HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 May 2009

MULTIHANCE 0.5 mmol/mL solution for injection in glass vial
5 mL vial (CIP: 347 411-2)
10 mL vial (CIP: 347 412-9)
15 mL vial (CIP: 347 413-5)
20 mL vial (CIP: 347 414-1)

Applicant: BRACCO IMAGING FRANCE

Gadobenate dimeglumine
ATC code: V08CA08

List II

Date of original Marketing Authorisation: 02 June 1998
Amendment for the indication to be evaluated: 10 July 2008.

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use in the indication extension "Magnetic resonance angiography (MRA) where it improves the diagnostic accuracy for detecting clinically significant stenosis or occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries".

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Gadobenate dimeglumine

1.2. Indications

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

- MRI of the liver for the detection of focal liver lesions in patients with known or suspected primary liver cancer (e.g. hepatocellular carcinoma) or metastatic disease.
- MRI of the brain and spine where it improves the detection of lesions and provides diagnostic information additional to that obtained with unenhanced MRI.
- **Contrast-enhanced MR-angiography where it improves the diagnostic accuracy for detecting clinically significant stenosis or occlusive vascular disease in patients with suspected or known vascular disease of the abdominal or peripheral arteries."**

1.3. Dosage

"MRA:
The recommended dose in adult patients is 0.1 mmol/kg body weight. This corresponds to 0.2 mL/kg of the 0.5 M solution.
MULTIHANCE should be drawn up into the syringe immediately before use and should not be diluted. Any unused product should be discarded and not be used for other MRI examinations. To minimise the potential risks of soft tissue extravasation of MULTIHANCE, it is important to ensure that the i.v. needle or cannula is correctly inserted into a vein. […]

MRA: the product should be administered intravenously as a bolus injection, either manually or using an automatic injector system.

The injection should be followed by a saline flush.

Post-contrast imaging acquisition:

MRA:	Immediately after the administration, with scan delay calculated on the basis of test bolus or automatic bolus detection technique. If an automatic contrast detection pulse sequence is not used for bolus timing, then a test bolus injection ≤ 2 mL of the agent should be used to calculate the appropriate scan delay.

The safety and efficacy of MULTIHANCE have not been established in patients under 18 years old. Therefore, use of MULTIHANCE in this patient group cannot be recommended."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005):

V : various
V08 : contrast media
V08C : magnetic resonance imaging contrast media
V08CA : paramagnetic contrast media
V08CA08 : gadobenic acid

2.2. Medicinal products in the same therapeutic category

2.2.1. Strictly comparable medicines

These are contrast agents containing a gadolinium chelate which have an indication in MRA. These agents are:

- DOTAREM (gadoteric acid): indicated in MRI for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including angiography).
- GADOVIST (gadobutrol): indicated in cranial and spinal MRI and in MRI for pathologies requiring angiographic investigation.
- MAGNEVIST (gadopentetic acid): indicated in cranial, spinal, and whole body MRI, in vascular investigation and other whole-body investigations.
- OMNISCAN (gadodiamide): indicated in MRI for cerebral and spinal disease, diseases of the vertebral column, and other whole-body pathologies (including those requiring angiographic investigation).
- PROHANCE (gadoteridol): indicated in MRI in adults and children for cerebral and spinal disease, diseases of the vertebral column and whole-body pathologies.
- VASOVIST (gadofosveset trisodium): indicated in contrast enhanced MR-angiography for visualisation of blood vessels in the abdomen in patients with known or suspected vascular disease.

2.2.2. Not strictly comparable medicines

- None

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1 Placebo-controlled clinical trials

Three phase III controlled intra-individual comparison trials were included in the dossier: a trial in 293 patients concerning examination of the renal arteries (43.779-11), another in 287 patients concerning examination of peripheral arteries (MH-103), and one in 164 patients concerning examination of the arteries of the foot (MH-104).

3.1.1.1 Trial 43.779-11

Aims:
1) Demonstrate the superior sensitivity in detecting clinically significant stenosis or occlusive disease of the renal arteries (i.e. 51-99% occlusion or stenosis) of MRA with MULTIHANCE compared with MRA without contrast enhancement, using digital angiography as the reference examination
2) Evaluate the safety profile of MULTIHANCE.

Design:
Open prospective intra-patient comparison trial of MRA with MULTIHANCE versus MRA without contrast enhancement in the territories of the abdominal and renal arteries.

Inclusion criteria: patients aged at least 18 years, with known or suspected renovascular disease[1]. Patients had to have undergone or undergo digital angiography during the 30 days preceding or following investigation with MULTIHANCE. Patients had to be clinically stable and not undergoing any other therapeutic intervention for the vascular disease concerned between the time of the MRA and that of the digital angiography.

Endpoints:
Primary endpoint: sensitivity in detecting significant stenosis or occlusive disease from off-site or on-site assessments of images from MRA without contrast, MRA with MULTIHANCE and digital angiography.

