TRANSPARENCY COMMITTEE

OPINION

20 February 2008

GADOVIST 1 mmol/ml, solution for injection
Pack of one 7.5 ml prefilled glass syringe – CIP 370 142-4
Pack of one 15 ml prefilled glass syringe – CIP 360 803-8
Pack of five 7.5 ml prefilled glass syringes – CIP 567 176-2
Pack of five 15 ml prefilled glass syringes – CIP 564 571-8

SCHERING S.A.S.

Gadobutrol
List I

Marketing authorisation (MA) date: 12 February 2003 (MRI of the CNS)
MA revision: 29 March 2004 (extension of indication to MRA)
MA revision: 16 July 2007 (extension of indication to MRI of liver or kidneys)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals in the extension of indication “Contrast enhanced magnetic resonance imaging (MRI) of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant”.

Medicine reimbursed by National Insurance and approved for use by hospitals
GADOVIST 1 mmol/ml, solution for injection
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Medical, Economic and Public Health Assessment Division
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Gadobutrol 604.72 mg (or 1 mmol)
Gadolinium equivalent 157.25 mg

1.2. Diagnostic indications
“This medicinal product is for diagnostic use only.
- Contrast enhancement in cranial and spinal magnetic resonance imaging (MRI).
- Contrast enhancement in magnetic resonance angiography (CE-MRA).
- Contrast enhanced magnetic resonance imaging (MRI) of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.”

1.3. Dosage
GADOVIST® should only be administered by physicians experienced in the field of clinical MRI practice.

General information
The dose required is administered intravenously as a bolus injection. Contrast-enhanced MRI can commence immediately afterwards (shortly after the injection depending on the pulse sequences used and the protocol for the examination).

Optimal opacification is observed during arterial first pass for CE-MRA and within a period of about 15 minutes after injection of GADOVIST® for CNS indications (time depending on type of lesion/tissue). Tissue enhancement generally lasts up to 45 minutes after injection.

T<sub>1</sub> scanning sequences are particularly suitable for contrast-enhanced examinations.

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

- Adults
CE-MRI of liver and kidneys
The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution.

- Children
GADOVIST® is not recommended for use in the population below age 18 due to a lack of data on efficacy and safety.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)
V: Various
### 2.2. Medicines in the same therapeutic category

The other gadolinium-based products used for abdominal examinations are the following:

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>INN</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOTAREM</td>
<td>gadoteric acid</td>
<td>Magnetic resonance imaging for: - cerebral and spinal disease - diseases of the vertebral column - other whole-body pathologies (including angiography)</td>
</tr>
<tr>
<td>MAGNEVIST</td>
<td>gadopentetic acid</td>
<td>Nuclear magnetic resonance imaging for: - cerebral and spinal examinations - examinations of the vertebral column - vascular examinations - other whole-body examinations</td>
</tr>
<tr>
<td>MULTIHANCE</td>
<td>gadobenate dimeglumine</td>
<td>Paramagnetic contrast agent for use in magnetic resonance imaging (MRI) of the liver and central nervous system (CNS). MultiHance is indicated for the detection of liver lesions in patients with known or suspected primary or secondary liver cancer (hepatocellular carcinoma). MultiHance is also indicated for the MRI of the brain and spine, where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.</td>
</tr>
<tr>
<td>PROHANCE</td>
<td>gadoteridol</td>
<td>Nuclear magnetic resonance imaging in adults and children: - cerebral and spinal disease - diseases of the vertebral column - whole-body pathologies.</td>
</tr>
<tr>
<td>OMNISCAN</td>
<td>gadodiamide</td>
<td>Nuclear magnetic resonance imaging: 5 ml vial; 10 ml, 15 ml and 20 ml syringes and vials: cerebral and spinal disease, diseases of the vertebral column, other whole-body pathologies (including those requiring angiographic examination). 50 ml bottle: vascular examination (angiography).</td>
</tr>
<tr>
<td>VASOVIST</td>
<td>gadofosveset</td>
<td>Contrast enhancement in magnetic resonance angiography (CE-MRA). VASOVIST is indicated for contrast-enhanced magnetic resonance angiography for visualisation of abdominal or limb vessels in patients with suspected or known vascular disease.</td>
</tr>
</tbody>
</table>

*Hepato-specific products*

<p>| CLIAVIST | Ferucarbotran | CLIAVIST® is a contrast agent for magnetic resonance imaging (MRI) of focal lesions of the liver, when the results of unenhanced imaging are unreliable. |</p>
<table>
<thead>
<tr>
<th>ENDOREM</th>
<th>Iron oxide (E172)</th>
<th>Detection of liver tumours in magnetic resonance imaging (MRI).</th>
</tr>
</thead>
<tbody>
<tr>
<td>TESLASCAN</td>
<td>Mangafodipir</td>
<td>Contrast medium for diagnostic Magnetic Resonance Imaging (MRI) for the detection of lesions of the liver suspected to be due to metastatic disease or hepatocellular carcinomas. As an adjunct to MRI in the investigation of focal pancreatic lesions.</td>
</tr>
</tbody>
</table>

2.3. **Medicines with a similar therapeutic aim**

none

3 **ANALYSIS OF AVAILABLE DATA**

Three studies were submitted by the manufacturer.

