

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-066

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY

MEDICAL OFFICER REVIEW

NDA: 22066
Product: Omniscan (gadodiamide)
Sponsor: GE Healthcare
Reviewer: Louis Marzella, M.D., Ph.D.

Date: April 6, 2007

Summary

On July 6, 2006, GE submitted an NDA for a Pharmacy Bulk Pack for Omniscan. The original submission contained no clinical data. The sponsor also provided a package insert that included only new content to support the Pharmacy Bulk Pack presentation.

In response to an Agency's request the sponsor revised the PI to PLR format and in addition also made important changes to the content particularly in the Warnings and Adverse Recation Sections. The sponsor also provided rationale for some of these changes in the form a document titled "Justification for Revision to Omniscan Pharmacy Bulk Package Labeling". The document included a brief summary of the sponsor's postmarketing safety database. Based on this analysis the sponsor proposed removal of some thirty terms and the addition of others terms. The documentation provided was incomplete or incorrect, the interpretation unreasonable.

Examples of these shortcomings include characterization of Omniscan –associated renal failure as reversible, proposal to omit seizures (a new warning is required due to seizures precipitated by inadvertent intrathecal administration of Omniscan). Moreover the basis for removing adverse reaction terms (e.g non-seriousness, reporting frequency) are not acceptable.

The agency conducted a review of the AERS database for Omniscan (see consultation reports from DMETS and DDRE) and reviewed the scientific literature. With regard to the issue of Nephrogenic Systemic Fibrosis the reports prepared by the Canadian and European Health Authorities were reviewed.

The principal labeling issues are summarized below. These issues were presented verbally and discussed with the sponsor at two teleconferences (see Project manager memoranda for summaries).

1. Hypersensitivity is the most common clinically important adverse event accounting for 47% of all the serious ADRs in the sponsor's safety database. In the sponsor's proposed label

The _____ warnings should be combined under the header Hypersensitivity Reactions and listed first.

2. Nephrogenic systemic fibrosis. The PI does not include information on this emerging condition seen almost exclusively in patients with severe renal insufficiency. To date the majority of the cases of NSF have been attributable to Omniscan and Magnevist. A contraindication in Omniscan is warranted in patients with severe renal insufficiency, hepatorenal syndrome or renal dysfunction of any severity in the perioperative liver transplantation, and in patients with pre-existing nephrogenic systemic fibrosis. A warning is necessary for patients with lesser degrees of renal insufficiency describing risk factors including the specific contrast agent, repeated or higher than recommended doses of Omniscan and the degree of renal insufficiency. Assessment of renal function before administration of Omniscan is advisable.
3. Acute Renal Failure. The AERS database and the literature support the finding of worsening of renal insufficiency including development of dialysis-dependent failure in patients receiving Omniscan. In the sponsor database there are 13 unique cases including one fatality and two serious disabilities. The sponsor proposed warning titled _____ requires revision because it does not cite worsening renal insufficiency /acute renal failure reactions observed following the administration of Omniscan and contains no specific risk management recommendations (e.g. use lowest possible dose, monitor renal function).
4. Seizures associated with other neurologic sequelae. Nervous system disorders is the second most common SOC contributing to the total number of SAEs in the sponsor's database. Nineteen of these reports include convulsions or epilepsy. Draft Information Request Letter. The AERS database contains eight reports of adverse reactions associated with the intrathecal or intraventricular administration of Omniscan. The reactions included seizures, coma, and sensory and motor neurologic deficits. In four of the reports the administration of Omniscan was inadvertent; and in two of these four reports Omniscan was administered instead of the intended contrast agent Omnipaque. DMETS and DDRE recommend that the warning "NOT for Intrathecal _____" be added to the label. A boxed warning on the PI and the outer packaging should be added. It should be noted that the carton label for Omnipaque and Omniscan are very similar and that this issue needs to be addressed by the sponsor (see CMC review and recommendations).
5. The sponsor's proposal for removal of thirty adverse reaction terms (based on one of more of the following: seriousness, assessment of causality by the investigator, number of cases observed in the clinical trials, and reporting frequency postmarketing) is not adequately supported. The sponsor needs to reinstate the terms and provide additional data.

6. The "Postmarketing Experience" section of the label needs revision _____

7. _____

With regard to the other sections of the label:

8. The Clinical Studies Section contains claims that the diagnostic performance of Omniscan _____ is similar for the CNS and Body indications. Unless the clinical studies were formally designed to compare the diagnostic performance of the two contrast agents, any mention of _____ study arms should be stricken from the label.

9. _____

Finally a number of other less substantive editorial revisions to the label have been made and will be sent to the sponsor.

Conclusions and Recommended Regulatory Action by Clinical Reviewer

The Pharmacy Bulk Pack package insert and the Single Administration package insert needs important clinical updates particularly with respect to safety.

In terms of priority the contraindication and warning for NSF are the highest priority and might be implemented by a request for a CBE labeling supplement requesting specific language.

Other important safety updates and various other content and format proposed changes to the label require further discussions with the sponsor and labeling negotiations
See appendix for proposed information request letter and revise label

10 Page(s) Withheld

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✓ Draft Labeling

 Deliberative Process

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/s/

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