CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-066

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

M EMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

RCM #: 2007-78

DATE: March 12, 2007

FROM: Susan Lu, R.Ph., Safety Evaluator Team Leader
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D. , Deputy Director for
Mark Avigan, M.D., C.M., Director
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TO: Rafel Dwaine Rieves, M.D., Acting Director
Division of Medical Imaging and Hematology Products

SUBJECT: OSE Postmarketing Safety Review
Product: Gadodiamide (Omniscan®)
NDA#: 22-066
Event(s): Seizures

EXECUTIVE SUMMARY

This consult follows a request made by the Division of Medical Imaging and Hematology Products to review revised product labeling for Omniscan® and determine if additional adverse events should be considered for inclusion in the labeling. This document provides both an overview of all adverse events and an analysis of reports of seizures associated with gadodiamide reported to the Adverse Event Reporting System (AERS) database.

A total of 623 crude adverse event reports associated with gadodiamide were identified in the AERS database, of which 253 reports had a serious outcome including 15 deaths. The majority of reports (84%) were from domestic sources. The 20 most frequently reported events were vomiting (115), nephrogenic fibrosing dermopathy (86), nausea (85), urticaria (77), dyspnea (45), pruritus (44), dizziness (28), dysgeusia (28), chest pain (27), edema peripheral (24), headache (21), anaphylactoid reaction (20), dermatitis (20), convulsion (19), vasodilatation (17), hypersensitivity (16), rhinitis (15), flushing (13), pharyngitis (13) and asthenia (12). Most of these events are expected, however, nephrogenic fibrosing dermopathy and seizures are not addressed in the current product labeling. Nephrogenic fibrosing dermatopathy associated with gadolinium use is addressed in a separate consult.

We reviewed 17 reports of seizures temporally related to gadodiamide administration.
The mean age of the patients was 52 years with a range of 1 month to 78 years. A female predominance (70%) was observed. There were no fatalities, however, other serious outcomes included hospitalization (7), and life-threatening (6) and required medical intervention (1). The time to onset of seizures ranged from within minutes to several hours following gadodiamide administration. The administered dose appeared generally within the recommended dosage guidelines although body weight information was not provided in the reports. The indications for use were reported as brain MRI (5), MRI (5), myelogram (4), angiogram (1), discogram (1) and neck pain (1). Two patients had a documented history of seizures.

Of note, are 5 cases describing off-label intrathecal administration of gadodiamide for myelogram (4 patients) and brain MRI (one patient). In general, seizures associated with intrathecal administration were accompanied by respiratory difficulty requiring intubation and other neurologic symptoms such as confusion, hallucinations or coma. Patients also experienced decline in respiratory function requiring intubation. In 4 out of 5 patients, the onset of seizures was delayed occurring 3-5 hours after gadodiamide administration. Two reports of intrathecal use involved a medication error; one patient accidentally received gadodiamide into a cerebroventricular drainage line instead of the intravenous line and a second patient was administered Omniscan instead of Omnipaque (as prescribed) for myelography.

In contrast to intrathecal administration, 9 cases of seizures associated with intravenous gadodiamide administration generally reported a relatively short time to onset; 8 patients experienced seizure activity within minutes to one hour after injection. However, one case which documented a positive rechallenge with a delayed onset of seizure 16 hours after IV Omniscan administration and upon re-exposure, the patient experienced a second seizure 5 hours after administration. All 9 patients appeared to recover without sequelae.

Based on our analysis of 17 spontaneous reports of seizures associated with gadiodiamide administration, we suggest the following revisions to the product labeling:

- Inclusion of information regarding possible risk of seizures

- A statement that gadodiamide is not indicated for intrathecal use which has been associated with seizures and other serious adverse events

BACKGROUND AND PRODUCT LABELING

Gadodiamide (Omniscan®), a gadolinium complex of diethylenetriamine pentaacetic acid bimethylamide, is indicated for intravenous use to visualize lesions with abnormal vascularity in central nervous system (brain, spine and associated tissues) and the body (thoracic, abdominal, pelvic cavities and retroperitoneal space). The FDA approval date was January 8, 1993.

According to proposed Omniscan product labeling, the most frequently reported adverse events in clinical trials were nausea, headache and dizziness of mild to moderate intensity which occurred in 3% or less of patients.