- **Study 304561**: A randomised, controlled study with blinded reading, assessing the diagnostic performance of GADOVIST compared with MAGNEVIST in renal examination (non-inferiority hypothesis).

- **Study 304562**: A randomised, controlled study with blinded reading, assessing the diagnostic performance of GADOVIST compared with MAGNEVIST in liver examination (non-inferiority hypothesis).

- **Study 94055**: Open-label, controlled study assessing the diagnostic performance of GADOVIST compared with unenhanced MRI in patients with suspected focal lesions in different anatomical regions (liver, bone/soft parts, pelvis, breast and lung). This study was conducted in 1995-98 before the EMEA guideline\(^1\) was issued. It was not conducted specifically in the indication given in the marketing authorisation and the comparator arm is no longer relevant for liver and renal examinations. The Transparency Committee was therefore unable to accept this study.

3.1. **Diagnostic efficacy**

The two phase III studies shared the same methodology.

They were randomised, controlled studies with a blinded reading phase that evaluated the diagnostic efficacy of GADOVIST® given as a single intravenous injection at a dose of 0.1 mmol/kg body weight compared with MAGNEVIST® in MRI of the liver or kidneys. The diagnostic accuracy of the two contrast agents was compared in a non-inferiority test and checked against a reference standard for each patient.

The MRIs were evaluated twice: during the clinical phase and during the blinded reading phase.

**Clinical phase**
In the clinical phase, the pre- and post-contrast MRI evaluations were compared with the final or gold standard diagnosis.

**Blinded reading phase**

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\(^1\) EMEA - Points to consider on the evaluation of diagnostic agents, CPMP/EWP/1119/98 – Nov 2001
Three independent radiologists who had not participated in the clinical study phase carried out blinded reading of the MRIs (pre-contrast images, post-contrast images, and combined pre- and post-contrast images comprising dynamic images acquired in the early vascular phase).

**Standard of reference used**

The standard of reference was established from all the available clinical information, the imaging results and the histopathology results obtained, which were taken to be the absolute standard of reference.

In the absence of an absolute standard of reference, a replacement standard of reference was used to establish the most reliable lesion diagnosis possible for each patient, taking into account the clinical data, the initial blood data, their changes over time, and/or the results of another imaging technique recognised and validated by the scientific community. In study 304562 (liver), a CT scan with injection or an MRI with a hepatospecific contrast agent was required. An independent expert panel composed of an radiologist and a hepatologist produced a consensus diagnosis of each lesion based on the clinical and biological data and on the imaging data excluding the MRIs performed with GADOVIST® or MAGNEVIST®.

**Study 304561, renal examination**

**Inclusion criteria**

Patients over 18 years of age with a known or suspected renal focal lesion based on clinical data, imaging data (reference abdominal-pelvic CT scan) and/or biopsy histology results.

**Primary endpoint:**

Evaluation of diagnostic performance (lesion analysis)
- Evaluation of the difference in diagnostic accuracy\(^2\) between the analysis by lesion of the pre-contrast MRIs and the joint reading of the pre- and post-contrast MRIs for GADOVIST® and that obtained with MAGNEVIST®
- Evaluation of sensitivity and specificity

**Limit of non-inferiority**

Non-inferiority was verified if the lower limit of the confidence interval of the difference was greater than or equal to the threshold set at -0.1 for all the independent radiologists (the mean in the blinded reading phase).

This lower limit was set based on the differential between the diagnostic efficacies of MAGNEVIST® obtained from the pre-contrast images (65-75%) and the combined pre- and post-contrast images (85-95%).

**Secondary endpoints (not exhaustive)**

Diagnostic accuracy at patient level
Sensitivity and specificity at patient level

**Results:**

**ITT population:** 466 patients (233 patients in each group)
**PP population:** 406 patients (Gadovist group = 200; Magnevist group = 206)

**Primary endpoint (PP population),**

The diagnostic accuracy rate, calculated from the mean of the three radiologists’ diagnostic accuracy rates, was 0.8366 for GADOVIST® and 0.8732 for MAGNEVIST®. The lower limit of the 95% confidence interval was -0.0941.

The hypothesis of non-inferiority was therefore validated (see Table 1).

