Presence of Gadolinium (Gd) in the Brain and Body

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Background: Bayer Experience with MRI Contrast

- Estimated 450 million doses with gadolinium based contrast agents (GBCAs) worldwide have been administered to patients since the introduction of the first GBCA by Bayer in 1988

<table>
<thead>
<tr>
<th>Bayer’s GBCA</th>
<th>FDA Approval</th>
<th>Administrations*</th>
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</thead>
<tbody>
<tr>
<td>Magnevist® (gadopentetate dimeglumine) 1st multi-purpose linear GBCA</td>
<td>1988</td>
<td>&gt; 148.8 million</td>
</tr>
<tr>
<td>Eovist® (gadoxetate disodium) 1st liver specific linear GBCA</td>
<td>2008</td>
<td>&gt; 4.3 million</td>
</tr>
<tr>
<td>Gadavist® (gadobutrol) 1st high relaxivity macrocyclic GBCA</td>
<td>2011</td>
<td>&gt; 40.8 million</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>~ 194 million</td>
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</table>

*Worldwide

- Clear clinical benefit: GBCAs provide crucial medical information
Overall, GBCAs demonstrate a favorable safety experience and very low reporting rate of adverse events (AEs)

- The most frequently reported reaction for all GBCAs is hypersensitivity

GBCA label updates have effectively addressed past safety observations partially related to stability:

- Interference with colorimetric calcium testing (2003)
  - In patients with severe renal impairment only

Latest observations of increased signal intensity (SI) / presence of Gd in the brain in patients with normal renal function (2013)

- Clinical significance unknown
39 signal intensity (SI) studies demonstrate differences based on chemical structure, associated with different molecule stabilities of GBCAs:

- **Multi-purpose linear GBCAs:** SI increase in the brain after multiple (generally ≥5) injections (Magnevist, MultiHance®, Omniscan™); and a dose dependent SI increase (after standard dose of 0.1 mmol Gd/kg BW)
  - All multi-purpose linear agents behave similarly at ≥5 injections

- **Liver-specific linear GBCA:** SI increase visible only after a significantly higher number (>20) of administrations (Eovist)
  - 1/4 of the standard dose, most stable linear agent, 50% hepatobiliary excretion

- **Macroyclic GBCAs:** No visual proof of a SI increase in the brain even after a high number (>50) of injections (Dotarem®, Gadavist, ProHance®)

No clinical effects associated with these findings have been confirmed.
Traces of Gd Can Be Found in Bone and Brain

- Traces of Gd can be found in bone and brain for both linear and macrocyclic GBCAs, however quantitative comparisons are limited by methodological constraints
  - 4 tissue studies - Gd in the bone and skin with macrocyclic & linear GBCAs
    - *Murata et al.* (2016): Gd concentrations in the bone were 23 times (median) higher than in the brain
  - 6 post mortem studies - traces of Gd in the brain
    - 2/6 studies indicated traces of Gd in the brain from patients receiving macrocyclic GBCAs (*Kanda et al.* 2015, *Murata et al.* 2016)
    - 6/6 studies showed Gd after linear GBCAs

- The (trace) concentration of Gd measured in the brain is not enough to explain the observed SI increase
### Bayer’s Extensive Non-clinical Research

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproduction of imaging findings?</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Jost et al., 2016 Investigative Radiology</td>
<td></td>
</tr>
<tr>
<td>How do GBCAs enter the brain?</td>
<td>Blood-CSF Barrier</td>
</tr>
<tr>
<td>Jost et al., 2016 European Radiology</td>
<td></td>
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<tr>
<td>Histopathological changes in the brain?</td>
<td>No tissue changes</td>
</tr>
<tr>
<td>Lohrke et al., 2017 Investigative Radiology</td>
<td></td>
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<tr>
<td>Molecular structure of Gd in the brain?</td>
<td>Macromolecular formation:</td>
</tr>
<tr>
<td>Frenzel et al., 2017 Investigative Radiology</td>
<td>Linear GBCAs only</td>
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<tr>
<td>Kinetic - elimination or accumulation?</td>
<td>Elimination:</td>
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<tr>
<td></td>
<td>Macrocyclic GBCAs only</td>
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<tr>
<td>Does Gd presence in the brain influence neurological capabilities or behavior of animals?</td>
<td>Studies ongoing</td>
</tr>
</tbody>
</table>
Gd Presence in the Rat Brain and Body

- Gd concentrations in the brain are higher for linear than macrocyclic GBCAs
- Gd can be detected in other organ systems
  - Gd concentration in skin is about factor 100 higher compared to brain and muscle

![Chart showing Gd concentrations in skin, skeletal muscle, and brain for different GBCAs andSaline at 8 weeks post injection.](chart.png)
Localization of Gd in the Rat Brain
Seen with Linear Agents Only

- All multi-purpose linear GBCAs show
  - Comparable concentrations of Gd in the brain (slightly higher concentrations for Omniscan)
  - Comparable distribution & localization of Gd in the brain (nuclei & granular layers)

- No Gd-trapping in the nuclei & granular layers after macrocyclic GBCAs (Gadavist, ProHance, Dotarem)
Partial Gd Release & Binding to Macromolecules in the Rat Brain Seen with Linear Agents Only

- Linear agents release some Gd from the intact GBCA which binds to soluble macromolecules and insoluble complexes
  - Control experiments exclude the possibility of intact GBCAs binding to macromolecules
- Macrocyclic GBCAs do not appear to dissociate or bind to macromolecules