DMIHP requested a review of the AERS database to identify adverse events for possible inclusion in the Omniscan Pharmacy Bulk Packaging product labeling. A review of AERS data identified 17 reports of seizures, which are summarized. A separate review of reports of nephrogenic system fibrosis for Omniscan and other gadolinium containing contrast agents is forthcoming.

SEARCH STRATEGY AND RESULTS

Adverse Event Reporting System

Summary of all events

The AERS database was searched on January 29, 2007 for all adverse events associated with gadodiamide. The AERS database contained a total of 623 *crude* reports for aprotinin. 253 reports had a serious outcome reported as death (15), hospitalization (100), life-threatening (57), disabled (52) and required intervention (40)[1]. There were 179 expedited (15-day), 90 direct, and 354 periodic reports. The years of reporting ranged from 1993 to 2007. Most reports (84%) were from domestic sources. The majority of reports were coded with Preferred terms (PTs) that are classified under the following System Organ Classes (SOCs): Skin and Subcutaneous Tissue Disorders (238), Gastrointestinal Disorders (208), General Disorders and Administration site (144), Nervous System Disorders (137), and Respiratory, Thoracic and Mediastinal Disorders (85). The 20 most frequently reported events were vomiting (115), nephrogenic fibrosing dermopathy (86), nausea (85), urticaria (77), dyspnea (45), pruritus (44), dizziness (28), dysgeusia (28), chest pain (27), edema peripheral (24), headache (21), anaphylactoid reaction (20), dermatitis (20), convulsion (19), vasodilatation (17),

[1] A case may report more than one outcome.

hypersensitivity (16), rhinitis (15), flushing (13), pharyngitis (13) and asthenia (12). A majority of these events are expected and mentioned in the product labeling.

Summary of AERS reports of Seizures

For the period through January 29, 2007, the AERS database contained 17 unduplicated cases that were identified by the active ingredient gadodiamide or the trade name Omniscan and the MedDRA PT terms, Convulsion and Grand Mal Convulsion. Demographic and summary information of these cases are provided in Table 1.

Table 1. Characteristics of Seizures case series (n=17)	
AGE (years) (n=11)	mean – 51.9 median - 53 range – 6 wks- 78 years
GENDER	male - 5 female - 12
TIME TO ONSET **(n=16)**	1-10 minutes after injection – 6 30 minutes-1 At completion of exam – 2 1 hour-2 3 hours-2 5 hours-2 16 hours-1
OUTCOME	Serious -14 Non-serious - 3 Serious outcomes reported as: Hospitalization - 7 Life-threatening – 6 Required medical intervention - 1
INDICATION FOR USE	Brain MRI – 5 MRI - 5 Myelogram – 4 Angiogram -1 Discogram - 1

	Pain management -1
ROUTE OF ADMINISTRATION	Intrathecal - 5 Intravenous -9 Epidural -1 Intra-arterial -1 Intra-discal -1
DOSE (ml) (n=15)	1- 5ml – 3 6-10 ml – 5 11-15 ml – 5 > 15 ml - 2
REPORTING COUNTRY	US – 13 Norway – 3 Japan - 1
TYPE OF REPORT	Expedited – 9 Direct – 1 Periodic – 7

17 patients experienced seizures temporally related to gadodiamide administration.

- 6 patients were reported to have grand mal convulsion and 11 patients had unspecified convulsion.
- The mean age of the patients was 52 years with a range of 0.1 to 78 years.
- A female predominance (70%) was observed.
- There were no fatalities, however, other serious outcomes included hospitalization (7), and life-threatening (6) and required medical intervention (1).
- The time to onset of seizures ranged from within minutes to several hours following gadodiamide administration.
- The administered dose ranged from 1.8-18 ml and appeared generally within the recommended dosage guidelines although body weight information was not reported.
- Two reports documented a previous seizure history.
- The indications for use were reported as brain MRI (5), MRI (5), myelogram (4), angiogram (1), discogram (1) and neck pain (1).

Of note, are 5 cases of off-label intrathecal administration of gadodiamide for myelogram (4 patients) and brain MRI (one patient).

