FDA MIDAC MEETING – SEPTEMBER 8, 2017

AN OVERVIEW ON GADOLINUM RETENTION AFTER GBCA USE

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Guerbet’s Macrocyclic GBCA (M-GBCA), Dotarem®
(gadoterate meglumine 0.5 M)

• Macrocyclic and ionic GBCA approved in the USA in adult and pediatric (including term neonates) patients for CNS indication

• Approved in 79 countries worldwide with more than 65 million doses administered since its launch in 1989

• Based on an extensive review of efficacy and safety studies (sponsored or not by Guerbet, interventional or observational) and on pharmacovigilance data, the risk/benefit balance of Dotarem® is considered favorable
• Linear non-ionic GBCA approved in the USA in adult patients for CNS, spinal and liver diseases imaging, and contra-indicated in case of renal impairment

• Integrated into the Guerbet portfolio at the end of 2015 following the acquisition of the contrast media and delivery systems business from Mallinckrodt Inc. To date, approved in 33 countries with approximately 22 million doses administered since launch

• Based on the increasing demand for macrocyclics, Guerbet decided to progressively phase-out Optimark® worldwide

• In 2016, Guerbet voluntarily proposed a labeling modification for Optimark® to the FDA Division of Medical Imaging Products (DMIP), in order to inform the medical and patients communities on the potential brain Gd deposition after repeated administration. This labeling change in section “12- Clinical Pharmacology / 12.3 Pharmacokinetics” of the Optimark® US-PI was approved by the FDA in August 2016
Gd$^{3+}$ is Highly Toxic → Necessity of a Strong Chelation

- Highly toxic
- Retained in body
- IV LD50 (median lethal dose)
  - Mouse: 0.34 mmol/kg
  - Rat: 0.38 mmol/kg

\[ \text{GdCl}_3 \, \text{(free gadolinium)} \]

Chelation dramatically decreases toxicity, ensures biocompatibility and allows rapid excretion

**Magnevist®**
- IV LD50
  - Mouse: 5.5 mmol/kg
  - Rat: 10.2 mmol/kg

**Dotarem®**
- IV LD50
  - Mouse: 10.6 mmol/kg
  - Rat: >12.5 mmol/kg

GBCA standard approved clinical dose: 0.1 mmol/kg

Bousquet et al., Radiology 1988
GBCA-induced Acute Phase and Long Term Reactions

Acute phase
- Allergic reactions
- Allergoid reactions
- Non-allergic reactions

1. Long term
- NSF & Brain hyperintensities
- GBCA presence
- GBCA stability & Gd dissociation

Timescale
- Minutes
- Days
- Months
- Years
What we know
Impact of Low Stability

Thermodynamic stability

K_{\text{cond}} (\text{mM}^{-1})

K_{\text{therm}} = \frac{[\text{Gd}^{3+}\text{-chelate}]}{[\text{Gd}^{3+}] [\text{chelate}]} \times X 40,000

Non-ionic GBCAs  Ionic GBCAs

Linear GBCAs  Macrocyclic GBCAs

Kinetic stability

Half-life (h)

X 200,000

Unconfounded and consistent reports of NSF

Hypersignal on conclusive publications

Seen by histopathologists

- a) Edwards et al, Br J Radiol, 2014;87:20140307
- b) Endrikat et al, Invest Radiol 2016;51:537-43
- d) Heverhagen et al, Rofo 2014;186:661-9
- e) USA PIs as of January 2017. de Kerviler et al, Invest Radiol 2016;51:544-51

Both are due to dissociated gadolinium
Both show differences between stable and less stable GBCAs
NSF is a clinical syndrome, a consequence of instability of some GBCAs in patients with severely impaired renal function.

Hyperintensities are markers of instability of L-GBCAs in all types of patients, including patients with normal renal function.

Brain hyperintensities and NSF are part of a continuum (from Gd accumulation to Gd toxicity).

Renal dysfunction is a catalyzer.

“high levels of gadolinium deposition […] similar to previously reported gadolinium levels within the skin of patients with nephrogenic systemic fibrosis […] increased CD34 immunoreactivity in the connective tissue septations of the subcutaneous adipose tissue”

“three patients with impaired renal function […] (two with confirmed NSF) whose unenhanced T1-weighted MRIs showed conspicuous high signal intensity in the dentate nucleus and the globus pallidus after they had been exposed to relatively low doses of linear GBCAs”

Interpretation of some Published Inconsistencies about Hyperintensities
Clinical data

**No brain hyperintensities with some L-GBCAs?**
(Ramalho 2015-2016, Conte 2017, Ichikawa 2017)

- **Results on Multihance®**
  - Weberling 2015: Mean of 7.7 injections – full dose
  - Ramalho 2015: Mean of 4.5-4.6 injections – full dose
  - Schneider 2017: Mean of 7.8 injections – half dose

- **Interpretation: key factors for hyperintensities**
  - Number of GBCA injections (threshold ~6)
  - Cumulative dose of GBCA

