
There’s no room
for compromise.
Clear Direction. From Diagnosis to Care.
Gadovist® 1.0
Gadobutrol

»There's no room for compromise with my most fragile patients.«

This two-month-old was brought in vomiting, stiff limbs, won't stop crying even when her mom picks her up: encephalitis. Maybe. No time to lose – she needed a contrast-enhanced MRI to guide treatment. In the end, everything worked out fine for her. I'm so glad to have a contrast agent for our most sensitive patients.

Proven Safety Profile in More Than 100 Million Applications[1]

- ✔ More than 100 million global applications in clinical practice
- ✔ > 6,800 patients evaluated in prospective studies during the clinical development program[2]
- ✔ Consistent low adverse drug reaction rate (ADR) of 0.7%[3]

Consistently High Level of Safety Proven in a Large Number of Patients in Different Geographic Regions

› The prospective GARDIAN[a] study included > 23,500 patients undergoing routine Gadovist® 1.0 contrast-enhanced MRI in > 270 study centers in Europe, Asia, North America, and Africa[3]

More than 4.3 million applications in clinical practice in Canada

a GARDIAN (Gadovist® 1.0 in routine diagnostic MRI – administration in non-selected patients) including > 23,500 patients

Gadovist® 1.0 Has a Good Safety Profile in Patients With and Without Renal Impairment

- ✔ Gadovist® 1.0 is well tolerated and has a favorable safety profile for patients of all age groups [2]
- ✔ Safety has been proven in patients with severe renal impairment [3,4]
- ✔ Gadovist® 1.0 is classified in group II MR contrast agents* by the ACR[b] and the CAR[d]

Gadovist® 1.0 Has Been Rated as a Low Risk Agent [a,5]

› Agents associated with few, if any, unconfounded cases of NSF [c,6]

No Skin Reaction Suggestive of NSF in Prospective and Retrospective Analyses

› More than 150 patients with renal impairment in GARDIAN and in retrospective analyses of renally impaired patients [3,7,8]

a European Medicines Agency. European Medicines Agency makes recommendations to minimise risk of nephrogenic systemic fibrosis with gadolinium-containing contrast agents. EMEA press office. 2009.
b by the ACR Committee on Drugs and Contrast Media, the European Medicines Agency (EMEA), and the U.S. Food and Drug Administration (FDA)
c NSF = nephrogenic systemic fibrosis
d Schieda N, Blaichman JI, Costa AF, et al. Gadolinium-based contrast agents in kidney disease: a comprehensive review and clinical practice guideline issued by the Canadian Association of Radiologists. Can J Kidney Health Dis 2018;5. 2054358118778573.
* Group II MR contrast agents are those agents associated with few, if any, unconfounded cases of NSF

