Optimark™ (gadoversetamid injection) **Dosage and Administration Chart**

<table>
<thead>
<tr>
<th>Kilograms (kg)</th>
<th>Pounds (lb)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>88</td>
<td>8.0</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>10.0</td>
</tr>
<tr>
<td>60</td>
<td>132</td>
<td>12.0</td>
</tr>
<tr>
<td>70</td>
<td>154</td>
<td>14.0</td>
</tr>
<tr>
<td>80</td>
<td>176</td>
<td>16.0</td>
</tr>
<tr>
<td>90</td>
<td>198</td>
<td>18.0</td>
</tr>
<tr>
<td>100</td>
<td>220</td>
<td>20.0</td>
</tr>
<tr>
<td>110</td>
<td>242</td>
<td>22.0</td>
</tr>
<tr>
<td>120</td>
<td>264</td>
<td>24.0</td>
</tr>
<tr>
<td>130</td>
<td>286</td>
<td>26.0</td>
</tr>
<tr>
<td>140</td>
<td>308</td>
<td>28.0</td>
</tr>
<tr>
<td>150</td>
<td>330</td>
<td>30.0</td>
</tr>
</tbody>
</table>

Optimark injection should be administered as a bolus peripheral intravenous injection at a dose of 0.2 mL/kg (0.1 mmol/kg) at a rate of 1 to 2 mL/sec. delivered by manual or power injection.

Safety and effectiveness of Optimark injection in pediatric patients have not been established.

**INDICATIONS FOR USE**
- CNS (CENTRAL NERVOUS SYSTEM) - Optimark gadoversetamide injection is indicated for use with magnetic resonance imaging (MRI) in patients with abnormal blood-brain barrier or abnormal vascularity of the brain, spine and associated tissues.
- LIVER - Optimark gadoversetamide injection is indicated for use with MRI to provide contrast enhancement and facilitate visualization of lesions with abnormal vascularity in the liver in patients who are highly suspect for liver structural abnormalities on computed tomography.

**WARNING: NEPHROGENIC SYSTEMIC FIBROSIS**
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.
- Do not administer Optimark to patients with:
  - chronic, severe kidney disease (GFR < 30 mL/min/1.73m²), or
  - acute kidney injury (see CONTRAINDICATIONS).
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.
- Do not exceed the recommended Optimark dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration (see WARNINGS).

**IMPORTANT RISK INFORMATION**
Optimark (gadoversetamide injection) is contraindicated in patients with chronic, severe kidney disease (glomerular filtration rate, GFR < 30 mL/min/1.73m²) or acute kidney injury or known allergic or hypersensitivity reactions to gadolinium, versetamide or any of the inert ingredients.

Gadolinium-based contrast agents (GBCAs) increase the risk for nephrogenic systemic fibrosis (NSF) among patients with impaired elimination of the drugs. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast enhanced MRI or other modalities.

NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs. Report any diagnosis of NSF following Optimark administration to Mallinckrodt Inc. (1-800-778-7898) or FDA (1-800-FDA-1088 or www.fda.gov/medwatch).

The risks of use of Optimark contrast agent in patients with sickle cell anemia, hemolytic anemias and other hemoglobinopathies has not been studied. The possibility of a reaction, including serious, life threatening, fatal anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered especially in those patients with a known clinical hypersensitivity, a history of asthma, or other respiratory disorders. In clinical studies, the most common adverse events were headache, vasodilation, taste perversion, dizziness, nausea and paresthesia. Postmarketing surveillance reports have identified cases of seizure. Pediatric patients may be particularly vulnerable to adverse GBCA reactions due to renal immaturity and/or unrecognized renal insufficiency. Please refer to Full Prescribing Information provided with this chart.

For more information, contact: Local Covidien Representative, 800-634-1515; Customer Service, 888-744-1414; Product Monitoring, 800-778-7898; Healthcare Economics, 800-645-2891; or visit our web site at [http://imaging.covidien.com](http://imaging.covidien.com).

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OptiMARK™ (gadoversetamide injection)

For Intravenous Injection Only

Mallinckrodt Inc.

PRESCRIBING INFORMATION

1.73 ± 0.40 (N = 4)
2.35 ± 1.09 (N = 2)
53 (41%)
41 (41%)
Statistically significant for both the median (Wilcoxon test)
27 (20%)
27 (21%)
23 (17%)
OptiMARK™ Injection contains gadoversetamide, a complex formed between a chelating agent (versetamide) and a paramagnetic ion, gadolinium (III).

1.73 ± 0.31 (N = 8)
1.160
16 (12%)

OptiMARK™ Injection is designated chemically as [8, 11-bis(carboxymethyl)-14-[2-(285 mOsm/kg water) and is hypertonic under conditions of use. OptiMARK™ Injection has an osmolality of approximately 3.9 times that of plasma.

The pharmacokinetics of intravenously administered gadoversetamide in normal subjects conform to a two-compartment open-model with an initial distribution phase followed by a terminal elimination half-life (measured as 1/2 of t1/2) of approximately 22 minutes and 13 hours, respectively. These kinetic parameters of OptiMARK™ injection in intravenous solutions are not known.