- In general, seizures associated with intrathecal administration were accompanied by decline in respiratory function requiring intubation as well as other neurologic symptoms such as hallucinations, confusion or coma.
- In 4 out of 5 cases, the onset of seizures was delayed occurring 3-5 hours after gadodiamide administration.
- Diagnostic CT scans revealed contrast media in the CNS in 4 patients.
- Two reports involved a medication error; one patient accidentally received gadodiamide into a cerebroventricular drainage line instead of the intravenous line and a second patient was administered Omniscan instead of Omnipaque (as prescribed) for myelography.

In contrast to intrathecal administration, 9 cases of seizures associated with intravenous gadodiamide administration reported a relatively short time to onset; 8 patients experienced seizure activity within minutes to one hour after injection. One patient had a delayed onset of seizure 16 hours after administration and upon re-exposure to Omniscan experienced a second seizure 5 hours after administration; this is the only case reporting a positive rechallenge to Omniscan. All 9 patients appeared to recover without sequelae.

Representative cases:

FDA# 5034023-9-00-01/Mfr# OSCN-PR-0510S-0207 US Periodic Positive RC

A 41-year old female with history of penicillin allergy received an intravenous administration of 15 ml Omniscan for an MRI of the left breast. During the administration, she complained of injection site burning and pain. Approximately 16 hours post administration, the patient experienced a grand mal seizure followed by nausea, vomiting, headache and flushing. Her symptoms resolved. The following day, she received a second intravenous dose of 15 ml Omniscan. Five hours later, she experienced another seizure followed by headache.

FDA# 4357801-8-00-01/Mfr#OSCN-PR-0405S-0081 US 15 Day Intrathecal use

A 53 year old female received off-label intrathecal administration of 15 ml Omniscan for x-ray myelogram in preparation for lumbar fusion surgery. She also received midazolam prior to myelogram for sedation. 3 hours after completion of myelogram at a hotel, she developed hallucinations and experienced a seizure. Paramedics administered 2 mg lorazepam and patient was admitted to stroke unit and treated with dexamethasone. The following day, she was confused and agitated and was treated with lorazepam, haloperidol and propofol. She was intubated and transferred to the CCU. A CT scan indicated that Omniscan was no longer in the brain. Patient also experienced deafness, inability to speak and pneumonia. She eventually recovered over a period of 2 weeks.

FDA# 32215-8-0-00-01/Mfr# OSCN004980042 US Periodic IV admin

A 31-year-old male with a history of headaches presented to a brain MRI. He had no history of allergies, concomitant medications or premedication. 16-18 ml of Omniscan was administered intravenously. Immediately following the injection, the patient reported feeling unwell and complained of chest pain. He was taken out of the MRI scanner and within a few minutes of injection, experienced a grand mal seizure. The physician called a code and opened the patient's airway. He was then transferred to the emergency room and treated (treatment unspecified). It was reported that the patient recovered.

Conclusion

We reviewed 17 reports of seizures temporally related to gadodiamide administration.
Although there were no reported fatalities, 14 reports had serious outcomes including hospitalization, life-threatening event and medical intervention. The time to onset of seizures ranged from minutes to several hours following gadodiamide administration. The indications for use were reported as brain MRI (5), MRI (5), myelogram (4), angiogram (1), discogram (1) and neck pain (1). Two patients had a documented history of seizures.

Of note, are 5 cases describing off-label intrathecal administration of gadodiamide for myelogram (4 patients) and brain MRI (one patient). In general, seizures associated with intrathecal administration were accompanied by respiratory difficulty requiring intubation and other neurologic symptoms such as confusion, hallucinations or coma. Patients also experienced decline in respiratory function requiring intubation. In 4 out of 5 patients, the onset of seizures was delayed occurring 3-5 hours after gadodiamide administration. Two reports of intrathecal use involved a medication error; one patient accidentally received gadodiamide into a cerebroventricular drainage line instead of the intravenous line and a second patient was administered Omniscan instead of Omnipaque (as prescribed) for myelography.

In contrast to intrathecal administration, 9 cases of seizures associated with intravenous gadodiamide administration generally reported a relatively short time to onset; 8 patients experienced seizure activity within minutes to one hour after injection. However, one case documented a positive rechallenge with a delayed onset of seizure 16 hours after IV Omniscan administration and upon re-exposure, the patient experienced a second seizure 5 hours after administration. All 9 patients appeared to recover without sequelae.

