MULTIHANCE, solution for injection
10 ml vial (CIP: 34009 347 412 9 6)
15 ml vial (CIP: 34009 347 413 5 7)
20 ml vial (CIP: 34009 347 414 1 8)
MULTIHANCE, solution for injection, pre-filled syringe
10 ml pre-filled syringe (CIP: 34409 388 796 6 7)
15 ml pre-filled syringe (CIP: 34009 388 797 2 8)
20 ml pre-filled syringe (CIP: 34009 388 798 9 6)

Applicant: BRACCO IMAGING France

<table>
<thead>
<tr>
<th>INN</th>
<th>Gadobenate dimeglumine</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2013)</td>
<td>V08CA08 (Paramagnetic contrast media)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Extension of indication</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>“Paramagnetic contrast agent for use in magnetic resonance imaging (MRI) indicated for: - MRI of the breast, for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results.”</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Substantial</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Improvement in Actual Benefit</td>
<td>The Committee considers that MULTIHANCE provides a minor improvement in actual benefit (IAB IV) in terms of diagnostic performance in MRI of the breast by comparison with MAGNEVIST.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>Like other gadolinium-based contrast media, MULTIHANCE is a first-line product for use where enhanced MRI examination is necessary; its role vis-à-vis other contrast media in diagnostic use in breast cancer has not been specified in national and international guidelines.</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (procedure) | Date initiated (mutual recognition procedure): 2 June 1998 (vials)  
Date initiated (decentralised procedure): 31 October 2008 (prefilled syringes)  
Date of extension of indication: 17/06/2013 |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MULTIHANCE is the subject of an RMP at European level on the same grounds as all gadolinium-based contrast media: Identified risk of nephrogenic systemic fibrosis (NSF).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prescribing and dispensing conditions /special status</th>
<th>List I</th>
</tr>
</thead>
</table>

| ATC Classification | 2013  
V08C  
V08CA08 | Various  
Contrast media  
Gadobenic acid |

| ATC Classification | V08  
V08C  
V08CA | Magnetic resonance imaging contrast media  
Paramagnetic contrast media |

02 BACKGROUND

This concerns the examination of the application for inclusion of the MULTIHANCE 10, 15 and 20 mL, solution for injection, proprietary medicinal products (vials and prefilled syringes), in a new indication, in MRI of the breast for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results, on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

MULTIHANCE is a gadolinium-based paramagnetic contrast agent used in magnetic resonance imaging (MRI).

For the record, the Committee has already assessed the MULTIHANCE proprietary medicinal products. Its conclusions were:
- on 03.03.1999, in the indication “MRI of the liver for the detection of liver lesions in patients with known or suspected secondary or primary liver cancer (hepatocellular carcinoma)”, a substantial AB and an IAB V,
- on 05.09.2001 in the indication “MRI of the brain and spinal cord where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI”, a substantial AB and an IAB V,
- on 27.05.2009 in the indication “Magnetic-resonance angiography where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries”, a substantial AB and an IAB V.
03 THERAPEUTIC INDICATIONS

“This medicinal product is for diagnostic use only. MULTIHANCE is a paramagnetic contrast agent for use in diagnostic magnetic resonance imaging (MRI) indicated for:

Vials and prefilled syringes:
- MRI of the liver for the detection of liver lesions in patients with known or suspected secondary or primary liver cancer (hepatocellular carcinoma).
- MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.
- MRI of the breast, for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results.

Vials:
- Magnetic resonance angiography (MRA) where it improves the diagnostic accuracy for detecting clinically significant steno-occlusive vascular disease in patients with known or suspected vascular disease of the abdominal or peripheral arteries.

04 DOSAGE

“MRI of the breast:
The recommended dose in adult patients is 0.1 mmol/kg body weight, i.e. 0.2 ml/kg of the 0.5 M solution.

Special populations:
Impaired renal function:
Use of MULTIHANCE should be avoided in patients with severe renal impairment (GFR < 30 ml/min/1.73 m²) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI (see Special warnings and precautions for use). If use of MULTIHANCE cannot be avoided, the dose should not exceed 0.1 mmol/kg body weight when used for MR of the brain and spine, MR angiography or breast MRI, and should not exceed 0.05 mmol/kg body weight when used for MR of the liver. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, MULTIHANCE injections should not be repeated unless the interval between injections is at least 7 days.

Elderly (aged 65 years and above):
No dose adjustment is needed. Use with caution in elderly patients (see Special warnings and precautions for use).

Children:
No dose adjustment is needed [....]"
05 THERAPEUTIC NEED

The aim of MRI of the breast is the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results. It facilitates the visualisation of abnormal structures or lesions and helps to differentiate healthy from diseased tissues.

