5.2 Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic Systemic Fibrosis (NSF) is a rare but serious adverse reaction that may occur in patients with impaired renal function when exposed to gadolinium-based contrast agents (GBCAs) used in MRI. NSF typically affects the skin, muscle, and internal organs, leading to progressive thickening and tightening of the skin, muscle stiffness, and joint contractures. The risk of NSF increases with higher cumulative doses of gadolinium and prolonged exposure time, particularly in patients with severely impaired renal function. NSF is distinct from reactive arthralgia/myalgia, which is a less severe and more common reaction to GBCAs.

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired renal function. NSF is more likely to occur in patients with chronic kidney disease (CKD) compared to patients with normal renal function. The risk appears highest among patients with chronic, severe kidney disease (GFR <30 mL/min/1.73m²), and lowest for patients with chronic, mild kidney disease (GFR 60-80 mL/min/1.73m²). The risk also increases with the cumulative dose of gadolinium administered, with higher cumulative doses associated with a greater risk.

5.3 Dosage and Administration

The dosage and administration of MultiHance are as follows:

- **DOSAGE FORMS AND STRENGTHS:**
  - MultiHance is available as a clear, colorless to slightly yellow aqueous solution for intravenous use. The dosage and administration differ depending on the patient's renal function and specific indications.

- **INDICATIONS AND USAGE:**
  - MultiHance is indicated for intravenous use in magnetic resonance imaging (MRI) of the central nervous system (CNS) to evaluate adults with known or suspected renal vascularity of the brain, spine, and associated tissues. It is also indicated for evaluation of renal and extrarenal vascularity in adults with normal renal function.

- **DOSAGE:**
  - The recommended dose for adults with normal renal function (GFR >90 mL/min/1.73m²) is 0.2 mL/kg (0.1 mmol/kg) administered as a rapid bolus intravenous injection. In pediatric patients below 2 years of age, one-half of the per kg dose may be used. For patients at highest risk for NSF, do not exceed the recommended MultiHance dose and allow a sufficient period of time for elimination of the drug from the body prior to re-administration.

- **ADVERSE REACTIONS:**
  - The most commonly reported adverse reactions were hypotension, tachycardia, asthma, fever, nausea, and phlebitis. Adverse events involving multiple organ systems have been reported in patients with chronic kidney disease (GFR >30 mL/min/1.73m²). Anaphylactic, anaphylactoid, and hypersensitivity reactions manifested with various signs and symptoms have been reported in patients with chronic kidney disease (GFR <30 mL/min/1.73m²).


5.4 Acute Renal Failure

Acute renal failure is a potential adverse reaction associated with the use of MultiHance. Patients with underlying renal insufficiency or other risk factors for acute kidney injury should be closely monitored post-administration.

5.5 Hypersensitivity Reactions

Hypersensitivity reactions are a rare but serious adverse reaction that may occur after administration of MultiHance. Symptoms may include anaphylactic, anaphylactoid, and hypersensitivity reactions manifested with various signs and symptoms. Patients with a history of hypersensitivity reactions to GBCAs should be monitored closely for any signs of allergies.

6. ADVERSE REACTIONS

6.1 General Disorders and Administration Site Conditions

Adverse events such as pain, burning, and phlebitis at the injection site have been reported with MultiHance administration. These events are typically mild to moderate in severity.

6.2 Nonspecific Changes in Laboratory Tests

Nonspecific changes in laboratory tests (including hematology, blood chemistry, and liver enzymes) have been observed with MultiHance administration.

6.3 Prevention of nephrogenic systemic fibrosis

To minimize the risk of NSF, MultiHance should be used with caution in patients with impaired renal function. The use of MultiHance in patients with chronic kidney disease (GFR <60 mL/min/1.73m²) should be avoided if possible.

6.4 Contraindications

MultiHance is contraindicated in patients with known or suspected GBCA allergy, severe hepatic dysfunction, or severe renal impairment (GFR <30 mL/min/1.73m²). It is also contraindicated in patients with a history of NSF.

6.5 Warnings and Precautions

Warnings and Precautions include the risk of NSF, potential for acute kidney injury, and the importance of monitoring patients for signs of reaction.

6.6 Patient Counseling Information

Patients should be counseled about the risks and benefits of MultiHance administration, including the possibility of NSF.

6.7 Description

MultiHance is a sterile, nonpyrogenic, clear, colorless to slightly yellow aqueous solution for intravenous use. It contains gadobenate dimeglumine as the active ingredient and is supplied in single-use vials.

6.8 Full prescribing information

A full prescribing information is available upon request from the manufacturer.
**CLINICAL PHARMACOLOGY**

Gadoteridol is a magnetic resonance contrast agent approved for use in magnetic resonance imaging (MRI) in the United States. It is a gadolinium-based contrast agent that is included in the class of macrocyclic GBCAs. Gadoteridol has an osmolality 6.9 times that of plasma (285 mOsmol/kg water) and is hypertonic under conditions simulating typical intravascular administration. It is supplied as a sterile, nonpyrogenic, clear, colorless to slightly yellow aqueous solution. Gadoteridol contains gadolinium (Gd) of the formula {\(\text{Gd(DTPA-BMA)}\)). Gadoteridol is indicated for use in patients with known or suspected CNS neoplasms for whom imaging is needed to establish disease extent or to monitor disease progression or treatment response. The drug is also indicated for use in patients with known metastatic disease of the CNS for whom imaging is needed to establish disease extent or to monitor disease progression or treatment response. Gadoteridol is administered as a single-dose intravenous injection administered over a period of approximately 60 seconds. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The safety and effectiveness of gadoteridol have been evaluated in the following studies:

- **Study A:** Patients highly suspected of having a lesion(s) of the CNS based on nuclear medicine imaging, computed tomography, or clinical symptoms and/or CT. Patients were randomized to receive two MRI evaluations with 0.05 mmol/kg (n=140) or 0.1 mmol/kg (n=136) of MultiHance. In Study B, patients with known metastatic disease to the CNS were randomized to receive two MRI evaluations with 0.05 mmol/kg (n=74) or 0.1 mmol/kg (n=140) of MultiHance.

