Optimark™ contrast medium

Optimark™ contrast medium is a gadolinium-containing, non-ionic contrast agent for use in MRI, which offers proven efficacy along with the benefit of being available for use with a power injector.

Optimark contrast medium is indicated for use with magnetic resonance imaging (MRI) of the CNS to help in the diagnosis of patients with known or highly suspected pathology. Its contrast enhancement enables visualisation and helps with the characterisation of focal lesions and abnormal structures in the CNS. Optimark contrast medium has the important characteristics of a gadolinium agent, which provides improved lesion detection, sensitivity and diagnostic accuracy together with a reliable tolerability profile.

In the CNS pivotal studies, 262 patients were examined receiving Optimark contrast medium at 0.1 mmol/kg as a bolus (1-2 ml/sec). The MRI scans were blinded and read by three qualified and independent readers, and the diagnosis was compared with a ‘final diagnosis’ derived from an appropriate combination of tests, clinical data and clinical follow up.

The three assessments were made:

- The degree of confidence in diagnosis before contrast and a combination of pre- and postcontrast scores.
- The level of conspicuity of all lesions visualised before and a combination of pre- and postcontrast scores.
- The ability to delineate lesion borders from parenchyma/structures before contrast and a combination of pre- and post-contrast scores.

The rationale underlying the use of Optimark contrast medium to visualize CNS pathologies is that, if the blood-brain barrier (BBB) is compromised through disease, it can accumulate in the CNS and cause signal changes. By contrast, in a healthy person, the intact BBB prevents the passage of the hydrophilic gadoversetamide into the CNS. The rate and extent of the signal change in the various portions of a CNS lesion depend on the degree of permeability of the BBB, the vasculature, and the size of the interstitial space in the lesion.

In a multi centre, double-blind, randomised, placebo controlled trial found Optimark contrast medium to be safe and well tolerated in subjects with CNS pathology (n=163).

In the 0.1 mmol/kg dose group, all adverse events were considered mild or moderate in severity.

A multi centre, double-blind, randomised, placebo controlled trial found Optimark contrast medium to be safe and well tolerated in subjects with CNS pathology (n=163).

Optimark™ contrast medium is well tolerated

<table>
<thead>
<tr>
<th>Number of patients with adverse events (AE) by body system (no. (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.1 mmol/kg</strong></td>
</tr>
<tr>
<td>(n=40)</td>
</tr>
<tr>
<td>Total no. of events</td>
</tr>
<tr>
<td>Total no. of patients with AE</td>
</tr>
</tbody>
</table>

Patients may have had more than one adverse event within a body system or in more than one body system. Adapted from Swan et al (1999):


Adverse events reported during Phase III trial

<table>
<thead>
<tr>
<th>Adverse events reported during Phase III trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimark contrast medium (0.1 mmol/kg)</td>
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<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

Adapted from Swan et al (1999)

Change in contrast score as assessed from pre- to post-contrast images in CNS lesions when the contrast agent was used.

<table>
<thead>
<tr>
<th>Optimark contrast medium</th>
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<tbody>
<tr>
<td>Confidence in diagnosis (SE)</td>
</tr>
<tr>
<td>Conspicuity (SE)</td>
</tr>
<tr>
<td>Border delineation (SE)</td>
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<table>
<thead>
<tr>
<th>Mean difference between (pre- + post-) - pre-contrast score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference CI</td>
</tr>
<tr>
<td>2.07 (0.16)*</td>
</tr>
<tr>
<td>0.09 (0.28)</td>
</tr>
<tr>
<td>-0.37, 0.54</td>
</tr>
<tr>
<td>1.44 (0.13)*</td>
</tr>
<tr>
<td>0.15 (0.23)</td>
</tr>
<tr>
<td>-0.22, 0.53</td>
</tr>
<tr>
<td>1.78 (0.15)*</td>
</tr>
<tr>
<td>0.16 (0.26)</td>
</tr>
<tr>
<td>-0.27, 0.59</td>
</tr>
</tbody>
</table>

Adapted from Grossman et al. (2000)

Optimark™ increases the confidence in diagnosis in comparison to pre-contrast imaging

Optimark™ contrast medium presentations

<table>
<thead>
<tr>
<th>Packaging</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-filled syringe</td>
<td>10ml, 15ml, 20ml, 30ml</td>
</tr>
<tr>
<td>Glass vial</td>
<td>10ml, 15ml, 20ml</td>
</tr>
</tbody>
</table>
Relaxivity

Relaxivities of Investigated Contrast Media in Plasma at 37 °C

Advances in magnetic resonance imaging (MRI) technology, in terms of hardware and software innovations, have resulted in progressive improvements in imaging. In addition, the diagnostic utility of MRI can be further enhanced with the use of a gadolinium contrast agent, which can significantly improve image quality and add important diagnostic information. With such a paramagnetic agent, the T1 (and T2) weighted relaxation time of tissues becomes shortened, which leads to an increase in signal intensity.