Diagnostic needs are covered by the use of other gadolinium-based products already available on the market (see section on comparators).
# Clinically Relevant Comparators

## Medicinal Products

<table>
<thead>
<tr>
<th>Name (INN)</th>
<th>Company</th>
<th>Same TC* Yes/No</th>
<th>Indication**</th>
<th>Date of Opinion</th>
<th>Actual Benefit</th>
<th>Improvement in Actual Benefit (wording)</th>
<th>Reimbursed Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOTAREM (gadoteric acid)</td>
<td>GUERBET</td>
<td>Yes: contrast media – gadolinium salts</td>
<td>Magnetic resonance imaging for: whole-body pathologies (including angiography).</td>
<td>18/12/2013</td>
<td>Substantial</td>
<td>DOTAREM provides a minor improvement in actual benefit (level IV) in terms of safety over gadolinium-based contrast media presenting a high (OMNISCAN, MAGNEVIST) or moderate (MULTIHANCE) risk of nephrogenic systemic fibrosis according to the European Medicines Agency classification.</td>
<td>Yes</td>
</tr>
<tr>
<td>MAGNEVIST (gadopentetic acid)</td>
<td>BAYER</td>
<td>Yes</td>
<td>Magnetic resonance imaging for: whole-body explorations</td>
<td>05/01/2011</td>
<td>Substantial</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>MAGNEGITA (gadopentetic acid)</td>
<td>AGFA Healthcare</td>
<td>Yes</td>
<td>Magnetic resonance imaging for: whole-body explorations</td>
<td>Not assessed (generic of MAGNEVIST)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMNISCAN (gadodiamide)</td>
<td>GE Healthcare</td>
<td>Yes</td>
<td>Magnetic resonance imaging for: Other whole-body pathologies (including those necessitating exploration by angiography).</td>
<td>05/12/2012</td>
<td>Substantial</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>PROHANCE (gadoteridol)</td>
<td>BRACCO Imaging France</td>
<td>Yes</td>
<td>Magnetic resonance imaging (MRI) in adults and children: whole-body pathologies</td>
<td>18/11/2009</td>
<td>Substantial</td>
<td>Opinion of 04.12.1996: PROHANCE provides no improvement in actual benefit by comparison with other gadolinium-based paramagnetic contrast media.</td>
<td>Yes</td>
</tr>
<tr>
<td>GADOVIST (gadobutrol)</td>
<td>BAYER</td>
<td>Yes</td>
<td>Magnetic resonance imaging of whole-body pathologies.</td>
<td>18/12/2013</td>
<td>Substantial</td>
<td>GADOVIST does not provide any improvement in actual benefit (IAB V non-existent) compared with the other available alternatives.</td>
<td>Yes</td>
</tr>
</tbody>
</table>
06.2 Other health technologies

Examination of the breast can also be carried out by mammography and by breast ultrasonography, as specified in the guide to the proper use of medical imaging examinations\(^1\) (guide prepared by the French Society of Radiology (SFR), the French Society of Biophysics and Nuclear Medicine (SFBMN), with the assistance of professionals belonging to various medical and surgical specialities, designated by their learned societies. It was prepared with the support of the Authority for Nuclear Safety (ASN), and of the Haute Autorité de Santé (HAS [French National Authority for Health]).

\section*{Conclusion}
The clinically relevant comparators are represented by all diagnostic medicinal products used in MRI that are based on gadolinium salts and are mentioned in the table above.

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Yes – 100% in hospital, 50% in retail pharmacies</td>
</tr>
<tr>
<td>Austria</td>
<td>Yes – outpatients: 100% hospitalised patients: 25% by the National Institute for Health Insurance and Invalidity (INAMI) and 75% at a flat rate</td>
</tr>
<tr>
<td>Belgium</td>
<td>No – included in the regional health budget</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes – 40% (vials)</td>
</tr>
<tr>
<td>Spain</td>
<td>Syringes: In progress</td>
</tr>
<tr>
<td>Finland</td>
<td>No – included in the departmental health budget</td>
</tr>
<tr>
<td>Greece</td>
<td>Yes – 75%</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes</td>
</tr>
<tr>
<td>Ireland</td>
<td>No – included in the regional health budget</td>
</tr>
<tr>
<td>Italy</td>
<td>No – product for hospital use</td>
</tr>
<tr>
<td>Norway</td>
<td>No – included in the regional health budget</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes – flat rate</td>
</tr>
<tr>
<td>Poland</td>
<td>No – included in the cost of the examination</td>
</tr>
<tr>
<td>Portugal</td>
<td>No</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Yes</td>
</tr>
<tr>
<td>Romania</td>
<td>No</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>No – included in the departmental health budget</td>
</tr>
<tr>
<td>Slovenia</td>
<td>No – included in the cost of the examination</td>
</tr>
<tr>
<td>Sweden</td>
<td>No – included in the regional health budget</td>
</tr>
</tbody>
</table>
08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

