



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/PRAC/188631/2016

PRAC List of questions

To be addressed by the marketing authorisation holders for gadolinium containing medicinal products

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1437

Optimark EMEA/H/A-31/1437/C/000745/0034

INN/active substance: gadolinium



1. Background

Gadolinium containing contrast agents (GDCAs) are complexes of gadolinium (III) with different types of organic chelators. They are used for contrast enhancement in magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Within the class, they can be differentiated in linear or macrocyclic compounds and whether they are ionic or not.

In a previous referral under Article 31 of Directive 2001/83/EC finalised in 2010, the Committee for Medicinal Products for Human Use (CHMP) concluded that the use of GDCAs is associated with the risk of nephrogenic systemic fibrosis (NSF) a serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with renal impairment. The CHMP concluded that the risk of NSF is different for the different gadolinium-containing contrast agents, which were then categorised into three groups for NSF risk (high risk, medium risk and low risk).

In addition, since the finalisation of the previous referral, data in animals and humans indicates the accumulation of gadolinium following administration of GDCAs in other tissues, including the liver, kidney, muscle, skin and bone.

Furthermore, recent publications indicated the accumulation of gadolinium in the brain. The PRAC reviewed all available literature and data related to this issue and recommended in January 2016 some actions to be implemented (removal of the statement that the product does not pass the intact blood brain barrier from the SmPC and request to update the safety specifications in the Risk Management Plan to reflect these findings).

The PRAC also considered that the current knowledge about the brain accumulation and its clinical consequences need to be further investigated, which would require a review at EU level.

The EC initiated on 9 March 2016 a Referral under Article 31 of Directive 2001/83/EC, to allow further investigation of accumulation of Gadolinium in the brain to consequently recommend any appropriate studies to be conducted, as well as to consult with relevant experts in order to provide meaningful clinical advice to healthcare professionals. Considering the accumulation of Gadolinium in different body tissues, this review will also enable an assessment of the whole safety profile of GDCAs in view of their use in MRI and MRA.

2. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1

Concerning your Gadolinium-containing contrast agent authorised in the EU please provide in the annexed table:

- a) Figures on sales and patient exposure by product, member state, indication and age. Data on the use in clinical practice including information on dose, duration of treatment and concomitant treatment (characterisation of users, prescriptions...).
- b) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) on posology, and, (if implemented) regarding the risks of accumulation of gadolinium in the brain or other tissues on contraindications, warnings and precautions, and undesirable

effects. Please highlight the main differences between the product information (PI) in the different EU member states.

- c) An overview of the approved indication(s) of your Gadolinium-containing contrast agent outside the EU.

Question 2

Provide complete product information (summary of product characteristics, labelling and package leaflet) in English if available.

Question 3

Please provide all available safety data relevant to evaluate the risk of accumulation of gadolinium in the brain with your Gadolinium-containing contrast agent authorised in the EU and an analysis of this data in each of its approved indications. Specifically, the following questions should be answered:

- a) What is the evidence on deposition of gadolinium in the brain with your product(s), including evidence on:
- location of regions of signal hyperintensity and gadolinium deposits within the brain;
 - the impact of the number of MRI scans or cumulative dose; any information on the impact of single doses and the amount of single doses used;
 - the influence of patient characteristics, including underlying diseases and renal function, on the potential for brain accumulation of gadolinium;
 - the potential for deposition of gadolinium with your product compared with other products in the class.
 - accumulation in brains with certain diseases (e.g. affecting the blood brain barrier) compared to brains without disease.
 - any information about gadolinium accumulation in the basal ganglia after multiple enhanced examinations of other organs than the brain (e.g. breast, prostate, liver)?.
 - the point in time different gadolinium measurements in the brain have taken place, considering that the sensitivity of quantification methods (e.g. relaxometry) has increased over time .

This should include non-clinical and clinical trial data (including both MAH sponsored and non-sponsored studies), pharmaco-epidemiological studies (including observational studies), published literature and CIOMS line listing as appropriate.

- b) The MAH should discuss the mechanism of transfer of gadolinium into the brain and the chemical form in which it is deposited.

Question 4

What are the possible clinical implications of accumulation of gadolinium in the brain, with your product(s) specifically and also across the class based on published literature? This should be based on any case reports and on existing knowledge of the toxicology (including neurotoxicology) of gadolinium and the regions of the brain where deposition has been observed.

Question 5

Please specify (and provide evidence to justify) if there are groups of patients (e.g. diseases, age groups, demographics) or specific circumstances where use of your product has particular clinical advantages, relative to other products in the class.

Question 6

Provide a full benefit/risk assessment of your Gadolinium-containing contrast agent in the currently approved indication(s) in the EU.

This should include an assessment on the impact of occurrence of accumulation of gadolinium in the brain and other tissues (including liver, kidney, muscle, skin and bone) and any potential difference in risk compared with other authorised GdCAs (based on published literature) on the benefit/risk balance. Discuss whether the benefit/risk balance - differs according to subpopulations based on age or other factors.

Question 7

Please provide proposals and justifications for any risk minimisation measures (including changes to the SmPC/PL) which may improve the benefit/risk balance of your Gadolinium-containing contrast agent authorised in the EU and how their effectiveness should be monitored.

Specifically, In view of the answers to questions 3 and 4, what advice to clinicians or other risk minimisation measures are needed for your product(s)? Points to consider are:

- a) the number of MRI scans or cumulative dose administered;
- b) the influence of patient characteristics, such as underlying disease and renal function, on the potential for brain accumulation of gadolinium;
- c) the potential for deposition of gadolinium with your product compared with other products in the class;
- d) Please comment and discuss whether use of your product or any other product of the class might influence renal function and whether this may have any impact on the potential for brain disposition.

Question 8

Summarise the previous, planned and ongoing studies into this area for your product, and make proposals for additional non-clinical, mechanistic and clinical research to:

- a) better characterise the risk of brain deposition across the class;
- b) understand the mechanism of transfer of gadolinium into the CNS, and the chemical form in which it is transferred and retained;
- c) understand the radiological and potential clinical manifestations of brain deposition.

Annex

Question 1

a)

INN	Product name	Type of marketing authorisation	Indications¹	Pharmaceutical forms and strengths	Sales figures	Estimated patient exposure²	Doses (in clinical practice)	Treatment duration (in clinical practice)

¹. MAH should clearly indicate for which country a specifically dedicated presentation has been granted for a particular indication

². Expressed in patient years and stratified by Member State, by indication and by age (paediatric and adult use). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b)

PI	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Posology			
Contraindications			
Warnings and precautions			
Undesirable effects			