs and tissues other than brain tissues	There is a possibility of gadolinium accumulation in organs and tissues other than brain tissues after repeated administration of Dotarem. However, no clinical study has documented accumulation of gadolinium after multiple examinations with Dotarem (gadoteric acid) in other organs than the brain.
Accumulation and retention of gadolinium in the brain	There is a possibility of gadolinium accumulation in brain tissues after repeated administration of Dotarem. According to [Robert et al. 2015], no abnormal signal of gadolinium in brain structures was observed in MR images after repeated administration of Dotarem.
None	Not applicable

VI.2.4.3 Missing information

Table 28 Summary of missing information

Risk	What is known
Clinical significance of Gadolinium accumulation in organs and tissues other than brain tissues	Information is missing on the clinical significance of gadolinium accumulation in organs and tissues other than brain tissues; in particular, manifestations of toxicity have not been documented.
Clinical significance of gadolinium retention in the brain	Information is missing on the clinical significance of gadolinium retention in the brain; in particular, manifestations of toxicity have not been documented.
Use in Pregnancy	There are no data from the use of gadoteric acid in pregnant women. The medicines should not be used during pregnancy unless clearly necessary. A risk of birth defects for the unborn child cannot be excluded.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

No post authorisation studies are planned.

VI.2.7 Summary of changes to the risk management plan over time

There was no agreed risk management plan before marketing authorisation.