In support of its application for inclusion of the extension of indication, the company supplied a phase III randomised, crossover, double-blind study comparing gadobenate dimeglumine (MULTIHANCE) with gadopentetate dimeglumine (MAGNEVIST): the DETECT study (MH-131). The company also supplied 3 studies from the literature which compared gadobenate dimeglumine (MULTIHANCE) with other gadolinium salts in the diagnosis of breast cancer.

8.1.1 DETECT study (MH-131).

This is a phase III, randomised, crossover, double-blind study, the aim of which was to demonstrate the superiority, in terms of sensitivity in the detection of malignant lesions of the breast on the basis of gross pathological results (diagnostic reference standard), of gadobenate dimeglumine (MULTIHANCE) versus gadopentetate dimeglumine (MAGNEVIST), in 162 women with a breast lesion known or suspected to be cancer after examination by mammography and/or breast ultrasonography.

Diagnostic regimen

The patients included in the study were randomised to two groups, A and B, before any MRI examination. The patients in group A received gadobenate dimeglumine (MULTIHANCE) in contrast medium for the first MRI examination then gadopentetate dimeglumine (MAGNEVIST) for the second MRI examination. The patients in group B received the same two contrast media in reverse order.

The first and second MRI procedures had to be separated by a minimum interval of 48 h (to ensure that the study substance was eliminated) and a maximum interval of 14 days (to minimise the risk of disease progression and thus to avoid any progression bias).

All these procedures were carried out using MRI machines with a field strength of 1.5 tesla.

Two successive procedures in the same patient were carried out with the same technical equipment and using the same imaging parameters.

The patients received an IV injection of 0.1 mmol/kg (i.e. 0.2 ml/kg) of MULTIHANCE 0.5 M or MAGNEVIST 0.5 M, either manually over about 10 sec, or via an automatic injector (1-2 ml/sec), followed by a 20-30 ml bolus of sodium chloride solution.

All the images were read blind, outside the study sites, in a centralised laboratory, by three separate, independent readers.

Inclusion and non-inclusion criteria

The inclusion criteria included, in particular:
- women >18 years,
- with ≥ 1 breast lesion(s) known or suspected to be cancer on the basis of either mammography (ACR BI-RADS 3, 4 or 5) performed within 30 days before the first procedure, and/or ultrasonography (ACR BI-RADS 3, 4 or 5) performed within 30 days before the first procedure, or performed within 30 days before the first procedure, and/or ultrasonography (ACR BI-RADS 3, 4 or 5) performed within 30 days before the first procedure,


3 ACR BI-RADS classification of the American College of Radiology: System of classification for radiological images, recommended for the detection of breast cancer, that can be used to propose a plan of action according to this classification of ACR 1 to ACR 5 according to the probability of malignancy.
- for which histological analysis of the breast lesion(s) by at least one of the following methods was specified: nonsurgical biopsy (including needle biopsy by trocar, assisted by aspiration or by drilling) performed within 14 days of, but not less than 2 hours after the second procedure, and/or breast surgery (including surgical biopsy, tumorectomy or mastectomy) performed within 30 days of, but not less than 24 hours after the second procedure.

- The main non-inclusion criteria included, in particular:
  - weight > 100 kg,
  - pregnant or breastfeeding women;
  - history of radiotherapy of the breast concerned within 18 months before the first examination,
  - history of breast surgery on account of a malignant lesion within 2 years before the first examination or, for a benign lesion, within 12 months before the first examination,
  - severe claustrophobia.

**Primary efficacy endpoint**
The primary efficacy endpoint was the sensitivity of MRI in the detection of malignant lesions of the breast, i.e. the ability of the test to correctly diagnose patients with malignant lesions of the breast (detection rate for malignant lesions of the breast).

To recap: \( \text{Sensitivity} = \frac{TP}{TP + FN} \)

*TP= true positives, FN= false negatives

**Secondary endpoints**
The secondary endpoints included:
- the other parameters of diagnostic performance in visualising lesions (specificity, positive predictive value, negative predictive value),
- parameters of diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value) in identifying regions with malignant/benign lesions of the breast,
- the inter-reader agreement in defining the nature of the lesions (benign or malignant): reliability/reproducibility of the test,
- safety.