Relaxivity

The relaxivity of an MRI contrast medium is an important feature which is essential for a good diagnosis. Optimark can be found in the top three of the highest relaxivity for commercially available contrast media with an indication for CNS investigations.3

Fig. 1a 26-year-old woman with multiple sclerosis. Axial FLAIR image shows lesion in left periventricular white matter.

Fig. 1c Axial T1-weighted image with magnetization transfer contrast obtained after administration of contrast material shows active plaque with peripheral enhancement.

Case Study 1:
MRI of the head

Patient history
26 year old female

MRI technique
Gyrocscan Intera 1.5 Tesla
Sense Head Coil
10ml of Optimark contrast medium was used in contrast enhanced scan.

Case Study 2:
MRI of the head

Patient history
46 year old female

MRI technique
Gyrocscan Intera 1.5 Tesla
Sense Head Coil
10ml of Optimark contrast medium was used in contrast enhanced scan.

Case Study 2:
MRI of the head

Patient history
46 year old female

MRI technique
Gyrocscan Intera 1.5 Tesla
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10ml of Optimark contrast medium was used in contrast enhanced scan.

Fig. 2a 46-year-old woman with bronchial carcinoma metastasizing to the brain. Axial T2-weighted image shows two small intraxial lesions in the occipitoparietal cortex.

Fig. 2b-c Axial T1-weighted images obtained after administration of contrast material show peripheral enhancement of both lesions (arrows).

Fig. 2d-e Coronal T1-weighted images depict same lesions in coronal plane (arrows).

Fig. 4a 46-year-old woman with bronchial carcinoma metastasizing to the brain. Axial T2-weighted image shows two small intraxial lesions in the occipitoparietal cortex.

Fig. 4b-c Axial T1-weighted images obtained after administration of contrast material show peripheral enhancement of both lesions (arrows).

Fig. 4d-e Coronal T1-weighted images depict same lesions in coronal plane (arrows).

Clinical case used with permission and courtesy of Diagnosezentrum Brigittenau, Vienna, Austria

Adapted from Rohrer et al. (2005)
Case Study 3: MRI of the head

A midline mass lesion 39x35x52 mm in size is showing irregular contours with marked peripheral edema and indentation to the midline structures. The mass lesion has heterogeneous signal with central hypointense areas and cystic components. Following the IV contrast media administration, peripheral rim-like irregular contrast enhancement is seen. Postero-superior to the mass lesion another ring enhancing lesion is also observed. Millimetric nodular pathological signal changes without contrast enhancement are seen on the right frontal, both parietal and subcortical white matter. Among the neoplastic processes, granulomatous (fungal) and infected cerebral echinococcosis are in the differential.

Case Study 4: MRI of the head

Brain MRI: Inflammatory thickness was diagnosed on para-nasal mucosal structures. Secondary to frontal craniotomy operation, post-operative changes were observed on the skin, subdural and bone structures. Two nodular lesions were significant in both temporal anterior lobes (6x7x6 cm on the right, 5x6x5 cm on the left) with the characterisation of iso-intense on T1-weighted sequences, hyper-intense on T2-weighted sequences, and shows increased conspicuity after intra-venous CM injection. Extra cranial extensions were observed on both sides of the lesion. Secondary to the lesion, bilateral exophthalmus were present and compression of the optic nerves was noted. The orbital laminae are defective secondary to the operation. Also a postoperative defect was seen on ethmoidal cellular. Temporal and frontal lobes were partially compressed on both sides. Invasion into the cavernous sinuses was noted. Frontal horn of right lateral ventricle also compressed.

Patient history
67 year old male
Presented with left frontal mass. Previous hydatidal cyst on left lung and left nephrectomy (cerebral echinococcus?).

Clinical case used with permission and courtesy of Dr. E. Turgut Tek, Gazi University, Ankara, Turkey.

Patient history
19 year old female
Patient presented with a history of headaches, nasal congestion and impaired vision in the left eye.

Brain MRI
Findings: Contrast enhanced scan showed a lesion with a 5 cm diameter in the anterior fossa at the base of the midline. The lesion was applying pressure bilaterally onto the optic nerves. Postoperatively the patient underwent radiotherapy and chemotherapy.