Gadovist® 1.0 Has a Good Safety Profile in Children and in Elderly Patients

Frequency and type of adverse events is similar to adults

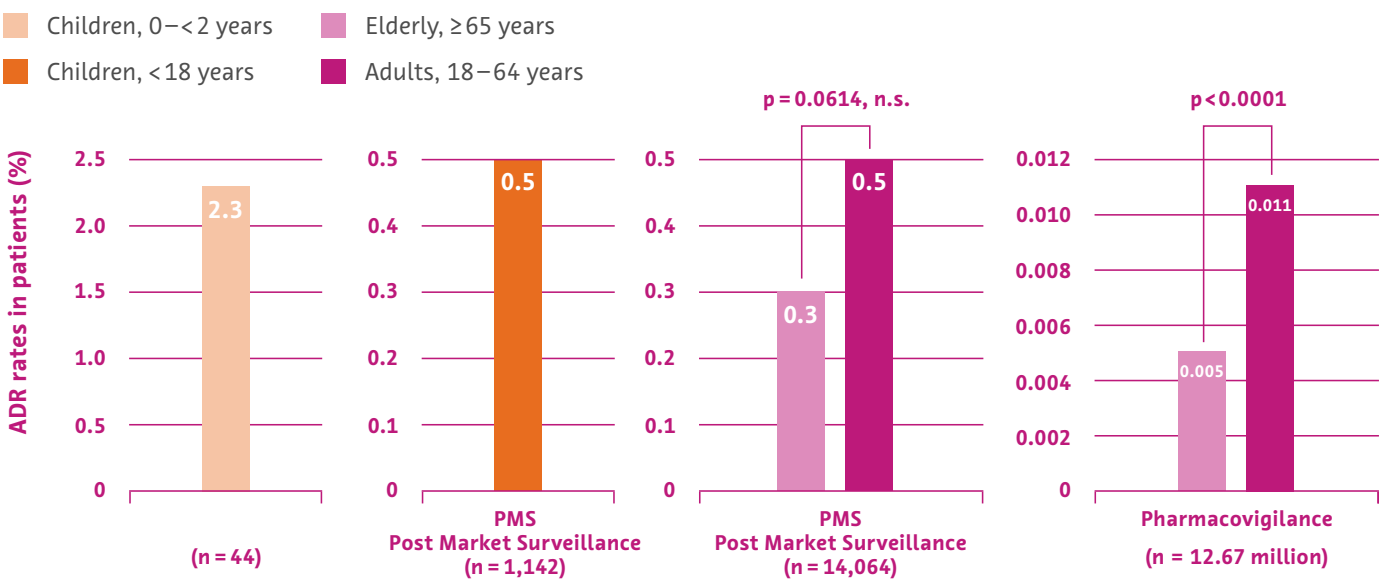

Figure 1 ADR rates in different age groups. Data from clinical studies, post-marketing surveillance and pharmacovigilance data[9–11]

Low ADR Rate of 0.5% and No SAEs[a] Were Reported in Pediatric Populations

- Analysis of >1,100 children from GARDIAN and 130 children included in clinical studies[3,10]

No Dose Adjustment Necessary in Pediatric Patients

- The dose of 0.1 mmol/kg for children is calculated based on body weight as in adults[12]

Lower Incidence of ADRs in Elderly Patients >65 Years

- Observation from a large database of >6,000 patients in clinical trials and nearly 4 million patients extrapolated from PMS reporting, compared with younger adults[9]

a SAE = serious adverse event

ADR Incidence in Patients With Cardiac or Renal Diseases is Not Increased

Based on evaluation of risk populations, i.e. patients with cardiac diseases or renal impairment. NSF was not observed.