**Statistical analysis**
Assuming a sensitivity (cancer detection rate) of 75% for MRI with MAGNEVIST and of 90% for MRI with MULTIHANCE, i.e. an expected difference in sensitivity of 15% between the two contrast media and assuming 25% of unpaired samples and each patient with a malignant lesion, a figure of 103 evaluable patients was needed to achieve a power of 90% in a two-sided test with a significance level of 0.05. Assuming a trial dropout rate of 20%, a total of 130 included subjects were required.

A total of 166 patients were included in this study, 162 of whom had been randomised and had received at least one study product. Among these patients, 153 had at least one MRI and had a diagnostic reference standard available.

For the analysis in terms of lesions, 136 randomised patients had the two MRIs and had a diagnostic reference standard available, 142 randomised patients had at least one MRI with injection of MULTIHANCE and had a diagnostic reference standard available, and finally 143 randomised patients had at least one MRI with injection of MAGNEVIST and had a diagnostic reference standard available.

For the analysis in terms of breast region (ten regions per woman), 138 randomised patients had the two MRIs and had a diagnostic reference standard available, 145 randomised patients had at least one MRI with injection of MULTIHANCE and had a diagnostic reference standard available, and finally 145 randomised patients had at least one MRI with injection of MAGNEVIST and had a diagnostic reference standard available.
Results:
Between July 2007 and May 2009, 162 patients were randomised in a ratio of 1:1 and received at least one dose of contrast medium (MULTIHANCE or MAGNEVIST).

The mean age of the patients was 52.8 years, and their mean weight was 67 kg. The percentage of patients with a family history of breast cancer was 31.5% (51/162) and the percentage of nonmenopausal women was 39.5% (64/162).

Two series of statistical analyses were carried out:
- a paired statistical analysis: analysis of the patients with a series of images with the two study products (and a diagnostic reference standard), regarded as the main analysis.
- a non-paired statistical analysis: analysis of all the patients with a series of images with at least one study product (and a diagnostic reference standard).

Primary efficacy endpoint
After the images had been read by three independent readers, each lesion was classified as follows:
- true positive (VP): lesion malignant in both MRI and histopathology
- false positive (FP): lesion malignant in MRI but benign in histopathology
- true negative (TN): lesion benign in both MRI and histopathology
- false negative (FN): lesion not seen or benign in MRI and malignant in histopathology

It should be noted that 7 patients who did not show any lesion in the diagnostic standard were excluded (the exclusion of these patients is questionable, since they could have been classed as TN or as FP, according to the MRI result).

In the paired statistical analysis (n=136), the sensitivity of the MRI examination in detecting malignant lesions of the breast was greater for MULTIHANCE (91.7% to 94.4%) than for MAGNEVIST (79.9% to 83.3%), (p ≤ 0.003).

In the unpaired statistical analysis (n=142 for MULTIHANCE and n=143 for MAGNEVIST), the sensitivity of the MRI examination in detecting malignant lesions of the breast was greater for MULTIHANCE (89.0% to 93.5%) than for MAGNEVIST (79.1% to 83.0%), (p ≤ 0.003).

Secondary endpoints
Diagnostic performance at lesion level:
- In the paired statistical analysis (n=136):
  - The specificity of the MRI examination in detecting malignant lesions of the breast (Sp = ability of the test to correctly diagnose patients with no lesion) was not greater for MULTIHANCE versus MAGNEVIST for readers 1 (59.7% versus 48.6%, p=0.074) and 2 (63.9% versus 58.3%, p=0.157) and was greater only for reader 3 (66.7% versus 30.6%, p<0.0001).
  - The positive predictive value of the MRI examination in detecting malignant lesions of the breast (TPP = probability of a malignant lesion being present if the test is positive) was greater for MULTIHANCE (82.0% to 85.0%) than for MAGNEVIST (70.6% to 79.5%), (p ≤ 0.0057).
  - The negative predictive value of the MRI examination in detecting malignant lesions of the breast (TPN = probability of a malignant lesion being absent if the test is negative) was greater for MULTIHANCE (78.2% to 85.7%) than for MAGNEVIST (47.8% to 60.0%), (p<0.001).
- In the unpaired statistical analysis (n=142 for MULTIHANCE and n=143 for MAGNEVIST):
  - The specificity of the MRI examination was not greater for MULTIHANCE than for MAGNEVIST for readers 1 (58.9% versus 47.3%, p=0.074) and 2 (64.4% versus 56.8%, p=0.157) and was greater only for reader 3 (65.8% versus 29.7%, p<0.0001).
• TPP: greater for MULTIHANCE (82.0% to 85.2%) than for MAGNEVIST (70.9% versus 79.4%), (p≤0.003).
• TPN: greater for MULTIHANCE (71.7% to 82.8%) than for MAGNEVIST (45.8% versus 58.3%), (p≤0.001).