\(^{2}\) i.e. the correct classification and location of each lesion in the blinded reading phase is obtained by comparison with the final diagnosis (benign lesion, malignant lesion, indeterminate lesion).
**Table 1:** Diagnostic accuracy for the classification of renal lesions

<table>
<thead>
<tr>
<th>Mean of the radiologists</th>
<th>GADOVIST®</th>
<th>MAGNEVIST®</th>
<th>Difference between GADOVIST® and MAGNEVIST®</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologist 1</td>
<td>0.8214</td>
<td>0.8459</td>
<td>-0.0245</td>
<td>[-0.0932, 0.0442]</td>
</tr>
<tr>
<td>Radiologist 2</td>
<td>0.8442</td>
<td>0.8836</td>
<td>-0.0395</td>
<td>[-0.1014, 0.0224]</td>
</tr>
<tr>
<td>Radiologist 3</td>
<td>0.8442</td>
<td>0.8899</td>
<td>-0.0458</td>
<td>[-0.1076, 0.0160]</td>
</tr>
<tr>
<td>Clinical study</td>
<td>0.7994</td>
<td>0.8781</td>
<td>-0.0788</td>
<td>[-0.1485, -0.00909]</td>
</tr>
</tbody>
</table>

**Sensitivity and specificity (lesion-based analysis)**

Mean sensitivity was 85% for Gadovist (against 89% for Magnevist) for the classification of malignant or benign renal lesions. Mean specificity was 82% for Gadovist (against 86% for Magnevist).

The hypothesis of non-inferiority was validated for both sensitivity and specificity.

**Secondary endpoints,**

In the patient-based analysis, the results observed suggest non-inferiority of Gadovist compared with Magnevist in terms of diagnostic accuracy (81% for Gadovist against 84%) and sensitivity (91% against 93%). The hypothesis of non-inferiority was not verified, however, in terms of specificity (52% for Gadovist against 61% for Magnevist).

**Conclusions from study 304561**

In the lesion-based analysis, GADOVIST was not inferior to MAGNEVIST in terms of diagnostic performance (sensitivity, specificity and diagnostic accuracy).

In the patient-based analysis, GADOVIST was not inferior to MAGNEVIST in terms of sensitivity and diagnostic accuracy.

**Study 304562, liver examination**

**Inclusion criteria**

Patients over 18 years of age with a known or suspected focal hepatic lesion (hepatocellular carcinoma, cholangiocarcinoma, metastases, adenoma, focal nodular hyperplasia, haemangioma, abscesses, hydatid cysts, etc.) based on clinical data, imaging data and/or biopsy histology results.

**Primary endpoint:**

Evaluation of diagnostic performance (patient analysis)

- Evaluation of the difference in diagnostic accuracy between the analysis by lesion of the pre-contrast MRIs and the joint reading of the pre- and post-contrast MRIs for GADOVIST® and that obtained with MAGNEVIST®
- Evaluation of sensitivity and specificity

**Limit of non-inferiority**

Non-inferiority was verified if the lower limit of the confidence interval of the difference was greater than or equal to the threshold set at -0.04 for at least 2 of the 3 independent radiologists (in the blinded reading phase).

**Secondary endpoints (not exhaustive)**

Diagnostic accuracy in the clinical phase
Rate of diagnostic agreement with the final diagnosis

Results:
ITT population: 572 patients (Gadovist group = 292; Magnevist group = 280)
PP population: 496 patients (Gadovist group = 250; Magnevist group = 247)

Primary endpoint (PP population).
The lower limits of the 95% confidence intervals were higher than the limit set at -0.04 for all the independent readers (see Table 2). The hypothesis of non-inferiority was therefore validated.
In terms of improving diagnostic accuracy per patient, GADOVIST was not inferior to MAGNEVIST® in comparisons of the pre-contrast images and of the combined pre- and post-contrast images.

Table 2: Increase in diagnostic precision – Pre- and post-contrast versus pre-contrast

<table>
<thead>
<tr>
<th></th>
<th>GADOVIST®</th>
<th>MAGNEVIST®</th>
<th>Difference between GADOVIST® and MAGNEVIST®</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical phase</td>
<td>0.116</td>
<td>0.117</td>
<td>-0.001</td>
<td>[-0.0056 ; 0.0028]</td>
</tr>
<tr>
<td>Radiologist 1</td>
<td>0.128</td>
<td>0.109</td>
<td>0.019</td>
<td>[0.0140 ; 0.0234]</td>
</tr>
<tr>
<td>Radiologist 2</td>
<td>0.344</td>
<td>0.340</td>
<td>0.004</td>
<td>[-0.0020 ; 0.0098]</td>
</tr>
<tr>
<td>Radiologist 3</td>
<td>0.124</td>
<td>0.130</td>
<td>-0.006</td>
<td>[-0.0108 ; 0.0003]</td>
</tr>
</tbody>
</table>

Secondary endpoints,
In the patient-based analysis, the results observed suggest that Gadovist is not inferior to Magnevist in the evaluation by the investigators (clinical phase).