Stability Plays an Important Role in Understanding SI Increase / Gd Presence in the Brain

- Release and binding of Gd to macromolecules for linear GBCAs are related to lower stability of linear GBCAs

<table>
<thead>
<tr>
<th>GBCA</th>
<th>Gd-release after 15d*</th>
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<tbody>
<tr>
<td>Non-ionic linear agents</td>
<td>Omniscan, OptiMark®</td>
</tr>
<tr>
<td>Ionic linear agents</td>
<td>Magnevist, MultiHance</td>
</tr>
<tr>
<td>Ionic linear liver agent</td>
<td>Eovist</td>
</tr>
<tr>
<td>Macrocyclic agents</td>
<td>Gadavist, Dotarem, ProHance</td>
</tr>
</tbody>
</table>

*Measured in human serum at body temperature

- Stability: Nonionic linears < ionic linears < macrocyclcics (kinetically inert)
  - Linear GBCAs characterized by **thermodynamic stability**
  - Macro cyclic GBCAs characterized by **kinetic stability** only
No Histopathological Changes in Rat Brain Tissue for any of the GBCAs
Elimination of GBCAs from the Rat Brain Between 5-52 weeks Seen with Macro cyclic Agents Only

- After 52 weeks, significantly higher Gd concentration in the brain for linear GBCAs
- No elimination observed for linear GBCAs between 5-52 weeks
- Continuous elimination of all macro cyclic GBCAs
Bayer’s Comprehensive Pharmacovigilance (PV) Approach

Bayer’s Global Pharmacovigilance Database
for all pharmaceutical products

• All case reports received on GBCAs
• All case reports received on MS* patients

* Multiple Sclerosis

- AEs from clinical trials, observational studies, scientific literature
- Spontaneous reports of AEs from HCPs, patients, regulatory authorities, active social media monitoring

- Ongoing evaluation of reported AEs
- Ongoing quantitative signal detection using computerized database screening
PV Search for Clinical Relevance: Brain

- Initial search focused on brain and any potential neurological symptoms related to GBCAs

- Safety observations from literature:
  - Welk et al. (2016): No association of GBCAs with Parkinson’s disease
  - Forslin et al. (2017): “Lower verbal fluency scores” observed in association with SI increase (exposed MS patients vs. unexposed healthy controls)
  - Terashima et al. (2017): No effect on disease progression in MS patients

- Expansion of PV search to include Bayer’s entire PV database (incl. ~300,000 case reports regarding patients with MS)

- Based on PV data: no adverse health effects confirmed to be associated with increased SI / presence of Gd in the brain
Safety observations from literature:

- Gathings et al. (2016): Gd associated plaques
- Semelka et al. (2016), Burke et al. (2016): “Gadolinium Deposition Disease” – term assigned by the authors to patients with normal renal function who experience persistent symptoms not attributable to other causes

Bayer’s PV database*: 40 reports noting persistent or elevated Gd levels in the body (blood, hair, nails, skin, urine)

- 21 reports describing a wide variety of symptoms reportedly associated with elevated levels of Gd
- 13 reports describing similar symptoms without evidence of Gd measurements

Many reports are not medically confirmed and most contain insufficient information for causality assessment

Bayer continues to investigate these reports with a targeted questionnaire

*from Bayer’s database (includes literature and spontaneous reports, excludes NSF reports); DLP August 31, 2017
Options For Further Signal Detection in Patients with Multiple Exposures to GBCAs

- Retrospective screening studies in large population-based longitudinal healthcare databases evaluating for any clinical signal detection in patients with multiple GBCA exposures, compared to unexposed controls

- **Exposed cohort:**
  - Women with multiple contrast-enhanced breast MRIs, without breast cancer (e.g. screening in high risk patients for breast cancer)
  - Patients with asymptomatic benign pancreatic tumors/cysts undergoing monitoring with CE-MRI for surveillance

- **Comparison cohort:**
  - Age, sex and comorbidity-matched population without MRI contrast exposure

- **Challenges:**
  - Relies on what is recorded and coded in routine clinical practice
  - Multiple comparisons/random error, unknown or residual confounding
  - Signals found need to be interpreted as data-derived hypotheses
Risk Mitigation

- Communication with HCPs about Gd presence in the brain and body
  - Label updates: class approach addressing the differences between linear and macrocyclic GBCAs. Important points to include:
    - Description of the signal intensity increase and Gd presence in the brain and body after repeated use, and its potential risk
    - Higher tissue concentrations of Gd seen for linear GBCAs compared to macrocyclics
    - No adverse clinical consequences have been confirmed
    - No histopathological changes detected in an animal model
  - “Dear Healthcare Professional” Letter
  - Ongoing medical education
- Continued non-clinical research
- Consideration of epidemiologic studies
GBCAs play a vital role in diagnosis and disease monitoring

- Scientific and medical evidence to date demonstrate a favorable benefit-risk profile of Bayer’s GBCAs in the vast majority of patients
- Bayer is committed to furthering our investigation into Gd presence in the body and whether there are any clinical implications through:
  - Non-clinical research
  - Pharmacovigilance surveillance, follow-up and analysis
  - Potential epidemiologic study

As we move forward Bayer will continue to:

- Actively communicate with healthcare providers about the presence of Gd in the brain and body
- Work with the FDA on proposed label updates to inform patients and healthcare providers about Gd presence