Diagnostic performance in the breast regions:
- In the paired statistical analysis (n=138):
  • The sensitivity of the MRI examination in detecting breast regions with malignant lesions was greater for MULTIHANCE (92.8% to 96.4%) than for MAGNEVIST (82.7% versus 85.6%), (p≤0.001).
  • The specificity of the MRI examination in detecting breast regions with malignant lesions was greater for MULTIHANCE (96.7% to 99.0%) than for MAGNEVIST (93.6% versus 97.8%), (p≤0.009).
  • TPP: greater for MULTIHANCE (76.6% to 90.9%) than for MAGNEVIST (60.1% versus 81.0%), (p≤0.0002).
  • TPN: greater for MULTIHANCE (99.2% to 99.6%) than for MAGNEVIST (98.1% versus 98.3%), (p<0.0001).

- In the unpaired statistical analysis (n=145):
  • The sensitivity of the MRI examination was greater for MULTIHANCE (91.1% to 95.2%) than for MAGNEVIST (81.2% versus 84.6%), (p≤0.001).
  • The specificity of the MRI examination was greater for MULTIHANCE (93.8% to 97.8%) than for MAGNEVIST (70.9% versus 79.4%), (p≤0.009).
  • TPP: greater for MULTIHANCE (77.2% to 91.1%) than for MAGNEVIST (60.9% versus 80.7%), (p≤0.0002).
  • TPN: greater for MULTIHANCE (99.0% to 99.4%) than for MAGNEVIST (97.8% versus 98.1%), (p≤0.0003).

The inter-reader agreement in the correct characterisation of the lesions detected (malignant/benign) was calculated and summarised as the percentage inter-reader agreement. The reliability level of the test was estimated for each test product using the Kappa coefficient (which represents the inter-reader agreement observed, corrected for random agreement); this coefficient determines the reproducibility of the diagnostic test. The agreement observed for the 3 readers in the detection/evaluation of the breast lesions (benign/malignant/not detected/technically inadequate) was 76.7% for MULTIHANCE and 66.5% for MAGNEVIST. The kappa value was 0.69 for MULTIHANCE (confidence/reliability level “good” according to the Landis and Koch classification, since it was between 0.61 and 0.80) and 0.58 for MAGNEVIST (confidence/reliability level “moderate” since it was between 0.41 and 0.60).

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4 Landis, Koch Classification, 1977: scale between < 0 and 1 that can be used to interpret the value of the Kappa coefficient: the closer the Kappa coefficient is to 1, the better the test reliability.
8.1.2 Data from the literature

The company supplied two studies,\(^5\)\(^6\) the aim of which was to compare the efficacy of gadobenate dimeglumine (MULTIHANCE) with gadopentetate dimeglumine (MAGNEVIST) in terms of diagnostic performance. The crossover diagnostic regimen for these two studies is similar to the regimen for the DETECT study (presented above). In view of the small number of patients included in these two studies (n<60 patients), it is not possible to reach any conclusion about the superiority of either of the two contrast media in terms of diagnostic performance. These two studies therefore will not be discussed in this Opinion.

The company supplied a study,\(^7\) the aim of which was to demonstrate non-inferiority in terms of sensitivity in the detection of malignant and benign lesions of the breast on the basis of gross pathological results (diagnostic reference standard) of gadobutrol (GADOVIST) by comparison with gadobenate dimeglumine (MULTIHANCE) in 72 patients with a malignant lesion proven to be breast cancer by biopsy. It is a crossover regimen (intra-patient comparison): the patients included in the study were randomised to two groups before any MRI examination. These patients then received, in reverse order according to randomisation group, gadobutrol or gadobenate dimeglumine in an initial examination by MRI then the second gadolinium salt at the second MRI examination 24 h to 7 days later. Overall, non-inferiority was demonstrated, and no difference was found between these two substances in terms of sensitivity in the detection of malignant and benign lesions of the breast (0.82 versus 0.81, p=0.79).

08.2 Adverse effects

8.2.1 Data from the DETECT study (MH-131)

The adverse effect data were analysed for all patients who received at least one of these two contrast media; the populations were as follows:
- patients who received at least one injection of MULTIHANCE (gadobenate dimeglumine):
  \(n=158/162\) randomised patients.
- patients who received at least one injection of MAGNEVIST (gadopentetate dimeglumine):
  \(n=155/162\) randomised patients.

