CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

MEMORANDUM DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 03/19/2013
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, Office of Drug Evaluation-IV
To: File, NDA-204781
Subject: Approval of NDA 204781, Dotarem (gadoterate dimeglumine), a contrast agent for magnetic resonance imaging of central nervous system

This is the ODE memo to concur with the approval of this NDA, as recommended by the Division of Medical Imaging Products (DMIP) and endorsed by the Medical Imaging Drugs Advisory Committee (MIDAC)[1]. Dotarem is a new gadolinium based contrast agent (GBCA), to be used in the magnetic resonance imaging (MRI) study of central nervous system (CNS).

Overall, the data submitted in this application support the approval of gadoterate as a GBCA indicated for adult and pediatric patients age 2 and above. For these patients, Dotarem is considered of relatively lower risk for nephrogenic systemic fibrosis (NSF)[2]. Use of this agent in infants under 2 was also proposed in this submission, but neither DMIP nor the MIDAC considered the evidence presented in the NDA as adequate to support expanding the indication to the youngest group. This position is concurred by the Office.

As summarized in the Division Director's memo by Dr. Dwaine Rieves, reviews by relevant disciplines and facility/data inspections have all been completed. There are no outstanding issues identified in the reviews or inspection that may preclude the approvability of this application for patients age 2 and above. The applicant and FDA have also agreed on the final version of the labeling. Further studies in juvenile animals and clinical pharmacological measurements in neonates will be conducted post-marketing for consideration of indication in younger patients.

Major regulatory and scientific issues of this NDA are summarized as follows.

Efficacy and Safety

The conclusion that gadoterate is an effective contrast agent, as reached by the review team and the Division Director, is correct and concurred by the Advisory Committee and this Office. As summarized in Dr. Rieves' memo and the primary/secondary clinical/statistical reviews, the advantage of adding gadoterate over non-contrasted imaging is statistically significant in the major efficacy trial (-050), a trial with 364 adults and 38 pediatric (>2 yrs old) patients. For all 3 endpoints of image quality (contrast enhancement, border delineation and internal morphology, as interpreted by three readers), 56% to 94% of patients had improved lesion visualization for paired images compared to pre-contrast images (see Table in Section 7 of Dr. Rieves' division director's memo). The results are consistent in primary/secondary analyses

[1] As concluded with a 17:0 vote for approval at the MIDAC meeting of Feb 14, 2013, transcript will be posted at http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee

[2] All GBCAs are classified as low or high risk for NSF in the class labeling change of 2010. See Dr. Rieves' review for more background on NSF and also discussion below.

and in adult/pediatric (>2 yrs) patients. The finding of this trial was confirmed in another study (-051), a re-read study of an earlier trial (-044). Despite that the primary endpoint of 044 failed (due to minimal improvement of imaging for large solid tumors by contrast agents) and other concerns (e.g., few African American), all analyses of Study -051 demonstrating the superiority of Dotarem to the comparative imaging methods for each lesion visualization category and by different readers (see primary/secondary medical reviews).

Other than the rare reports of anaphylaxis and acute renal failure (one each, both described for other GBCAs), there is no other serious safety issue identified in the safety database of 2813 patients (5% < 18 yrs old) from 49 clinical trials. As noted in the medical reviews, most of the reported adverse events were considered to be mild and/or unrelated to Dotarem. There were no deaths or NSF attributable to Dotarem reported in the NDA. The most common adverse reactions in the clinical trial database occurring in over 0.2% of patients were nausea, headache and injection site reactions. Analyses of post-marketing safety experiences conducted by the Office of Surveillance and Epidemiology (OSE) have identified 51 reports (47 adult cases and 4 pediatric, with 3 being less than 2 years of age) of adverse events associated with the use of Dotarem in the FDA Adverse Event Reporting System (FAERS) database and the medical literature in both adult and pediatric patients. The postmarketing experience in the OSE report is notable for 22 cases of hypersensitivity, 10 cases of NSF (all confounded by other GBCAs, also see discussion below) and 4 cases of acute renal failure. The remaining safety reports are, although serious, isolated and unlikely attributable to Dotarem.

