FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Medical Imaging Drugs Advisory Committee Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
September 8, 2017

QUESTIONS

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1. In the evaluation of risk of gadolinium-based contrast agents (GBCAs) in 2009, FDA considered: the thermodynamic stability of the drugs; the in vitro kinetics of release of free gadolinium; histopathologic evidence of toxicity in juvenile and adult animals; clinical evidence of toxicity based on reports of systemic fibrosis; susceptible patient populations (i.e. those with moderate to severe renal insufficiency). GBCAs were risk-stratified based on the totality of this evidence. Risk mitigation steps included warnings and contraindications in the prescribing information, public communications, increased pharmacovigilance and reporting for systemic fibrosis.

   DISCUSSION: Given the new concerns raised by gadolinium retention in patients with normal renal function, please discuss how FDA should weigh this new finding in relation to the known risks.

   In the absence of scientific criteria (e.g. toxicological or clinical thresholds) to inform risk assessment, which factors should FDA consider?

   Include in your discussion the evidence of differential retention, establishment of empirically defined retention thresholds (e.g. retention with linear vs. macrocyclic agents), retention levels in specific organs (e.g. CNS, skin, bone), molecular forms of gadolinium (free vs. chelated vs. bound to biologic macromolecules).

2. **DISCUSSION:** Based on FDA Adverse Event Reporting System (FAERS) and literature reports, is there evidence of a causal relationship between symptoms and signs in patients with normal renal function and gadolinium retention?

   Please consider in your discussion the shortcomings of FAERS and other uncontrolled data sources. Please discuss whether the potential risks of gadolinium retention might be greater in patient subgroups (e.g. pregnant women, pediatric patients, patients with inflammatory disorders in CNS and other organs, patients with chronic conditions requiring multiple exposures to GBCAs).

QUESTIONS (cont.)

3. There are gaps in our understanding of gadolinium retention including toxicological thresholds, potential mechanism of toxicity, potential clinical and subclinical manifestation of toxicity in CNS and other organs.

   DISCUSSION: Please discuss the types of preclinical studies (e.g. comparative toxicokinetic studies of levels of gadolinium retention and functional and pathologic correlates in the CNS of juvenile and adult animals). Please discuss what clinical studies should be performed to better understand any potential safety risk associated with gadolinium retention; include in your discussion prospective studies such as registries, epidemiologic surveys, parallel arm studies of neurologic function, and retrospective studies using existing databases.

4. **VOTE:** Our plan for addressing the potential consequences of gadolinium retention is to revise the prescribing information for GBCAs as a class to include: a warning for retention for all GBCAs, with greater retention of all or some of the linear GBCAs compared to the macrocyclics in certain organs including the brain; recommended risk minimization steps for certain patient populations.

   Do you agree with this plan? Please summarize the reasons for your vote.

5. **VOTE:** A number of clinical and preclinical studies are ongoing and we might request that manufacturers conduct additional studies that will inform our decisions about the need for further regulatory actions including withdrawal of approval and restriction of indicated populations.

   Do you agree with this plan? Please summarize the reasons for your vote.