The percentage of adverse events was 5.7% (9/158 patients) in the MULTIHANCE group and 5.2% (8/155 patients) in the MAGNEVIST group. There was no discontinuation of treatment on account of adverse events.

The commonest adverse events were (MULTIHANCE versus MAGNEVIST):
- gastrointestinal disorders: nausea, vomiting (0% versus 3.2%),
- balance disorders and dizziness (1.9% versus 0.6%),
- nervous system disorders: fatigue, dysgeusia, headache (1.9% versus 2.6%).

In terms of the monitoring of vital signs at 1 h post-contrast, an increase or a reduction in systolic pressure of \(\geq 15\) mmHg was recorded in 11.6% of patients who received MULTIHANCE versus 13.0% of patients who received MAGNEVIST. An increase or a reduction in diastolic pressure of \(\geq 10\) mmHg was also recorded in 25.8% of patients who received MULTIHANCE versus 24.7% of patients who received MAGNEVIST.

patients who received MAGNEVIST. Finally, an increase or a reduction in heart rate of ≥ 20 beats/min was recorded in 2.6% of patients who received MULTIHANCE versus 3.2% of patients who received MAGNEVIST.

No change in the corrected QT interval (Bazett formula and Fridericia formula) exceeding 60 ms was detected after MULTIHANCE or after MAGNEVIST in the ECG trace recorded one hour after administration of the product by comparison with the trace before that administration.

8.2.2 PSUR data

The company provided the latest pharmacovigilance report covering the period from 01.12.2009 to 30.11.2012.

A total of twenty deaths were reported during this period; no causal link was directly established between the use of MULTIHANCE and the occurrence of these deaths. Out of these twenty cases, five occurred after anaphylactic shock.

In addition, 9 new cases of mixed nephrogenic fibrosis (cases for which the patient received several gadolinium-based contrast media) were reported; a fatal outcome was reported for 2 of these cases.

No new safety signals were generated during this period.

8.2.3 Specific adverse effects

Since 2006, international pharmacovigilance data have revealed a link between the occurrence of a systemic pathology, nephrogenic systemic fibrosis (NSF), and exposure to gadolinium chelates. NSF is a rare (400-700 identified cases to date worldwide according to sources8,9), late (median time to onset of five weeks after exposure) and potentially fatal complication of gadolinium-based contrast media. It affects patients with renal impairment and is characterised by cutaneous fibrosis that can spread to the muscles and other organs such as the lungs, liver and heart.

Nephrogenic systemic fibrosis is a sclerodermiform disorder first described in 1997, in dialysis patients. It is manifested in the form of skin lesions starting most often on the legs before spreading to the arms and trunk, but not the face and neck. The lesions take the form of indurated brownish plaques or papules often combined with dimpled-looking skin. These skin lesions can cause difficulty in extending joints and impaired mobility. In addition, systemic lesions involving organs such as the heart or lungs may be observed. The prognosis in NSF depends on the extent and severity of the fibrosis. A progressive deterioration in clinical condition is generally observed, leading to death in 20-30% of cases. There is currently no treatment of proven efficacy for this disease.

There are two types of NSF: “pure” (or “non-mixed”) cases, in which the patient received only a single type of contrast medium, and “mixed” cases, in which the patient received more than one gadolinium-based contrast medium (identical or otherwise) prior to developing the disease.

In 2009, the European Medicines Agency (EMA) carried out an evaluation of the risk of developing NSF for each gadolinium chelate and issued guidelines and a classification of proprietary medicinal products into three risk categories10,11.

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8 International Nephrogenic Systemic Fibrosis Registry. The International Center for Nephrogenic Systemic Fibrosis Research (ICNSFR) ; Yale University. http://www.icnfdc.org/
10 European Medicines Agency guidelines on minimisation of the risk of nephrogenic systemic fibrosis associated with administration of contrast media containing gadolinium salts - Bulletin, 02/12/2009.
- high risk: OMNISCAN, MAGNEVIST;
- medium risk: MULTIHANCE;
- low risk: GADOVIST, PROHANCE and DOTAREM.

For all contrast media containing gadolinium salts, the EMA:
- warns of a risk of NSF in the elderly because of their renal function;
- stresses the lack of data on the efficacy of using haemodialysis as NSF prophylaxis and for treating NSF in patients not on haemodialysis;
- emphasises the need to record the name and administered dose of gadolinium salt-based contrast medium in the patient’s records.

Products leading to the highest risk of developing NSF (OMNISCAN, MAGNEVIST) are contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), patients who are awaiting a liver transplant or have recently received one, and in neonates.