Overall, Dotarem appears to be well-tolerated and the safety profile as acceptable as other approved GBCAs. In view of the extensive marketing history (30 million patients) of Dotarem, the numbers (NDA and postmarketing) of hypersensitivity (23) and acute renal failure (4) cases are not numerically alarming. But the DMIP is reasonably prudent to impose strong warnings in the labeling on these two potentially very serious reactions (e.g., contraindication for hypersensitivity and warning on acute renal failure).

No additional signal of safety issue was identified in the non-clinical studies.

Relative Risk of Nephrogenic Systemic Fibrosis

As noted above, all GBCAs currently approved in the U.S. are divided into two subgroups in the class labeling changes of December, 2010. Members of the higher risk group are contraindicated for patients with renal impairment, and those of lower risk carry only a box warning for NSF. There has been much effort to differentiate the GBCAs, in search of distinctive characteristics that can help predict the risk of NSF for specific agent. Many of the proposed mechanisms to account for the differential risks of NSF remain hypothetical and have been subject to challenge by the exceptions to the suggested rules[3]. While no single characteristic can predict the NSF risk with complete confidence, several of the physicochemical properties and other relevant attributes should be viewed collectively for a reasonable estimate. The currently available GBCAs are compared with Dotarem in Table 1 below.

[3] In addition to those listed in Table 1, other properties of GBCA have been proposed, but not yet well-established either, to account for the difference in NSF risk. They include selective stability (competitive binding relative to other ions) and relaxivity (lower dose can be used for GBCA of higher relaxivity). An alternative hypothesis emphasizing stimulation of fibrotic process by the chelated Gd (not free Gd) has also been suggested. To further complicate the matter, macrocyclic GBCAs are not necessarily more stable than the ones with linear ligands and not all linear ionic GBCAs have the same NSF risk (e.g., Magnevist vs Multihance) (see references in Footnote 4).

Table 1*

GBCA	structure, charge	pK_{therm}	Stability pK_{cond}	Kinetic $t_{1/2}$	Gd release %/day	animal model** nm /g	case^	dose# million	rate^^
Omniscan+	chain, non-ionic	16.9	14.9	< 5s	0.16	132	505	49	10.31
Optimark+	chain, non-ionic	16.6	15.0	< 5s	0.44	47	35	3.5	10.00
Magnevist+	chain, ionic	22.1	17.7	< 5s	0.16	36	179	105	1.70
Multihance	chain, ionic	22.6	18.4	< 5s	0.18	7	2	7.5	0.27
Eovist	chain, ionic	23.5	18.7		0.07	--	0	0.4	< 0.8
Ablavar	chain, ionic	22.1	18.9		0.12	--	0	0.1	< 3.3
Prohance	macrocyclic, non-ionic	23.8	17.1	3.9h	<0.007	1	2	15	0.13
Gadavist	macrocyclic, non-ionic	21.8	14.7	43h	<0.007	2	2	6	0.33
Dotarem	Macrocyclic, ionic	25.6	19.3	338h	<0.007	2	0	30	<0.01

* Compiled from data submitted in this NDA and references in Footnote 4.
** Deposit of Gd, nmol per gram of rat skin, Day 35
^ unconfounded or single agent case, world-wide reports and distribution.
# Number of patients received Dotarem from this NDA, exposures to other GBCAs from sources of Footnote 4.
^^ cases per million; for 0 case reported, the estimate is < 1/ (3 x number of dose), see discussion below for limitation in interpretation.
+ high risk for NSF, contraindicated for patients with renal impairment.