**Common Adverse Reactions**

- **Gastrointestinal:** Abdominal pain, nausea, vomiting
- **Cutaneous:** Rash, pruritus
- **Respiratory:** Dyspnea
- **Skin and Appendages:** Tachyphylaxis

**How Supplied and Storage and Handling**

MultiHance is supplied as a single-use vial containing 30 mL of 0.5 mmol/mL gadoteridol injection (15 mL prefilled syringe), 5.4 mmol gadoteridol/mL. The drug is available in a clear, colorless to slightly yellow solution in a glass vial. Each mL of solution contains 0.5 mmol/mL of gadoteridol. The drug contains 6.1 mg/mL of mannitol as a nonionic, low-osmolar contrast agent. The excipients are water for injection, sodium hydroxide, and hydrochloric acid.

**Warnings and Precautions**

- **Allergic Reactions:** Patients with a history of severe allergic reactions to gadolinium-based contrast agents should not receive MultiHance.
- **Injection Site Reactions:** Patients who have previously received MultiHance should be closely monitored for adverse reactions at the injection site.
- **Rash, Pruritus:** Patients with a history of rash, pruritus, or other skin reactions to MultiHance should be monitored for similar reactions.
- **Tachyphylaxis:** Patients who have previously experienced tachyphylaxis to MultiHance should be monitored for similar reactions.
- **Pressor Response:** Patients with a history of pressor response to gadolinium-based contrast agents should be monitored closely.
- **Renal Impairment:** Patients with renal impairment who receive MultiHance are at increased risk for adverse renal reactions.
- **Cardiac and Pulmonary Functions:** Patients with cardiac and pulmonary functions should be monitored for adverse reactions.
- **Immunosuppressed Patients:** Patients who are immunosuppressed should be monitored for adverse reactions.
- **Pregnancy:** MultiHance is not recommended for use during pregnancy.

**ADVERSE REACTIONS**

The most common adverse reactions associated with MultiHance are headache, nausea, vomiting, and diarrhea. Other common adverse reactions include rash, skin reactions, and respiratory reactions. The frequency of these reactions is typically lower than that observed with gadolinium-based contrast agents. The incidence of adverse reactions for MultiHance is generally similar to that observed with gadolinium-based contrast agents.
MEDICATION GUIDE
MULTIHANCE® (mol-tē-han(t)s)
gadobenate dimeglumine)
Injection for intravenous use

What is MULTIHANCE?
• MULTIHANCE is a prescription medicine called a gadolinium-based contrast agent (GBCA). MULTIHANCE, like other GBCAs, is injected into your vein and used with a magnetic resonance imaging (MRI) scanner.
• An MRI exam with a GBCA, including MULTIHANCE, helps your doctor to see problems better than an MRI exam without a GBCA.
• Your doctor has reviewed your medical records and has determined that you would benefit from using a GBCA with your MRI exam.

What is the most important information I should know about MULTIHANCE?
• MULTIHANCE contains a metal called gadolinium. Small amounts of gadolinium can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
• It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
• Rarely, patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
• There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist, or ProHance.
• People who get many doses of gadolinium medicines, women who are pregnant and young children may be at increased risk from gadolinium staying in the body.
• Some people with kidney problems who get gadolinium medicines can develop a condition with severe thickening of the skin, muscles and other organs in the body (nephrogenic systemic fibrosis). Your healthcare provider should screen you to see how well your kidneys are working before you receive MULTIHANCE.

Do not receive MULTIHANCE if you have had a severe allergic reaction to GBCAs including gadobenate dimeglumine, or any of the ingredients in MULTIHANCE.

Before receiving MULTIHANCE, tell your healthcare provider about all your medical conditions, including if you:
• have had any MRI procedures in the past where you received a GBCA. Your healthcare provider may ask you for more information including the dates of these MRI procedures.
• are pregnant or plan to become pregnant. It is not known if MULTIHANCE can harm your unborn baby. Talk to your healthcare provider about the possible risks to an unborn baby if a GBCA such as MULTIHANCE is received during pregnancy.
• have kidney problems, diabetes, or high blood pressure.
• have had an allergic reaction to dyes (contrast agents) including GBCAs.

What are the possible side effects of MULTIHANCE?
• See “What is the most important information I should know about MULTIHANCE?”
• Allergic reactions. MULTIHANCE can cause allergic reactions that can sometimes be serious. Your healthcare provider will monitor you closely for symptoms of an allergic reaction.

The most common side effects of MULTIHANCE include: nausea, headache, feeling hot, or burning at the injection site.
These are not all the possible side effects of MULTIHANCE.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of MULTIHANCE.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about MULTIHANCE that is written for health professionals.

What are the ingredients in MULTIHANCE?
Active ingredient: gadobenate dimeglumine
Inactive ingredients: water
Manufactured by: BIPSO GmbH-78224 Singen (Germany)
Manufactured for: Bracco Diagnostics Inc., Monroe Township, NJ 08831
US Patent No. 4,916,246
For more information, go to www.imaging.bracco.com or call 1-800-257-5181.

This Medication Guide has been approved by the U.S. Food and Drug Administration
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