**Gadoversetamide is removed from the body by hemodialysis.**

At the 3-month dose, the effect is primarily on T1 relaxation time, and produces an increase in signal intensity that occurs with: 1) changes in proton density; 2) alterations of the extracellular compartment, which affects T2 relaxation times; 3) T1 effects of the paramagnetic ion; and 4) the ability to delineate lesion borders from parenchyma/structures, the number of lesions and confidence in the diagnosis. Although improvement over baseline was noted, the diagnosis was not rigorously confirmed in the 3-month study.

**Endpoints**

**Table 2.** Results of MRI Central Nervous System Studies with 0.5 mmol/L OptiMARK™ Injection

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OptiMARK™ Injection p&lt;0.05</th>
<th>OptiMARK™ Injection p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conspicuity: Differences in Signal Intensity (a) vs. Pre</td>
<td>0.38</td>
<td>0.14</td>
</tr>
<tr>
<td>Water</td>
<td>2.14</td>
<td>4.11</td>
</tr>
<tr>
<td>Bound Water</td>
<td>2.38</td>
<td>4.34</td>
</tr>
<tr>
<td>Bound Oxygen</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Bound Oxygen Difference of Means</td>
<td>0.76</td>
<td>1.46</td>
</tr>
<tr>
<td>Number of Lesions</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Confidence in Number of Lesions</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
| **Table 3.** Results of MRI Central Nervous System Studies with 1.0 mmol/L OptiMARK™ Injection

**Table 4.** Results of MRI Liver Studies with 1.0 mmol/L OptiMARK™ Injection

**INDICATIONS AND USAGE**

OptiMARK™ Injection is indicated for use with MRI to provide contrast enhancement of tissues and/or structures and to delineate lesion borders from adjacent normal structures in normal subjects.

**CONTRAINDICATIONS**

**WARNINGS**

Gadoversetamide-based contrast agents (GBCAs) increase the risk for NSF among patients with abnormal renal function (GFR <30 mL/min/1.73 m²), or any of the inert ingredients.

**REFERENCES**

Hemodialysis: Gd[(CH₃CO)$_2$]($COO$)$_2$H₂O

This appendix provides the following information:

**Table 1.** Evaluations of Prognosis, Normally Impaired and Hypersensitivity Impaired Men and Women (mean ± SD)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OptiMARK™ Injection p&lt;0.05</th>
<th>OptiMARK™ Injection p&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of Lesions</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Conspicuity: Differences in Signal Intensity (b) vs. Pre</td>
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<td>0.14</td>
</tr>
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<td>Water</td>
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<td>1.46</td>
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</tbody>
</table>

Hepatically impaired patients with normal renal function had a significantly lower plasma clearance rate (144 ± 16 mL/hr, mean = 144 ± 16 mL/hr, using ABC drugs previously are used to treat certain hepatic dysfunction. However, hepatic dysfunction did not significantly compensate for the absence of renal elimination.

**Pharmacokinetics**

The pharmacokinetics of intravenously administered gadoversetamide in normal subjects conforms to a two-compartment open-model with an initial distribution phase followed by a terminal elimination half-life (measured as 1/2 of t½) of approximately 22 minutes and 13 hours, respectively. These kinetic parameters of OptiMARK™ injection in intravenous solutions are not known.

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Volume (mL) 24.0

Peptide Use

The safety and effectiveness of OptiMARK Injection in pediatric patients has not been established.

Depot

OptiMARK Injection may be given by IM injection into the gluteal, deltoid, or vastus lateralis muscle. The recommended route for depot IM injection is given in Table 2.

Infectious lesion

Some paramagnetic contrast agents may impair the visualization of existing lesions, which are seen on the unenhanced, non-contrast MRI. This may be particularly significant in patients with sickle cell anemia and other hemoglobinopathies who have been transfused.

The potential risk of hemolysis after injection of OptiMARK Injection in patients with other hemolytic anemia has not been studied.

Patients receiving OptiMARK Injection should be instructed in a fertility study was shown to have irreversible steroid and degeneration of the germinal epithelium of the testes, presence of germ cells in the epididymides, and impaired male fertility, following intravenous doses of 2.0 mmol/kg/4 hrs times the human dose based on body surface area for 7 weeks. These effects were not observed at 0.5 mmol/kg (1 times the human dose based on body surface area).

In a separate 28-day repeat dose study in rats, OptiMARK Injection was shown to have irreversible effects on male reproduction system 24 hours and 14 days after intravenous administration of 65 to 15 mg/mL to 1 to 25 times the human dose based on body surface area.

The following reactions occurring in less than 1% of the patients:
- Arthralgia
- Pain in joints
- Pain in extremities
- Paresthesia
- Numbness
- Hypersensitivity

GBCA increases the risk for NSF among patients with impaired elimination of the drugs. To guide patients at risk for NSF:

- Describe the clinical signs and symptoms of NSF.
- Advisor patients to report any signs and symptoms of NSF.
- Advise patients to report immediately any signs and symptoms, especially if the patient is older than 65 years.
- Advise patients to seek medical attention if they experience swelling, joint pains, or skin thickening.

Infectious lesion

The safety and effectiveness of OptiMARK Injection in pediatric patients has not been established. OptiMARK Injection may be given by IM injection into the gluteal, deltoid, or vastus lateralis muscle. The recommended route for depot IM injection is given in Table 2.

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