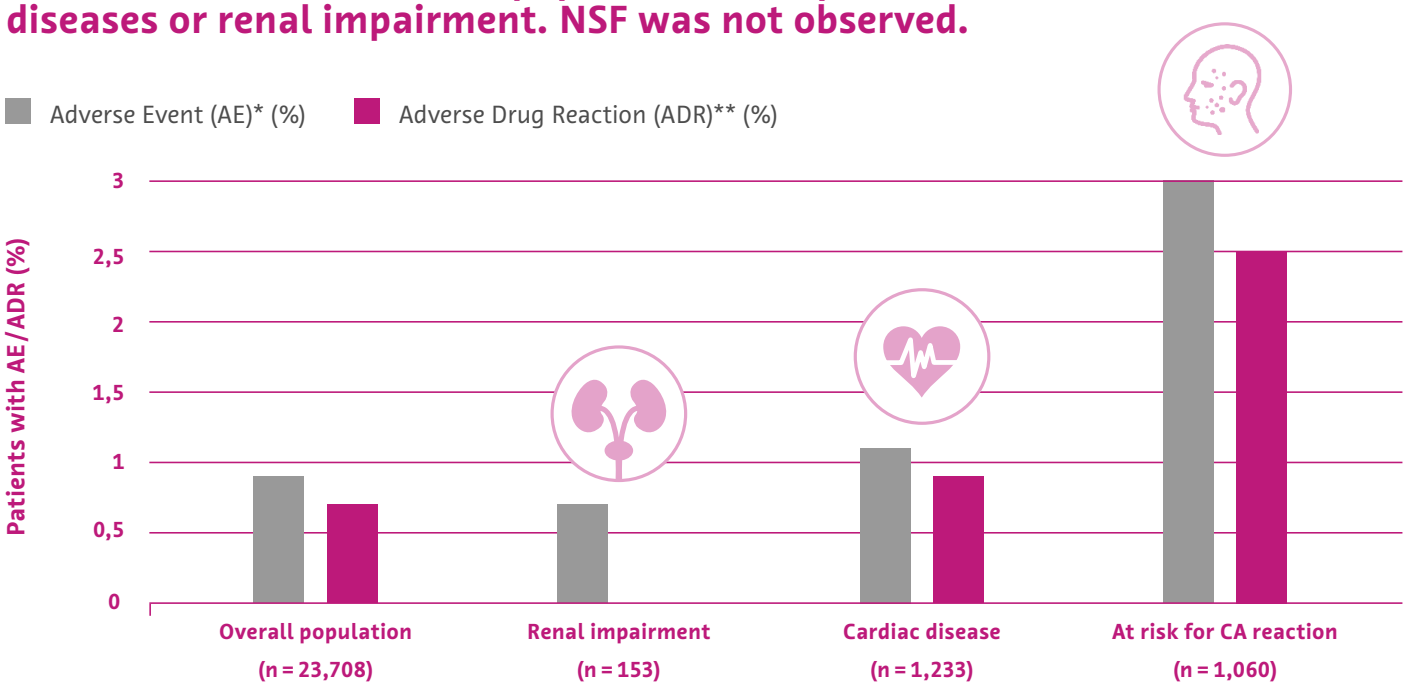

Figure 2 AE/ADR rate in patients with different risk factors[3]

Incidence of Drug-Related AEs Was Not Increased

- Evaluation done in patients with renal impairment, elevated liver enzymes, or cardiovascular diseases[2]

Demonstration of Gadovist® 1.0's Uniform Safety Profile Across Diverse Patient Groups in GARDIAN

- ADR rate not increased in patients with moderate or severe renal impairment[3]
- Rate of ADRs not increased in patients with cardiac disease. All their ADRs were of non-cardiac type[3]

a NSF: Nephrogenic Systemic Fibrosis
* AE: Adverse Event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
**ADR: Adverse Drug Reaction A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.
Note how ADR differs from AE (above). When we use the word "reaction", we assign at least a reasonable possibility of a causal relationship, whereas the term AE does not imply a causal relationship. Source: PHARMACOVIGILANCE Glossary 2017 https://www.emwa.org/media/2640/pv-sig-glossary-august-2017.pdf

What You Need to Know About Contrast Media Stability

The time frame of < 24 hours in which GBCA[a] circulates in the body is much shorter than the dissociation half-life of > 1,000 years for macrocyclic agents.

Figure 3 Based on Schmitt-Willich H. 2007[15], Sarka L et al. 2002[16], Staks T et al. 1994[17], Carr DH et al. 1984[18]

Half-Life of Gd^{3+} Release [15]

✔ For all macrocyclic GBCAs, the half-life at a physiological pH of 7.4 is > 1,000 years

GBCAs Are Eliminated at 99% From the Body Within 24 Hours [14]

✔ Any differences in conditional thermodynamic stability and kinetic stability between macrocyclic GBCAs are clinically irrelevant

The Macrocyclic Chemical Structure Contributes to High Kinetic Stability

- Gadovist® 1.0 is much more stable than linear contrast agents [6,13,14]
- The risk of GBCAs triggering NSF seems to be related to the stability of the agent [4]

Two Constants Illustrate the Complex Stability of MR Contrast Agents

- Thermodynamic constant represents the equilibrium of Chelate ↔ Ligand + Gd^{3+}
- Dissociation half-life represents the time taken to reach this equilibrium