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Susan Lu, R.Ph.
Safety Evaluator Team Leader, DDRE

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Attachment A
Case Summary of Seizure Cases Reported to AERS

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CSENUM	Mfr Cntl#	Cntry	Age	Sex	Out come	Onset	Rte	Indication	Dose	Event(s)	COMMENT	MED HX
4992144	18413	US	66	M	None	3 min	IV	MRI	15 ml	Grand Mal seizure		Seizures
5578606	OSCN004 960022	US	47	F	None	P exam	IV	Brain MRI	10 ml	seizures (3)	Hx leg/arm numbness	arm/leg numbness
3002014	OSCN004 970122	NO	41	F	LT/ Hosp	5 hours	IT	Brain MRI	10 ml	seizures, med error, coma	Injection into cerebroventricular drainage line, intubation required,	
3228778	OSCN004 980042	US	31	M	LT	few min	IV	Brain MRI	16-18 ml	Grand mal seizures, chest pain	Code called, Airway opened and transferred to ER	
3457971	OSCN-PR-9911S-0060 (0)	US		F	Hosp	6 min	IV	Brain MRI	17 ml	seizure 8-10 min	Transferred to ER	
3552434		US	53	F	Hosp	3 hr	IT	Lumbar myelogram	7 ml	seizures, respiratory decline req intubation	Intubation. Improvement in 3 weeks. Subsequent CT scan showed slow clearing of Omniscan from CNS	myelitis, recent UTI, renal compromise, anemia, ulcer, HTN, diabetes
3812381	OSCN-PR-0105S-0051(0)	US	59	F	LT	2-3 min	IV	Brain MRI	13 ml	grand mal seizure, nausea, syncope	Transferred to ER.Recovered	small seizures, sulfa allergy
3809568	OSCN-NO-0206S-0073 (0)	NO	45	F	LT/ Hosp	unk	IT	Myelogram	unk	seizure, coma,	Intubation	Discopathy
3866008	OSCN-NO-0209S-0166 (1)	JP	72	M	LT	1 hr	IV	MRI	10 ml	seizures, rigors, fever, shock		Gingival carcinoma
3926031	OSCN-PR-0204S-	US	68	F	Hosp	5 min	IV	MRI of neck	14 ml	seizure 5 min and 45 min p injection	Rx with epi and benadryl and Transfer to ER	

	0041 (0)											
4102736	OSCN-PR-0402L-0025	US	0.1	F	Hosp	1 hour	intra-arteri-al	angiogram	4.5 ml	seizure	Complicated med history in 6 wk old infant	hemorrhagic telangietectasia, intracerebral hemorrhages, arteriovenous fistulas
4136630	OSCN-PR-04045-0081	US	53	F	Hosp	3 hr	IT	myelogram	15 ml	seizure,hallucinations, confusions,agitation,fever, deafness, CCU	Intubation req	contrast media reaction,cervical dysplasia
4178270	OSCN-PR-04068-0181(3)	US	56	M	Hosp	5 hr	IT	myelogram	10 ml	seizures (3), confusion, fever, deafness, rhabdomyolysis, renal failure;	Also received Isovue concomitantly;CT showed contrast media in subarachnoid space	cervical spondylosis
5993234	OSCN-PR-0602S-0036	US	75	F	Hosp	10 min	Epi-dural	Pain management	5 ml	seizures,vomit, unresponsive, confusion,amnesia, ventricular tach	Concom methylprednisolone, CT showed contrast in subarachnoid space	contrast media reaction; diarrhea
5993232	OSCN-PR-0602S-0037	US	46	F	LT/ Hosp	20 min after procedure	intra-discal	Disco-gram	1.8 ml	Seizures, vomit, hallucination, myocardial infarction	concom cefazolin adm, Possible contrast leak into CSF	contrast media reaction; neck pain; headache
6017646	OSCN-NO-0603S-0070	NO	78	M	None	30 min	IV	MRI	unk	seizures, left sided paresis,		
6102943	OSCN-PR-0510S-0207	US	41	F	Med Inter-vent	16 hours	IV	MRI	15 ml	seizures, N,V,headache, flushing	***Positive RC-pt received a second iv 15 ml Omniscan and 5 hours later had another seizure.***	penicillin allergy

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/s/

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