The current prevailing concept suggests that NSF is caused by the free gadolinium released from GBCAs[4]. The stability of the chelation between the gadolinium ion and the ligands is thus critical for predicting the risk. The GBCA with the linear or chain ligands, especially the non-ionic, are considered most unstable, and with the highest risk of releasing free Gd and causing NSF. This stability is measured as dissociation constants, including thermodynamic K_{therm} and conditional[5] K_{cond}, and rates/extent of dissociation (kinetic stability in half life and percentage of free Gd released). The differences in stability appear to correlate with the amount of gadolinium deposit in rat skin[4].

For all hypotheses, the ultimate confirmation is the numbers of clinical reports of NSF. The identification of first 3 high risk GBCAs (Omniscan, Optimark and Magnevist) is likely due to the relatively high number of reported NSF cases. In contrast, the rates of NSF reports were mostly lower than 1 per million for the safer GBCAs[6]. However, the relative rates of case reports should be viewed with caution. Besides the inherent limitation of such calculation, the overall incidence of NSF has been declining over the years (older agents had more cases) and the newer agents are used less frequently in the renally impaired (not the same base for comparison) because of the new warning in the labeling. Thus, the correlation between the available rates of NSF reports and risk of individual GBCA remains tenuous, and the physicochemical properties and testing in animal model are still the practical criteria to differentiate the risk of NSF (see references in Footnote 4).

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[4] For review of the subject, see *J of Magn Reson Imaging* 36:1060–1071 (2012); *J of Med Imaging & Radia Onco* (2008) 52, 339–350; *Invest Radiol* 2008;43: 817–828; *Toxicology*, 2008; 248:77-8; See also Advisory Committee discussion in 2009 at http://www.fda.gov/downloads/advisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM190850.pdf, and FDA reviews on Gadavist http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201277Orig1s000TOC.cfm http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201277Orig1s000SumR.pdf,

[5] Conditional stability is measure at physiologic condition. See below for further discussion on stability of Dotarem.

[6] The rates were calculated as there is no other measure for comparison; it is not intended to be a rigorous mathematical exercise. The estimated rates should be compared in the order of magnitude, not numerically.

The parameters in Table 1 suggest that Dotarem is probably one of the safest GBCAs regarding the risk of NSF. Dotarem is the only ionic macrocyclic (more stable than chain and non-ionic, respectively) agent, and compared with other GBCAs, it has the strongest Gd-ligand binding constants, very slow Gd release rate and low deposit on rat skin. The lowest rate of unconfounded NSF reports also reflects the favorable physicochemical properties of Dotarem.

Dotarem is thus a GBCA of low NSF risk. It will not be contradicted in patients with renal impairment, but should carry the same GBCA class warning on NSF and monitored by the spontaneous reporting system and other standard pharmacovigilance practices. This position of DMIP is concurred by the Advisory Committee and this Office.

Dose for the Renally Impaired

Similar to other GBCAs, renal impairment increases the bioavailability of gadoterate, with more pronounced increase in AUC (from 870 to 8122 μmol*hr/L for severely impaired[7]) than in the C_{max} (from 551 to 671 μmol/mL, see clinical pharmacology review Table 6, Section 2.6.2.6). Since reducing the dose for renally impaired may lower the C_{max} to an ineffective range resulted in poor image quality, and the clinical effect of lower dose has not been studied in such patients for Dotarem[8], both the clinical pharmacology and medical review teams do not recommend dose adjustment for the renally impaired patients. This position is consistent with dosage recommendation for other GBCAs and concurred.

Use of Dotarem in Pediatric Patients

The data submitted in this NDA support approval of Dotarem for adult and pediatric patients 2 yrs of age and above, meeting the same data requirements and to be used for the same age range as for all other GBCAs. Unlike other GBCAs, the applicant of this submission also seeks approval of Dotarem for use in infants aged down to neonate on the basis of the extensive global marketing history and the substantial safety records.