Pathological results
Olfactory Neuroblastoma

Clinical case used with permission and courtesy of Dr. K. Arda, Oncology Education and Research Hospital, Ankara, Turkey.

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<td></td>
<td>20ml</td>
</tr>
<tr>
<td></td>
<td>30ml</td>
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* Additional syringe to be filled manually is required in case of use of saline

Ideal synergy

An integrated MRI delivery solution

The Optistar™ Elite MRI injector, compatible with Optimark contrast medium in pre-filled syringes for a perfect fit.

Ideal synergy

- Specifically designed Optimark contrast medium in pre-filled syringes for use with Optistar™ Elite MRI injector.*
- Easy handling
  - Easy drop-in syringe loading is fast and convenient with Optimark contrast medium in pre-filled syringes and the Optistar™ Elite MRI injector.
**Prescribing Information**

**Optimark™ 500 micromol/ml solution for injection in a vial or a pre-filled syringe.**

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

**COMPOSITION:** 1 ml contains 330.9 mg gadoversetamide, equivalent to 500 micromol.

**INDICATIONS:** Optimark™ is indicated for use in Magnetic Resonance Imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualisation and helps with the characterisation of focal lesions and abnormal structures in the CNS and liver in patients with known or highly suspected pathology. **DOSAGE, METHOD OF USE, AND ROUTE OF ADMINISTRATION:** Optimark™ should only be administered by physicians experienced in clinical MRI practice. The agent should be administered as a bolus peripheral intravenous injection at a dose of 0.2 ml/kg (100 micromol/kg) body weight. The imaging procedure should be completed within 1 hour of administration of the contrast medium. In cranial MRI, a strong clinical suspicion of a lesion persists despite a single dose contrast-enhanced MRI or when more accurate information on the number, size or extent of lesions might influence management or therapy of the patient; in subjects with normal renal function, a second bolus injection of 100 micromol/kg may be administered within 30 minutes of the first injection. The safety of repeat doses has not been established in children and adolescents, in patients with renal impairment, or the elderly. Limited data with other gadolinium contrast agents suggests that for the exclusion of additional cranial metastases in a patient with a known solitary resectable metastasis, an MRI exam with the injection of the dose of 300 micromol/kg body weight of Optimark™ may lead to higher diagnostic confidence.

**Special Populations:** Renal impairment: Optimark is contraindicated in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and in patients who have had liver transplantation or in patients in the perioperative liver transplantation period. Optimark should only be used after careful risk/benefit evaluation in patients with moderate renal impairment (GFR 30-50 ml/min/1.73m2) at a dose not exceeding 100 micromol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Optimark injections should not be repeated unless the interval between injections is at least 7 days. Neonates up to 4 weeks of age, infants up to 1 year of age and children: Optimark is contraindicated in neonates up to 4 weeks of age. Use of Optimark is not recommended in children less than 2 years of age because the safety, efficacy and impact of immature kidney function have not been studied in this age group. Optimark has been studied in children of 2 years and older with a similar safety profile as shown in the adult population. Elderly (aged 65 years and above): No dosage adjustment is considered necessary. Caution should be exercised because transient decreases in serum iron and zinc parameters have been observed in clinical trials. The clinical significance of this is unknown. **UNDESIRABLE EFFECTS:** Most of the undesirable effects were of mild to moderate intensity and transient in nature. The most common undesirable effects were dysgeusia, feeling hot, headache and dizziness. The majority of adverse reactions observed after the use of gadoversetamide were found to be adverse reactions of the nervous system, followed by general adverse reactions, gastrointestinal disorders/skin and subcutaneous tissue disorders. Serious adverse reactions have been reported and include anaphylactic reactions, cardiovascular reactions, and allergic respiratory disorders. Treatment should be symptomatic and immediate access to necessary medicinal products and emergency equipment should be available should a serious event occur. Local reactions have occurred at the injection site and may lead to local irritation type reactions. Serious adverse reactions have been reported and include anaphylactic reactions, cardiovascular reactions, and allergic respiratory disorders. Treatment should be symptomatic and immediate access to necessary medicinal products and emergency equipment should be available should a serious event occur. Cases of Nephrogenic Systemic Fibrosis (NSF) have been reported with Optimark. **LEGAL STATUS:** Prescribing only. **DATE OF PREPARATION:** October 2013. **MARKETING AUTHORISATION HOLDER:** Mallinckrodt Deutschland GmbH, Josef-Dietzgen-Str. 1, 53773 Hennef, Germany

Please note: For the full prescribing information refer to the package insert/summary of product characteristics and/or contact your local Mallinckrodt Sales Representative.