Since 2010, the FDA has also taken the view, based on pharmacovigilance data, that some gadolinium chelates (OMNISCAN, MAGNEVIST and OPTIMA RK, which is not on the market in France) present a higher risk of NSF and has contraindicated their use in patients with acute renal failure or a glomerular filtration rate of less than 30 ml/min/1.73 m². At the same time, the American College of Radiology (ACR) has issued guidelines and a classification of proprietary medicinal products on the market in the United States according to the risk of NSF occurring.

Table 1: Classification of gadolinium-based contrast media according to risk of nephrogenic systemic fibrosis occurring

<table>
<thead>
<tr>
<th>Risk (EMA)</th>
<th>ACR group</th>
<th>Structure</th>
<th>Charge</th>
<th>Gadolinium chelate</th>
<th>Proprietary Medicinal product</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>I</td>
<td>Linear</td>
<td>Nonionic</td>
<td>Gadodiamide (Gd-DTPA-BMA)</td>
<td>Omniscan</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gadoversetamide (Gd-DTPA-BMEA)</td>
<td>OptiMARK*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ionic</td>
<td>Gadopentetate dimeglumine (Gd-DTPA)</td>
<td>Magnevist, Magnegita</td>
</tr>
<tr>
<td>Medium</td>
<td>II</td>
<td>Linear</td>
<td>Ionic</td>
<td>Gadobenate dimeglumine (Gd-BOPTA)</td>
<td>MultiHance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gadoxetic acid disodium (Gd-EOB-DTPA)</td>
<td>Primovist*, Eovist*</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td></td>
<td></td>
<td>Gadofosveset trisodium</td>
<td>Vasovist*, Ablavar*</td>
</tr>
<tr>
<td>Low</td>
<td>II</td>
<td>Macro-cyclic</td>
<td>Nonionic</td>
<td>Gadobutrol (Gd-DO3A-butriol)</td>
<td>Gadovist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gadoteridol (Gd-HP-DO3A)</td>
<td>ProHance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ionic</td>
<td>Gadoterate meglumine (Gd-DOTA)</td>
<td>Dotarem</td>
</tr>
</tbody>
</table>

I: Products associated with the highest number of cases of NSF
II: Products associated with a low number of “pure” cases of NSF, i.e. cases where only one gadolinium-based contrast medium may be involved.
III: Products recently launched on the market.
*: in grey, proprietary medicinal products not marketed in France

These classifications were made on the basis of physicochemical properties, animal studies and pharmacovigilance data for different gadolinium chelates.

08.3 Summary and discussion

In a phase III randomised, double-blind study (DETECT study, MH-131) performed in 162 women with a lesion known or suspected to be breast cancer after examination by mammography and/or breast ultrasonography, gadobenate dimeglumine (MULTIHANCE) in breast MRI was superior in terms of sensitivity (primary efficacy endpoint) to gadopentetate dimeglumine (MAGNEVIST) as contrast medium; 91.7% to 94.4% versus 79.9% to 83.3%, (p≤0.003). This is a study of good methodological quality which has no bias due to variable factors (the population studied corresponds to the target population for the test), or any bias concerning verification, inclusion or disease progression.

As regards safety, the main adverse events were: gastrointestinal disorders (nausea, vomiting: 0% after use of MULTIHANCE versus 3.2% after use of MAGNEVIST), balance disorders and dizziness (1.9% versus 0.6%), and nervous system disorders (fatigue, dysgeusia, headache: 1.9% versus 2.6%).

For the record, the European Medicines Agency (EMA) carried out an evaluation of the risk of developing NSF (nephrogenic systemic fibrosis) for each gadolinium chelate and issued guidelines and a classification of proprietary medicinal products into three risk categories:10,11
- high risk: OMNISCAN, MAGNEVIST;
- medium risk: MULTIHANCE;
- low risk: GADOVIST, PROHANCE and DOTAREM.

In conclusion, the use of gadobenate dimeglumine (MULTIHANCE) as contrast medium in breast MRI showed superiority in terms of diagnostic performance (sensitivity, specificity, positive and negative predictive values) by comparison with the use of gadopentetate dimeglumine (MAGNEVIST). Nevertheless, there are other gadolinium-based contrast media. The company has not supplied any comparative data by comparison with these products (network meta-analysis, etc).

08.4 Usage data

The GERS sales data for MULTIHANCE (all indications taken together) in units, for all sectors (pharmacies and hospitals) between September 2013 and August 2014, are shown below.