Gadovist® 1.0 is a Second-Generation Macrocyclic MRI Contrast Agent

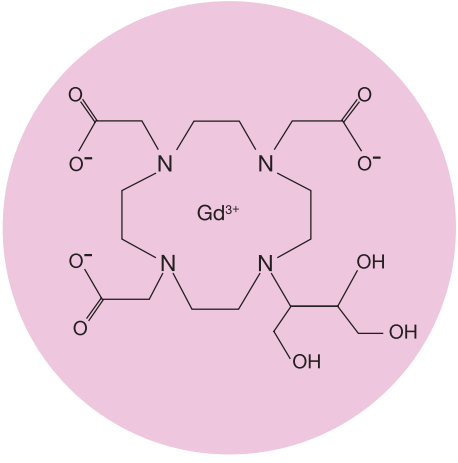

Figure 5 Gadobutrol molecular structure

a GBCA = gadolinium-based contrast agent

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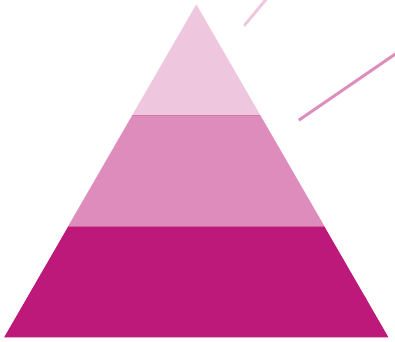
Appendix: How to Read Clinical Study Safety Data



Thousands of Patients, Higher AE Rate Reported (e.g. GRIP)

- Prospective clinical study: (relatively) small number of patients & (very) intensive and long-term patient monitoring. Unbiased evidence for the safety of a contrast agent.

Tens of Thousands of Patients, Lower ADR Rate, Lower Than AE Rate in Controlled Prospective Studies (e.g. GARDIAN)

- Post-marketing surveillance studies: Valuable data on "real-life" use of a contrast agent in a large and varied population of patients, including the occurrence and frequency of rare ADRs. Mostly acute reactions reported.

Millions of Patients, Mostly Severe Intensity ADRs Reported (e.g. Allergic Reactions), Underreporting of (Low-Intensity) ADRs

- Pharmacovigilance data: Number of patients with reported ADR known, total number of people who received the contrast agent during the reporting period is unknown. To estimate the incidence rate of ADRs, utilization data is estimated based on drug volume.

GADOVIST® 1.0 mmol/mL solution for injection. Composition: GADOVIST 1.0 is a clear, sterile, aqueous solution. Each mL of GADOVIST 1.0 contains 604.72 mg (1.0 mmol) of gadobutrol, 1.211 mg trometamol, 0.013 mg sodium (0.00056 mmol), and 0.513 mg calcium sodium butrol in water for injection. The pH of GADOVIST 1.0 is adjusted to between 6.6 and 8.0 with hydrochloric acid. **Indications:** GADOVIST 1.0 (gadobutrol) is a medicinal product for diagnostic use only. GADOVIST 1.0 (gadobutrol) is indicated in adults and children of all ages including term newborns for: contrast enhancement during cranial and spinal MRI investigations and for contrast-enhanced magnetic resonance angiography (CE-MRA); contrast enhanced MRI of the breast to assess the presence and extent of malignant breast disease, and MRI of the kidney. GADOVIST 1.0 is particularly suited for cases where the exclusion or demonstration of additional pathology may influence the choice of therapy or patient management, for detection of very small lesions and for visualization of tumors that do not readily take up contrast media. GADOVIST 1.0 is also suited for perfusion studies for the diagnosis of stroke, detection of focal cerebral ischemia and tumor perfusion. **Contraindications:** GADOVIST 1.0 should not be administered to patients who have experienced a life-threatening reaction to GADOVIST 1.0 previously. **Serious warnings and precautions for use:** Gadolinium-based contrast agents (GBCAs) increase the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with: chronic severe renal insufficiency (glomerular filtration rate <30 mL/ min/1.73m^2), or acute renal failure / acute kidney injury. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast-enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration. Adverse reactions: Patients with a history of previous reaction to contrast media, allergic disorders or bronchial asthma suffer more frequently from hypersensitivity reactions than others. As with other contrast media, delayed allergoid reactions occurring hours or days after administration have been observed, though rarely. Anaphylactoid reactions may occur. Transient sensations of taste or smell perversion may occur during or immediately after injection of GADOVIST 1.0.

Clear Direction. From Diagnosis to Care.

The patient data that appears in this document is actual health information but all personal identifiers have been removed or otherwise anonymized. No personally identifiable information is shown.

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