The MRA scan was reviewed by a reviewer who was unaware of the digital angiography results. The quality of visualisation of each artery segment was evaluated using the following scale: 1 = segment visualised clearly and continuously; 2 = segment visualised poorly and intermittently, and detection or exclusion of stenosis was possible; 3 = segment visualised poorly and intermittently, and detection or exclusion of stenosis was not possible; 4 = segment not visualised (a score ≥ 3 ended the evaluation). The presence and degree of stenosis was then evaluated, for each segment.

MRA was evaluated off-site by three independent reviewers. The technical quality of each segment visualised was scored (1 = technically satisfactory, 2 = technically inadequate).
Digital angiography was evaluated on-site by a different practitioner who had not evaluated the MRA and was unaware of the MRA results.

[1] Patients had to have either severe hypertension (dBP > 100 mmHg), or refractory hypertension, or sudden aggravation of known hypertension, or sudden onset of hypertension (in patients aged under 35 years), or progressive renal failure, and/or abnormalities on digital angiography, Doppler ultrasound, CT angiography or other diagnostic procedure.

The digital angiography images were assessed off-site using the same criteria by an independent practitioner experienced in conventional angiography and unaware of all the clinical and imaging data.

McNemar's test was used to test the equivalence of both MRA modalities in terms of sensitivity, specificity and precision in detecting clinically significant stenosis or occlusive lesions, with a 5% threshold in the two-sided test.

Results:

Diagnostic efficacy

A total of 293 patients were included in the efficacy and safety analysis; there were 154 men (52.6%) and 139 women (47.4%). Mean age was 61 years (range =18-93 years). The mean volume of MULTIHANCE injected in the 293 patients included was 15 mL, i.e. 0.2 mL/kg, and the mean dose was 0.1 mmol/kg.

A total of 268 patients (91.5%) underwent both an MRA and a digital angiography procedure and were included in the analysis of diagnostic performance.

In terms of sensitivity, the difference between the two MRA modalities was between 29.7 and 51.1%. [see Table 1]

Table 1: Diagnostic performance of MULTIHANCE compared with digital angiography - main renal arteries

	Reviewer 1		Reviewer 2		Reviewer 3		On-site	
	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE
Sensitivity	28.2%	60.1%*	33.2%	74.5%*	44.2%	73.9%*	33%	84.1%*
Specificity	67.5%	93.1%*	87.1%	94.7%*	77.7%	89.4%*	60.2%	87.7%*
Reliability	52.5%	80.4%*	66.3%	86.9%*	64.9%	83.4%*	50.7%	86.4%*

* difference statistically significant compared with MRA without contrast (McNemar's test)

The assessments of all three reviewers agreed with each other for all segments in 79.9% of cases with MULTIHANCE versus 57.0% for images without contrast.

For all three reviewers and for the main renal arteries, failure levels were between 1.9 and 2.8% for MRA with MULTIHANCE compared with between 14.1% and 29% for MRA without contrast ($p<0.001$).

Adverse effects

A total of 49 patients out of 293 (16.7%) had adverse events (AE). AEs considered to be related to the product were observed in 9.2% of patients. Twelve patients (4.1%) had 13 local AEs, 8 of which (2.7%) were regarded as related to the product. No cases were reported of study discontinuation related to an adverse event.

The most commonly reported AEs (independently of any causal relationship) were fatigue, ecchymosis at the injection-site and taste disorders (1.4% for each AE); nausea, headache and hypotension (1% for each AE) were also observed.

3.1.1.2 Trial MH-103 (peripheral arteries)

Aims:
1) Demonstrate the superiority of MRA with MULTIHANCE versus MRA without contrast in terms of global sensitivity in detecting clinically significant stenosis or occlusive disease (51-99% occlusion or stenosis) in the peripheral arteries, using digital angiography as the reference examination;
2) Evaluate the safety of MULTIHANCE.

Design:
Open intra-patient comparison study of MRA with MULTIHANCE versus MRA without contrast enhancement in the territory of peripheral arteries (bifurcation of the aorta and iliac arteries, and lower limbs).

Inclusion criteria: patients had to be aged at least 18 years; have stenosis or occlusive disease of the peripheral arteries known or suspected from clinical data or ultrasound; had to have undergone or have to undergo standard-compliant digital angiography during the 30 days preceding or following investigation with MULTIHANCE; have not received or undergone any therapeutic intervention for the vascular disease concerned in the territory in question; and their clinical status had to have remained stable between MRA and digital angiography.

Evaluation:
The MRA scan was evaluated on-site by an experienced reviewer unaware of the digital angiography results. The quality of visualisation of each artery segment was evaluated using the following scale: 1 = segment visualised clearly and continuously; 2 = segment visualised poorly and intermittently, and detection or exclusion of stenosis was possible; 3 = segment visualised poorly and intermittently, and detection or exclusion of stenosis was not possible; 4 = segment not visualised. A score of 3 or 4 ended the evaluation. The presence and degree of stenosis was then evaluated for each segment. The presence of a collateral circulation, and the presence and type of concomitant disease, had to be evaluated for each segment.