<table>
<thead>
<tr>
<th>Presentations of MULTIHANCE</th>
<th>GERS sales data (boxes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml vial</td>
<td>10,537</td>
</tr>
<tr>
<td>15 ml vial</td>
<td>59,186</td>
</tr>
<tr>
<td>20 ml vial</td>
<td>33,099</td>
</tr>
<tr>
<td>10 ml pre-filled syringe</td>
<td>6781</td>
</tr>
<tr>
<td>15 ml pre-filled syringe</td>
<td>78,687</td>
</tr>
<tr>
<td>20 ml pre-filled syringe</td>
<td>52,298</td>
</tr>
</tbody>
</table>
Bilateral mammography is the reference examination for breast lesions. It can be carried out in patients with clinical warning signs or as part of screening (organised national screening programme, for women aged 50-74 years).
Mammography can be combined with bilateral breast ultrasonography including examination of the armpits; it is recommended in patients with dubious images in mammography, or in patients with an abnormal mammary examination and an inconclusive mammography.
In addition, other imaging examinations may prove necessary in exceptional cases, but there are insufficient data to justify the use of breast MRI in the initial assessment of breast cancer. Its indication can be discussed only in certain special circumstances which will be assessed in specialist facilities.

The place of breast MRI in the diagnostic strategy is as follows:
When breast cancer is diagnosed by mammography and, possibly, breast ultrasonography, breast MRI may be indicated only in particular cases to check for the presence of multiple lesions (conservative surgical treatment considered). Although MRI is the most sensitive examination, this gain in detection is not accompanied by an improvement in initial surgical management. Performance of this examination is therefore not indicated in all cases. Its addition must not delay the treatment process. Its indication and its results must be discussed in a multidisciplinary consultation meeting.

The potential indications for MRI are:
- lobular histology,
- disagreement between clinical features and standard imaging that could lead to a change in therapeutic management,
- in patients with difficult treatment choices (oncoplastic surgery, conservative treatment or mastectomy, neoadjuvant treatment),
- in women under 40 years of age,
- in women with a high familial risk of breast cancer.

MRI is not indicated in regular monitoring after breast cancer if there are no clinical or radiological warning signs. Annual MRI is indicated in the regular monitoring of women with a high genetic risk of breast cancer. Breast MRI may be indicated where a local recurrence is suspected in standard imaging or if there are suspicious clinical signs in the normal standard imaging assessment.

In women identified as being at high genetic risk after an oncogenetic consultation, the monitoring of this population starts at age 30 years, apart from exceptional cases specified in the oncogenetic consultation. MRI is the most powerful imaging technique in this population. It is the first monitoring examination to perform (scheduled for the second week of the cycle if possible) before mammography, plus or minus ultrasonography.

Like other gadolinium-based contrast media, MULTIHANCE is a first-line product for use where enhanced MRI examination is necessary; its role vis-à-vis other contrast media in diagnostic use in breast cancer has not been specified in national and international guidelines.

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In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

**010.1 Actual benefit**

- Breast cancer diagnosed by MRI is a serious disease.
- This medicinal product is intended for diagnostic use. It can be used to increase detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results, by improving the MRI contrast.
- The efficacy/adverse effects ratio is high.
- There are other gadolinium-based MRI contrast media.
- MULTIHANCE is used in first-line diagnostic examinations when breast MRI with contrast medium is required.

Public health benefit: In the absence of any criterion that can be used to assess the impact of MULTIHANCE in terms of morbidity, and given the availability of other magnetic resonance imaging contrast media, there is not expected to be any public health benefit from this proprietary medicinal product.

Taking account of these points, the Committee considers that the actual benefit of the proprietary medicinal products MULTIHANCE 10, 15 and 20 mL, solution for injection (vials and pre-filled syringes), is substantial in “MRI of the breast, for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results.”

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication “MRI of the breast for the detection of malignant lesions in patients where breast cancer is known or suspected on the basis of previous mammography or ultrasonography results” and at the dosages in the Marketing Authorisation.

- Proposed reimbursement rate: 65%

**010.2 Improvement in actual benefit (IAB)**

The Committee considers that MULTIHANCE provides a minor improvement in actual benefit (IAB IV) in terms of diagnostic performance in breast MRI by comparison with MAGNEVIST.
010.3 Target population

The target population of MULTIHANCE is represented by the number of breast MRI procedures. According to health insurance data, the number of MRI procedures reimbursed in 2013 was 75,172.\textsuperscript{15}

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

- Packaging
  Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

\textsuperscript{15} Aggregated data mart of CCAM-classified procedures from the data warehouse of the National Health Insurance Cross-Scheme Information System (SNIIRAM) (search made on 24.10.2014)