As summarized in medical reviews and Dr. Gorovets' CDTL review, the pediatric (age 18 and younger) database for Dotarem consisted of the following[9]:

- 140 (5% of 2813) in 49 clinical trials, which include
  - 38 (none younger than 2) in the major efficacy trial (Study -050)
  - 99 from 3 observational, single site studies (7 < 2 yrs old)
- 1,203 (177 < 2yrs old) in 13 publications retrieved by OSE

The following were submitted by the applicant, but no source data available for verification:

- 80 (< 2 yrs old) in SECURE, an ongoing postmarketing study
- 2,500 in postmarketing observational experience (some < 2yrs old but no break down by age)
- 52,000 infants less 2 yrs old from global marketing 2005-2011, indirect estimates from the French medical service utilization data over one year.

While there is no separate pediatric efficacy study, improvement of the imaging by Dotarem in children is similar to that in adults, both in the major trial (-050) and in the

[7] CL_{Cr} 10-30 mL/min, with less increases for moderately impaired (CL_{Cr} 30-60, AUC 3013, C_{max} 591)

[8] In fact, there is evidence that in non-renal failure patients, imaging quality of 0.1 mmol/kg was better than the 0.03-0.05 mmol/kg dose for other GBCAs. See labeling of Multihance and the discussion on ProHance and Magnevist in http://www.clinical-mri.com/pdf/CMRI/8036XXP14Ap454-472.PDF

[9] The datasets could be overlapping and the numbers should not be added up for a sum.

observational studies (total 137 patients, with 7 < 2yrs old). The review team considers it reasonable, and both the MIDAC and this Office concurred, to extend the efficacy to pediatric patients of 2 yrs and above. The large numbers of younger infants who have received Dotarem for imaging studies in the global market suggest that the contrast agent also improves image quality for infants younger than 2 yrs. The appropriate dose in these youngest patients, however, may need further studies. Pharmacokinetic data will be useful for this purpose.

The safety profile of Dotarem use in the pediatric patients appears to be no significantly different that that of adults in the clinical trials, the reports in the FDA FAERS system, or in the publications reviewed by OSE. There were no reports of deaths, NSF, or other specific alarming adverse events in the pediatric population. While the risks in children over 2 yrs are acceptable based on the overall experience, the review team, including this Office, and the Advisory Committee (MIDAC) are not comfortable to extrapolate such confidence to the younger infants. The numbers of the youngest patients are limited (none in controlled trials, 7 in observational studies, 177 in publications) and the other postmarketing safety experiences are difficult to interpret because the numbers and the cases cannot be verified and reviewed[10].

The MIDAC members, in their vote of 10:6 against approval of Dotarem for the younger infants, suggested that such approval should wait for the completion of the SECURE study, further assessment of overall safety profile in this age group (including premature infants), pharmacokinetic data for such patients, and safety study in juvenile animals. The Agency agrees.

Conclusions

Dotarem is to be approved as a new GBCA for CNS MRI in adult and pediatric patients 2 yrs of age and above.

It is considered of relatively lower risk of NSF, thus labeled without contraindication for renally impaired patients. Similar to other GBCAs, the labeling should carry a class box warning about NSF and appropriate warnings about hypersensitivity and acute renal failure. It is not necessary to reduce the recommended dose for patients with severe renal failure.

The applicant agrees to conduct studies in juvenile animal and pharmacokinetic studies in infants younger than 2 yrs post-approval of the above indication, so the safety of Dotarem in younger infants can be assessed.

cc:
ORIG: NDA- 201277
Director, ODE-IV
Director, DMIP

[10] For example, the large number of 52,000 0-2 yrs old infants noted above was a crude estimate only, not directly linked to utilization of this specific drug in this age group and could not be otherwise verified. It should be acknowledged, however, that, in this age group, no significant safety signals have been identified through the applicant's postmarketing pharmacovigilance reporting program.

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/s/

SHAW T CHEN
03/19/2013