The agreement (patient analysis) between the MRI diagnosis and the final diagnosis was analysed and classed at 4 levels: ‘no agreement’, ‘poor agreement’, ‘moderate agreement’ and ‘full agreement’. The diagnostic agreement of GADOVIST® was comparable to that obtained with MAGNEVIST® on the ‘full agreement’ and ‘majority agreement’ criteria.

Conclusions from study 304562
In the patient-based analysis, GADOVIST was not inferior to MAGNEVIST in terms of diagnostic accuracy.

3.2. Adverse effects/safety
The adverse effects most frequently associated with the medicinal product during the clinical trials were: dizziness, paraesthesia, headache, nausea, vasodilatation and dysgeusia.
Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site were uncommonly observed.

As with other intravenous contrast media, this product may be associated with anaphylactic or hypersensitivity reactions characterised by skin, respiratory and/or cardiovascular disorders, which may result in shock.

Cases of nephrogenic systemic fibrosis (NSF) associated with the use of certain contrast media containing gadolinium (MAGNEVIST in particular) have been reported in patients with severe renal failure (glomerular filtration rate < 30 ml/min/1.73 m²). Therefore, since a potential risk of NSF may occur with all gadolinium-based contrast media, caution should be exercised when the use of GADOVIST is being considered for patients with severe renal failure.
3.3. Conclusion

In light of the data presented, the diagnostic performance results show that GADOVIST is not inferior to MAGNEVIST for the detection and characterisation of suspected malignant focal lesions of the liver and kidneys.

It is regrettable, however, that histology was not always used as a gold standard. Only histology could have allowed the lesions to be irrefutably characterised as malignant or benign.

In addition, the comparator used, MAGNEVIST, does not have specific marketing approval for MRI examination of the liver or kidneys.

GADOVIST was well tolerated. However, from the example of other gadolinium-based contrast agents, the possibility that NSF might occur cannot be ruled out. The product should therefore be used in patients with severe renal failure only after careful consideration.
4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The severity of the condition is determined from the renal or hepatic examination results. This product is a paramagnetic contrast medium used for diagnostic purposes. Its efficacy/safety ratio in MRI contrast enhancement is high. This medicinal product is for first-line therapy. There are alternative diagnostic methods available.

Public health benefit
In the absence of data on the impact of GADOVIST on the health of the population and in view of the available data which suggest that this product will not provide any additional aid to diagnosis compared with the other gadolinium-based contrast agents used for abdominal examination, GADOVIST is not expected to have any public health benefit in this indication extension.

The actual benefit of this proprietary drug is substantial.

4.2. Improvement in actual benefit

The available data do not lead to the conclusion that GADOVIST is superior to other gadolinium salts in terms of either diagnostic performance or safety. Consequently, GADOVIST does not provide any improvement in actual benefit (IAB V) compared with the other gadolinium salts used in abdominal examinations (of the kidneys and liver).

4.3. Therapeutic use

Gadolinium-based contrast agents are the first choice when an enhanced MRI examination is needed. The situations when an MRI is recommended are given in the Good Practice Guide to medical imaging examinations (2005). These products enhance the image contrast for certain tissues. Use of these products improves recognition of vascular anatomical structures by improving image quality and generally allow an accurate diagnosis to be made.

The available data do not lead to the conclusion that GADOVIST is superior to other gadolinium salts in terms of either diagnostic performance or safety. Consequently, GADOVIST is an additional diagnostic aid for contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.

4.4. Target population

The target population for GADOVIST corresponds to all situations in which diagnostic MRI with a paramagnetic contrast agent is recommended for examination of the kidneys or liver, in accordance with the Good Practice Guide to medical imaging examinations (2005).

According to the AMR database, the number of contrast-enhanced MRI examinations performed in France in 2006 was approximately 1,155,000. The same database shows that 10.7% of these examinations concerned the kidneys and/or liver, making approximately 120,000 examinations.

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4 Arlington Medical Resources 2006
The proportion of examinations in which non-gadolinate hepatospecific products are injected is negligible (expert opinion).

Thus the annual target population, represented by the number of kidney and/or liver MRI examinations, is in the order of 120,000 examinations.

4.5. **Transparency Committee recommendations**

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the extension of indication and at the posology of the Marketing Authorisation.

4.5.1. **Packaging**: Appropriate to the prescription requirements.
4.5.2. **Reimbursement rate**: 65 %