CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-066

SUMMARY REVIEW

DIVISION DIRECTOR'S REVIEW MEMORANDUM

NDA:	022-066
DRUG:	gadodiamide; this NDA is a Pharmacy Bulk Presentation for Omniscan™ that is already marketed under another NDA number.
TRADE NAME:	Omniscan™ (gadodiamide) Injection
FORMULATION:	Pharmacy Bulk Presentation containing 287 mg/mL of gadodiamide with specified additional solution contents in a 50 mL or 100 mL presentation; single dosages are to be extracted from these bulk presentations.
ROUTE:	Intravenous
DOSE:	The dose has not changed from the currently approved dosages specific for CNS and body imaging (0.2 mL/kg which is the same as 0.1 mmol/kg); a second dose may be administered.
SPONSOR:	GE Helathcare
SUBMITTED:	July 7, 2006
PDUFA DUE DATE:	May 3, 2007
DD MEMO COMPLETED:	April 30, 2007
DD MEMO PREPARER:	Dwaine Rieves, MD, Acting Division Director Division of Medical Imaging and Hematology Products

OVERVIEW:

This NDA was submitted to support the approval of a pharmacy bulk presentation of Omniscan. Omniscan was originally approved by the FDA in 1993 for use in magnetic resonance imaging (MRI). The pharmacy bulk NDA was submitted without a request for change in indication or dosage. During the review cycle, safety data were reviewed (both from FDA MedWatch reports and sponsor-supplied safety information) that necessitated a request for updating the product's label. The sponsor was also requested to change the label format to comply with the Physician's Labeling Rule. During the review cycle, special concerns were raised regarding the occurrence of nephrogenic systemic fibrosis (NSF) among patients exposed to gadolinium-based contrast agents, including Omniscan. These concerns are currently under review and will ultimately impact the Omniscan label. Additionally, the sponsor must supply a labeling supplement for the currently marketed Omniscan presentation to maintain consistency with the pharmacy bulk presentation's label.

The review team is not able to concur with the approval of the NDA due to constraints for revised product labeling. Specifically, the following items must be supplied:

-a labeling supplement to NDA 020123 that maintains consistency with the 022-066 product label

-submission of labeling that incorporates the most recent label requests from FDA.

The sponsor will also be informed that additional labeling changes may be necessary following completion of the FDA review of NSF safety concerns for gadolinium-based contrast agents.

REVIEWS:

Clinical:	Louis Marzella, M.D., Ph.D.
Statistics:	Not applicable--no new efficacy data submitted.
Chemistry:	Eldon Leutzinger, Ph.D.
Pharm-toxicology:	None--not applicable.
Microbiology:	Robert Mello, Ph.D.
Clin Pharmacology:	None--not applicable.
DMETS:	Todd Bridges, R.Ph.
Advisory Committee:	None

RECOMMENDED REGULATORY ACTIONS:

1) Supply of an "approvable" letter to the sponsor:

During the review cycle, the review team examined MedWatch reports and summary safety data from the sponsor that necessitated revisions to the proposed product label. These alterations were to be applied to a label that attempted to maintain consistency with the expectations of the Physician's Labeling Rule (PLR). The Omniscan product label for the currently marketed presentation of Omniscan is not in the PLR format.

The review team has outlined important label textual changes that will facilitate the informativeness of the Omniscan label and the sponsor should supply a revised label that meets these expectations. Additionally, a labeling supplement for the currently marketed presentation of Omniscan must be submitted and approved concurrently with this Pharmacy Bulk Pack Presentation.

2) Requirement of the sponsor to conduct post-marketing studies and to submit additional information:

None are required.

3) Compliance with Pediatric Research Equity Act (PREA) of 2003 expectations:

Not applicable.

REVIEW COMPONENTS:

Background

As outlined above, Omniscan is currently approved for use in MRI. This NDA relates solely to the approval of a new presentation, a Pharmacy Bulk Package from which pharmacists will extract individual doses. A similar marketing paradigm (pharmacy bulk presentation) has been approved for Magnevist, another gadolinium-based contrast agent.

Brief Regulatory Timeline

- Original submission: July 7, 2006
- PDUFA action: May 3, 2007

Clinical Review

The clinical review was performed by Dr. Louis Marzella who noted that MedWatch reports and sponsor-supplied information highlight risks for:

-hypersensitivity reactions (a risk currently implied in the marketed Omniscan's label); reports. As Dr. Marzella notes, hypersensitivity reactions are the most common cause for submission of MedWatch reports and the currently marketed Omniscan label provides no definitive information regarding this risk. The requested label text will include hypersensitivity reactions within the Warnings and Precautions Section.

-renal failure: MedWatch reports and sponsor data cite at least 13 cases of worsening renal function, a risk not currently stated clearly in the marketed Omniscan product label. This risk will also be described within the requested label's Warnings and Precautions Section.

-NSF: as noted above, the review of this safety concern is on-going and the sponsor will be informed of the plan for requesting a Changes Being Effected labeling supplement. The response to this request may or may not directly impact this NDA, due to the on-going nature of the FDA review of this concern for all gadolnium-based contrast agents.

-Seizures: inadvertent intrathecal administration has been reported to cause seizures and this risk will be highlighted within a black box warning for the requested label.

Multiple other sections of the product label will be requested to be revised to enhance the informativeness of the information.

CMC Review and Microbiology Review:

Dr. Eldon Leutzinger completed a detailed chemistry review and concluded that the NDA could be approved. Dr. Leutzinger noted that the formulation of the product is identical to that currently marketed.

Dr Robert Mello reviewed the microbiological aspects of the submission and concluded they were acceptable.

Division of Scientific Investigation (DSI)

No inspection was performed. Establishment inspection revealed acceptable compliance.

Consultations

The DMETS consultants recommended revisions of the label to lessen the risk for medication errors, especially with respect to intrathecal administration.

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/s/

Rafel Rieves
4/29/2007 11:22:18 AM
MEDICAL OFFICER