6.1 Clinical Trials Experience

These highlights do not include HIGHLIGHTS OF PRESCRIBING INFORMATION. These highlights do not include all the information needed to use MultiHance safely and effectively. See full prescribing information for Multihance. Multihance (gadobenate dimeglumine) Injection. Initial U.S. Approval: 2004

WARNINGS AND PRECAUTIONS (5.2)

Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents (GBCAs) increase the risk of nephrogenic systemic fibrosis (NSF) in patients with impaired renal function. NSF is a serious and potentially irreversible condition characterized by local pain or burning sensation, swelling, blistering, and nodules. In patients with renal dysfunction, gadolinium is excreted through the biliary system and may accumulate. Some cases of NSF have been diagnosed in healthy volunteers and in 3 subjects who received placebo. None of those cases had a history of renal dysfunction.

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5.2 Hypersensitivity Reactions

Systemic and cutaneous adverse reactions have been reported, including urticaria, urticarial vasculitis, angioedema, rash, vasculitis, and anaphylactic reactions. In 1 patient with a history of multiple systemic drug reactions following daunorubicin (an anthracycline), a hypersensitivity reaction was observed with MultiHance. When MultiHance was used in this patient, a vasculitis reaction occurred and the patient died.

5.3 Acute Renal Failure

MultiHance is contraindicated in patients with chronic, moderate to severe renal dysfunction. The risk of acute renal failure associated with MultiHance is lower for patients with chronic, moderate renal dysfunction compared to those with chronic, severe renal dysfunction. MultiHance is contraindicated in patients with chronic, moderate renal dysfunction.

5.4 Other Adverse Reactions

The most commonly reported adverse reactions in clinical trials with MultiHance were local pain or burning sensation, swelling, and skin discoloration. These adverse reactions were reported in 0.5%–1% of patients who received MultiHance. Local pain or burning sensation, swelling, and skin discoloration were reported in 0.5%–1% of patients who received MultiHance. These adverse reactions were reported in 0.5%–1% of patients who received MultiHance. These adverse reactions were reported in 0.5%–1% of patients who received MultiHance. These adverse reactions were reported in 0.5%–1% of patients who received MultiHance.
2.2 Pharmacokinetics

Three single-dose intravenous studies were conducted in 32 healthy adult volunteers, 15 males, 17 females, aged 18-74 years (mean 46 years) with normal renal function (creatinine clearance >80 mL/min). The dose administered in these studies ranged from 0.170 ± 0.016 to 0.282 ± 0.079 L/kg. These studies showed that the pharmacokinetic behavior of gadobenate dimeglumine in humans is consistent with its equilibrium distribution in extracellular fluid. The mean elimination half-life of gadobenate dimeglumine in extracellular fluid ranged from 1.17 ± 0.26 to 2.02 ± 0.60 hours. The mean volume of distribution of gadobenate dimeglumine in extracellular fluid was approximately equal to the average volume of extracellular fluid (19 L). The mean volume of distribution in extracellular fluid was 0.074 ± 0.017 L/kg for males and 0.158 ± 0.038 L/kg for females. Estimates of volume of distribution by area ranged from 0.050 ± 0.012 to 0.130 ± 0.035 L/kg in males and 0.057 ± 0.016 to 0.170 ± 0.047 L/kg in females. These latter estimates are consistent with those calculated for the parent drug gadobenate dimeglumine in monkeys and are consistent with the volume of distribution for normal extracellular space. Two healthy adult volunteers were studied in clinical trials of MultiHance in MRI of the CNS. A total of 217 pediatric subjects (93% of subjects aged 2 years and above) were studied in clinical trials of MultiHance in MRI of the CNS.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Neither MultiHance nor any other gadolinium-containing agent has been studied in long-term (>1 year) carcinogenicity, mutagenesis, and reproduction studies. Three single-dose intravenous studies were conducted in 32 healthy adult volunteers, 15 males, 17 females, aged 18-74 years (mean 46 years) with normal renal function (creatinine clearance >80 mL/min). The dose administered in these studies ranged from 0.170 ± 0.016 to 0.282 ± 0.079 L/kg. These studies showed that the pharmacokinetic behavior of gadobenate dimeglumine in humans is consistent with its equilibrium distribution in extracellular fluid. The mean elimination half-life of gadobenate dimeglumine in extracellular fluid ranged from 1.17 ± 0.26 to 2.02 ± 0.60 hours. The mean volume of distribution of gadobenate dimeglumine in extracellular fluid was approximately equal to the average volume of extracellular fluid (19 L). The mean volume of distribution in extracellular fluid was 0.074 ± 0.017 L/kg for males and 0.158 ± 0.038 L/kg for females. Estimates of volume of distribution by area ranged from 0.050 ± 0.012 to 0.130 ± 0.035 L/kg in males and 0.057 ± 0.016 to 0.170 ± 0.047 L/kg in females. These latter estimates are consistent with those calculated for the parent drug gadobenate dimeglumine in monkeys and are consistent with the volume of distribution for normal extracellular space. Two healthy adult volunteers were studied in clinical trials of MultiHance in MRI of the CNS. A total of 217 pediatric subjects (93% of subjects aged 2 years and above) were studied in clinical trials of MultiHance in MRI of the CNS.