- **Adapted from Adin et al., 2015**

**Brain hyperintensities with some M-GBCAs?**
(Stojanov 2016, Rossi-Espagnet 2017)

- **Results on Gadovist® and Dotarem®**
  - Higher SI ratio increases than with L-GBCAs but without visible hypersignals
  - Not confirmed by Tibussek 2017 nor Radbruch 2016-2017

- **Interpretation: key factor for SI ratio increases**
  - Ageing is a potential confounder

- **Adapted from Steen and Schroeder, 2003**

- **All L-GBCAs may induce brain hyperintensities**

- **No brain hyperintensity with M-GBCAs**
Inconsistencies about Gadolinium Deposition: “All GBCAs deposit”? Confusion between transitory presence of chelated Gd (observed with all GBCAs while progressively washed-out) and permanent presence of dissociated Gd (only observed with linear GBCAs).

M-GBCA  L-GBCA

7 days post-injection

“organ tissue deposition is reduced but not eliminated following administration of macrocyclic GBCA chelates in lieu of linear”

McDonald et al, 2017

Unpublished data from Guerbet research confirming data from Frenzel et al, 2017

Faster washout of M-GBCAs
No detectable dissociated Gd with M-GBCAs

Unpublished data from Guerbet research confirming data from Frenzel et al, 2017

McDonald et al, 2017

Courtesy of Pr. Karst
A Complete Set of Evidence of Gadolinium Dissociation and Deposition Related to the GBCA Structure

✓ Chemical stability (Port 2008)
  ▪ Kinetic stability: M-GBCAs > L-GBCAs
  ▪ Thermodynamic stability: Ionic GBCAs > non-ionic GBCAs

✓ In vitro stability in physiological conditions (Frenzel 2008)
  ▪ Stability in serum: M-GBCAs > L-GBCAs

✓ NSF in patients with renal failure (Edwards 2014)
  ▪ NSF cases most exclusively associated with L-GBCAs
  ▪ No cases with Multihance® possibly due to clinical practice following risk minimization measures

✓ Brain hyperintensities in adults and children with normal renal function (Kanda 2014 ... Radbruch 2017)
  ▪ Hyperintensities with all L-GBCAs
  ▪ No hyperintensities with any M-GBCA

✓ Chemical form of Gd in the brain (Jost 2016, Frenzel 2017)
  ▪ Gd deposition (following dissociation) only for L-GBCAs
  ▪ Presence of M-GBCAs (without dissociation)
Chemistry

- Kinetic stability: M-GBCAs > L-GBCAs
- Thermodynamic stability: Ionic GBCAs > non-ionic GBCAs

In vitro Stability

- Stability in serum: M-GBCAs > L-GBCAs

NSF

- NSF cases most exclusively associated with L-GBCAs
- No cases with Multihance® possibly due to clinical practice following risk minimization measures

Brain Hyperintensities

- Hyperintensities with all L-GBCAs
- No hyperintensities with any M-GBCA

Chemical form of Gd

- Gd deposition (following dissociation) only for L-GBCAs
- Presence of M-GBCAs (without dissociation)
Differences between brain T1 hypersignals and NSF:

- Brain T1 hypersignals occur in patients with normal renal function
- The linear GdCA Multihance® induces brain T1 hypersignals
- No evidence of a clinical impact of Gd deposition in brain

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<thead>
<tr>
<th></th>
<th>GFR &gt; 60 mL/mn</th>
<th>GFR 30-59 mL/mn</th>
<th>GFR &lt; 30 mL/mn</th>
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<tbody>
<tr>
<td>Omniscan®</td>
<td>Brain T1 hypersignals +++</td>
<td>No brain T1 hypersignal</td>
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<tr>
<td>Magnevist®</td>
<td>Non-clinical evidence of Gd dissociation</td>
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<td>* OptiMark®</td>
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<tr>
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<td>Brain T1 hypersignals ++</td>
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<td>* Ablavar®</td>
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<td>Eovist®</td>
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<td>ProHance®</td>
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* No data available

In September 2010, the FDA required changes in the drug label for GBCAs: no use of Omniscan®, Magnevist®, OptiMark® in patients with acute kidney injury or with chronic or severe kidney disease.

Montagne et al., JAMA Neurol. 2015; Radbruch et al., Radiolgy 2015, 2017a,b, Invest. Radiol. 2015a,b, Rasschaert et al, Invest Radiol 2017
## On-going Regulatory Changes in Europe Following the CHMP Decision

After an extensive review period of 17 months of published/unpublished material evaluation, including 2 ad hoc expert meetings, 5 oral explanations and assessment reports of hundreds of pages, the PRAC made recommendations, and then the CHMP made the following decision:

<table>
<thead>
<tr>
<th>Type</th>
<th>Product</th>
<th>EMA's recommendation</th>
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<tbody>
<tr>
<td>M-GBCAs</td>
<td>Dotarem® (gadoteric acid)</td>
<td>Maintain as non-specific GBCA</td>
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<tr>
<td></td>
<td>Gadovist® (gadobutrol)</td>
<td>Maintain as non-specific GBCA</td>
</tr>
<tr>
<td></td>
<td>Prohance® (gadoteridol)</td>
<td>Maintain as non-specific GBCA</td>
</tr>
<tr>
<td>L-GBCAs</td>
<td>Optimark® (gadoversetamide)</td>
<td>Suspend</td>
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<td></td>
<td>Omniscan™ (gadodiamide)</td>
<td>Suspend</td>
</tr>
<tr>
<td></td>
<td>Magnevist® (gadopentetic acid)</td>
<td>Suspend</td>
</tr>
<tr>
<td></td>
<td>Multihance® (gadobenic acid)</td>
<td>Restrict use to liver scans → Liver specific*</td>
</tr>
<tr>
<td></td>
<td>Primovist® (gadoxetic acid)</td>
<td>Maintain as liver specific</td>
</tr>
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### Post-PRAC worldwide Regulatory Authorities’ requests:
- **Canada and Australia**: Change of the labeling information of all GBCAs
- **New Zealand**: Possibility of a Product Information update
- **Kuwait**: Suspension of Optimark® Marketing Authorization
- **Singapore, Japan, China, Russia and South Korea**: Additional requests of information

*Not an approved indication in the USA for Multihance*
GBCA-induced Acute Phase and Long Term Reactions

2. Acute phase
- Allergic reactions
- Allergoid reactions
- Non-allergic reactions

1. Long term
- NSF & Brain hyperintensities
- GBCA presence
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Timescale
- Minutes
- Days
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- Years
**GBCA-induced Acute Phase Reactions**

**Adverse Events (AEs)**
Meta-analysis of 9 publications
716,978 injections / 1034 AEs (14/10,000) according to ACR definition

No link between acute reactions and ionicity/non-ionicity
No link between acute reactions and linear/macrocyclic structure

**Adverse Drug Reactions (ADRs)**

- **Omniscan**: 48 millions of injections 1993 to 2009
- **Magnevist**: 120 millions of injections 1988 to 2011
- **Dotarem**: 50 millions of injections 1989 to 2015
- **Gadovist**: 29 millions of injections 1998 to 2015
- **Multihance**: 1.5 millions of injections 1997 to 2005

*2.12 in 1988, 1.44 in 2011*
GBCA-induced Acute Phase and Long Term Reactions

**Timescale**

- **Acute phase**
  - No difference between L-GBCAs and M-GBCAs

- **Long term**
  - Difference between L-GBCAs and M-GBCAs

Does the choice of the GBCA impact patient management?
**Efficacy of GBCAs:**
No diagnostic gap between the agents has been demonstrated in terms of patient management despite differences in relaxivity

“In common with previous studies of this type, a principal limitation is that the clinical impact (...) on patient management and outcome was not directly evaluated” (Vaneckova et al., AJNR 2015)

**Vaneckova 2015:** Dotarem vs Multihance in CNS

→ “patient management and outcome was not directly evaluated”

**Anzalone 2013:** Dotarem vs Gadovist in CNS

→ “no differences in the number of lesions”

**Haneder 2011:** Dotarem vs Gadovist in MRA

→ “Gadobutrol yielded significant higher SNR/CNR while gadoterate was better in terms of overall image quality and diagnostic confidence”

**Loewe 2015:** Dotarem vs Gadovist in MRA

→ “No statistically significant differences were detected between the two MRA groups”

**Hansmann 2014:** Dotarem vs Gadovist in MRA

→ “Does not translate into substantial difference into image quality”

**Fallenberg 2015:** Dotarem vs Gadovist in Breast

→ “Gadobutrol has higher Relative Enhancement values compared with Gd-DOTA, whereas Gd-DOTA shows more marked washout in malignant lesions. This might improve the detection of breast lesions and influence the specificity of breast MRI imaging.”

**Rahsepar 2017a, 2017b:** Dotarem vs Magnevist and Gadovist in Cardiac

→ “gadoterate meglumine is comparable to gadobutrol in identifying myocardial scar at LGE-CMR”

→ “T1 and ECV values with gadoterate meglumine are comparable to more routinely used gadopentetate dimeglumine and gadobutrol CMR measurements”

* Some indications are not approved in the US
Guerbet’s Opinion and Proposal

- GBCA injections improve diagnostic accuracy
- The clinical impact of lower stability GBCAs (L-GBCAs) is demonstrated with NSF
- Brain hyperintensities and NSF are part of a continuum
- GBCA stability is directly related to their chemical structure: M-GBCA > L-GBCA

Guerbet’s proposal for risk mitigation

- Adopt a precautionary approach: it took 9 years to link NSF with gadolinium
- Change the labeling of the GBCAs:
  - Restrict the use of the L-GBCAs as second line agents in accord with the NIH recommendations*:
    - “When GBCAs are required, consider the use of a macrocyclic GBCA rather than a linear agent”
    - “For patients with documented sensitivity (eg, hives) to macrocyclic agents, it is appropriate to use linear agents when clinically indicated”
  - Include same statement on retention as done with Optimark®
- Continue prospective, mechanistic, non-clinical studies and retrospective large-scale clinical studies