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

Procedure No: EMEA/H/A-31/1437

Procedure No: Optimark EMEA/H/A-31/1437/C/000745/0034

Gadolinium containing medicinal products

Divergent statement

The following CHMP members do not agree with the CHMP's opinion recommending that the marketing authorisation(s) for gadobenic acid (full body indication), gadodiamide, gadopentetic acid (intravenous), and gadoversetamide should be suspended based on the following grounds:

It is agreed that available data from in vitro and non-clinical studies suggest that gadolinium contrast agents have a potential to release gadolinium from the ligand molecules. Furthermore, there is evidence showing that gadolinium can accumulate in the brain following exposure to gadolinium contrast agents.

While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is data showing gadolinium retention also from macrocyclic agents, albeit at lower levels than for the linear products. It is also notable that levels of retention appear to differ between products within the linear class of agents.

Available non-clinical studies with gadolinium contrast agents administered via the intended route have not identified signs of central nervous system toxicity, although there are limitations, including the lack of chronic toxicology data.

No clinical adverse effects have been identified from Gd brain retention following use of gadolinium contrast agents, and there is no scientifically justifiable threshold linked to a potential toxic effect.

Research both within the non-clinical and clinical area is ongoing, and data from some of the studies will become available within the coming year.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents than for the macrocyclic agents, and that the level of concern is related to the levels of retention described for each agent. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains largely hypothetical.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the hypothetically increased risk related to greater gadolinium brain retention than seen with other available agents. Thus, restricting the use of the linear agents to contexts where an enhanced MRI scan is required to obtain sufficient diagnostic information, to the use of the lowest effective dose and that repeated use should be avoided to the extent possible, are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

CHMP Members expressing a divergent opinion:

Agnes Gyurasics (HU)	20 July 2017	Signature: .....
Alar Irs (ET)	20 July 2017	Signature: .....
Andrea Laslop (AT)	20 July 2017	Signature: .....
Bruno Sepodes (PT)	20 July 2017	Signature: .....
Daniela Melchiorri (IT)	20 July 2017	Signature: .....
David Lyons (IE)	20 July 2017	Signature: .....
John Joseph Borg (MT)	20 July 2017	Signature: .....
Kristina Dunder (SE)	20 July 2017	Signature: .....
Natalja Karpova (LV)	20 July 2017	Signature: .....
Romaldas Mačiulaitis (LT)	20 July 2017	Signature: .....
Tomas Boran (CZ)	20 July 2017	Signature: .....
Ewa Balkowiec Iskra (PL)	20 July 2017	Signature: .....

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While studies show a greater potential for gadolinium to accumulate in the brain with the linear gadolinium contrast agents than with the macrocyclic gadolinium contrast agents, it should be acknowledged that currently fewer studies have been done with the macrocyclic agents. Further, there is data showing gadolinium retention also from macrocyclic agents, albeit at lower levels than for the linear products. It is also notable that levels of retention appear to differ between products within the linear class of agents.

Available non-clinical studies with gadolinium contrast agents administered via the intended route have not identified signs of central nervous system toxicity, although there are limitations, including the lack of chronic toxicology data.

No clinical adverse effects have been identified from Gd brain retention following use of gadolinium contrast agents, and there is no scientifically justifiable threshold linked to a potential toxic effect.

Research both within the non-clinical and clinical area is ongoing, and data from some of the studies will become available within the coming year.

It can be concluded that concerns about gadolinium retention and its potential clinical consequences are greater for the linear agents than for the macrocyclic agents, and that the level of concern is related to the levels of retention described for each agent. However, without evidence for a link to adverse clinical consequences and no clear understanding of the quantitative relation between cerebral tissue levels and potential toxic effects, the risk for adverse clinical consequences of brain accumulation of gadolinium has not been identified and remains largely hypothetical.

Taken together, the efficacy and the clinical benefit of these products are established. In the absence of toxicological and clinical adverse findings, we do not find it proportionate to conclude that the absolute benefit/risk balance for the linear agents are negative, if further restrictions to their use are made to address the hypothetically increased risk related to greater gadolinium brain retention than seen with other available agents. Thus, restricting the use of the linear agents to contexts where an enhanced MRI scan is required to obtain sufficient diagnostic information, to the use of the lowest effective dose and that repeated use should be avoided to the extent possible, are considered a more proportionate regulatory measure than suspension of the marketing authorisations.

CHMP Members expressing a divergent opinion:

Kolbeinn Gudmundsson (IS)	20 July 2017	Signature: .....
Svein Rune Andersen (NO)	20 July 2017	Signature: .....