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Gadolinium Based Contrast Agents (GBCAs)

Medical Imaging Drugs Advisory Committee (MIDAC)

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Errata to Advisory Committee Briefing Materials: Available for Public Release

Briefing Book Errata Description:

The following errata is noted in the Sponsor's briefing book:

1. Section 2.1.1. was missing a bullet of text summarizing the evidence of hyperintensity. This text is noted below, in red and underlined text

2. The Kuno, 2017 reference, noted in the added bullet, is provided.

Page 13-14:

2.1.1 Overall results on published clinical imaging and post mortem studies

Signal intensity (SI) increase on T1-weighted (T1w) unenhanced MR images in the basal ganglia of the brain and the presence of Gd* in these regions after repeated administrations of GBCAs has been a topic of research and scientific discussion for more than three years. A number of publications have emerged during this time mainly describing retrospective, single-center trials reporting the effect of various GBCAs on the signal intensity on non-contrast T1w images in the brain, and Bayer is actively researching this topic. The publications related to imaging findings reporting SI increase data on the following GBCAs: Gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), gadobenate dimeglumine (MultiHance), gadobutrol (Gadavist), gadoterate meglumine (Dotarem), gadoteridol (ProHance) and gadoxetic acid (Eovist). Only a very few articles describe actual measurements of Gd concentration in brain tissue (in patients who received Omniscan, Magnevist, ProHance, Eovist, and Gadavist) for a single patient or for very small numbers of patients (**McDonald, 2015**; **Murata, 2016**; **Kanda, 2015a**; **Roberts, 2017**; **McDonald RJ, 2017**).

The published clinical and non-clinical studies to date provide evidence of the following:

- Hyperintensity in the dentate nucleus (DN) and globus pallidus (GP) brain areas has been observed after 5 or more administrations of multi-purpose linear GBCAs with standard dose (0.1 mmol/kg bw) **(Kanda, 2014; Kanda 2015b; Ramalho, 2015; Errante, 2014; Quattrocchi, 2015; Radbruch, 2015; Schlemm, 2016; Weberling, 2015; Kuno, 2017; Bae, 2017**).
- No visual SI increase is observed after multiple administrations of macrocyclic GBCAs (Dotarem, Gadavist, ProHance) (Error! Reference source not found.**; Radbruch, 2016; Radbruch 2017a; Radbruch 2017b; Eisele, 2016; Bae, 2017; Langner, 2017; Tibussek, 2017**).
- Pediatric studies (**Radbruch, 2017b; Flood, 2017; Hu, 2016**) with standard dose (0.1 mmol/kg/bw) administered had similar results as in adults
- When exposed to a very high number (35 or more) of administrations of multi-purpose linear GBCAs the SI increase according to one publication (**Zhang, 2017**) can also be observed in other brain areas besides the DN and GP (e.g. posterior thalamus, substantia nigra, red nucleus, cerebellar peduncle, colliculi) whereas in patients who received 20 or

*Since the terms accumulation, retention and deposition imply a somewhat permanent situation (which is not scientifically confirmed), at this point in time Bayer would prefer to use "presence of gadolinium (Gd)" as a more accurate descriptor of the current state of scientific understanding.

more macrocyclic GBCA administrations no SI increase was seen in any area of the brain (**Radbruch. 2017a**).

- For the liver-specific linear agent Eovist such a SI increase has been reported in only one out of three recently published articles (**Kahn, 2017; Ichikawa, 2017; Conte, 2017**) and only after a significantly higher number of administrations (11-37) whereas in the other two publications no SI increase is seen after up to 15 or 18 administrations (**Ichikawa, 2017; Conte, 2017**).
    - The finding that an increased SI becomes visible for Eovist only after a higher number of administrations is not unexpected given that Eovist has a higher stability than all other linear GBCAs (**Frenzel, 2008**), is administered at a quarter of the dose of multi-purpose linear agents, and has a unique dual elimination pathway (50% renal, 50% hepatobiliary). All these features together lower the systemic Gd burden and thus the potential for Gd presence in the brain substantially when compared to all multi-purpose linear GBCAs.
- The SI increase or the presence of Gd in the brain is not limited to patients with impaired kidney function, which is an important differentiation from what has been observed with NSF. However, earlier appearance of a SI increase after multi-purpose linear GBCAs is seen in renally impaired patients (**Cao, 2016**).
- The influence of radiation therapy and chemotherapy on the observed SI and specifically if there is any additive affect is subject to ongoing clinical evaluations. Initial data suggest that such additive effect may exists (**Kasahara, 2011**; Kinner 2016 conference report at ISMRM).
- Some post-mortem (6 in total) studies provide explorative data on the presence of Gd in some brain areas as well as bone tissue (**McDonald, 2015; Murata, 2016; Kanda, 2015a; Roberts, 2017; McDonald RJ, 2017; McDonald JS, 2017**). Murata et al. reported on the presence of Gd traces from macrocyclic as well as linear GBCAs Gd in the brain areas and also bone tissue. Gd concentrations in bone tissue from all nine patients involved in this study were several times higher than brain Gd levels after the administration of linear and macrocyclic agents (**Murata, 2016**).
- Despite differences in SI, no histopathological changes to brain tissue and no adverse health effects have been confirmed to be associated with these findings.

8 References

[Kuno, 2017] Kuno H, Jara H, Buch K, Qureshi MM, Chapman MN and Sakai O. Global and Regional Brain Assessment with Quantitative MR Imaging in Patients with Prior Exposure to Linear Gadolinium-based Contrast Agents. *Radiology*. 2017;283:195-204.