NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the European Commission:

Procedure name	Gadolinium-containing contrast agents
Active substance(s)	Nationally authorised: gadodiamide, gadopentetic acid, gadobenic acid, gadoxetic acid, gadoteridol, gadobutrol, gadoteric acid (including salts if applicable). Centrally authorised: gadoversetamide (OptiMARK)
Pharmaceutical form(s)	All pharmaceutical forms
Strength(s)	All strengths
Route(s) of Administration	All routes of administration
Marketing Authorisation Holder(s)	Various

Gadolinium containing contrast agents (GDCAs) are complexes of gadolinium (III) with different types of organic chelators. They act by shortening the relaxation times of tissue water protons within body tissues. 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. Based on the different characteristics of these complexes, they are used in several magnetic resonance contrast enhancement indications.

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, data in animals and humans indicates the accumulation of gadolinium following administration of GDCAs in other tissues[i], including the liver, kidney, muscle, skin and bone.

Furthermore, several recent publications indicated the accumulation of gadolinium in the brain[ii]. The PRAC reviewed all the literature and data related to this issue and recommended in January 2016 some actions to be implemented (removal of the statement that gadolinium does not pass the intact blood brain barrier from the summary of product characteristics, and to include as important

potential risk in the risk management plan "Gadolinium accumulation in organs and tissues other than brain tissues" and "accumulation and retention of Gadolinium in the brain", and as missing information "Clinical significance of Gadolinium retention in brain" and "clinical significance of Gadolinium accumulation in organs and tissues other than brain tissues").

However, the PRAC considered that the deposition of gadolinium in the brain reported in the scientific literature, and its clinical consequences, need to be further investigated.

A European review of these products, both nationally and centrally authorised, would allow further assessment of the evidence of accumulation of gadolinium in the brain, potentially including consultation with relevant experts.

Considering the accumulation of gadolinium in different body tissues, such a review will also enable an assessment of the whole safety profile and overall benefit-risk balance of GDCAs in view of their use in MRI and MRA.

In view of the elements described above and the necessity to take action at EU level, the European Commission considers that it is in the interest of the Union to refer the matter to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the procedure encompasses a centrally authorised product, pursuant to Article 31(1) of Directive 2001/83/EC the PRAC recommendation shall be referred to the Committee for Medicinal Products for Human Use to issue the opinion.

Signed [redacted] Date 03/03/2016

Robert Vanhoorde
Head of Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General

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i

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ii

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