MRA was evaluated off-site by three experienced independent reviewers. The technical quality of each segment visualised was scored (1 = technically satisfactory, 2 = technically inadequate).

Digital angiography was evaluated on-site by a different practitioner who had not evaluated the MRA and was not aware of the MRA results.

The digital angiography images were assessed off-site using the same criteria by an independent practitioner experienced in conventional angiography and unaware of all the clinical and imaging data.

The efficacy analysis concerned sensitivity in detecting significant stenosis or occlusive disease (≥ 51%) at segment level for the iliofemoral arteries, based on evaluations of MRA images without contrast enhancement, MRA with MULTIHANCE and digital angiography (primary endpoint).

Agreement between reviewers in detecting and quantifying stenosis at segment level during MRA was evaluated.

Results:
Diagnostic efficacy
A total of 287 patients were included, 207 of whom were men (72.1%). Mean age was 65.7 (40-93) years, and 59.6% of patients were aged 65 years or over. At inclusion, 99.3% of

patients had claudication, ischaemic pain at rest, ulceration or gangrene, and 80.8% of patients had moderate to severe peripheral arterial disease.

The mean volume of MULTIHANCE injected in the 287 patients included was 15.268 mL, i.e. 0.204 mL/kg, and the mean dose was 0.102 mmol/kg.

The difference in sensitivity between the two MRA modalities was between 17.7% and 24.9%. The difference in specificity was between 5.0% and 27.4% ($p<0.001$). The difference in reliability was between 9.9% and 26.1% ($p<0.001$) [see Table 2].

Table 2: Diagnostic performance of MULTIHANCE compared with digital angiography - iliofemoral arteries

	Reviewer 1		Reviewer 2		Reviewer 3		On-site	
	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE
Sensitivity	33.2%	54%*	62.8%	80.9%*	42%	67.4%*	39.9%	61.6%*
Specificity	79.4%	95.3%*	74.3%	89.7%*	88.9%	94%*	59.4%	86.9%*
Reliability	68.0%	85%*	71.4%	87.5%*	77.3%	87.4%*	55%	81.3%*

* difference statistically significant compared with MRA without contrast (McNemar's test)

The assessments of all three reviewers agreed with each other for all segments in 82% of cases with MULTIHANCE versus 65.2% for images without contrast.

Adverse effects
Out of a total population of 287 patients, 30 (10.5%) had 43 adverse events (AE). These AE were mild to moderate. Twenty-two patients (7.7%) had AE considered to be related to the product; 2.4% of patients reported 7 local AE, 6 of which (2.1%) were considered to be related to the product. No serious AE were reported, and no patients left the study because of an AE.

The most commonly reported AE (independently of any causal relationship) were a feeling of heat at the injection site (1.7%), raised systolic blood pressure (1.4%), and raised diastolic blood pressure (1%).

3.1.1.3 Trial MH-104 (arteries of the foot)

Aim:
To compare the performance of MRA with MULTIHANCE with that of MRA without contrast in detecting clinically significant stenosis of the arteries of the foot.

Design:
Open trial with intra-individual comparison of MRA without contrast and MRA with MULTIHANCE, using digital angiography as the reference examination.
The vascular territory explored was situated between a line passing 5 cm above the tibiotarsal joint and the most distal metatarsophalangeal joints.
Stenosis of 50% was classed as clinically significant.

Inclusion criteria:
Patients included were aged at least 18 years and had either intermittent claudication; or ischaemia likely to compromise the leg, with pain at rest; or moderate loss of substance; or major loss of substance; in at least one foot.

Evaluation:
All images were evaluated by independent reviewers who were unconnected with the investigating centres or sponsor and were unaware of patients' clinical and radiological data.

The primary endpoint was global quality of visualisation of arteries of the foot.
Secondary endpoints were analysis of sensitivity, specificity, precision and predictive values. Other parameters assessed were: contribution of MRA with MULTIHANCE compared with MRA without contrast in terms of quality of visualisation of individual segments of the arteries of the foot; technical failure rate; detection of collateral circulation; and detection of concomitant disease compared with digital angiography;

Reviewers off site evaluated the global quality of visualisation of previously defined artery segments (primary endpoint) using the following scale:
1: no segments visible;
2: partial, incomplete and non-diagnostic visualisation (up to 50% of the segments were visualised, but with poor, intermittent and diagnostically inadequate definition);
3: partial diagnostic visualisation (only 50% of segments were visualised sufficiently for diagnostic assessment);
4: all segments were visualised, but visualisation was poor and intermittent; diagnosis remained possible;
5: all segments were visualised clearly and continuously with adequate quality;
6: all segments were visualised clearly and continuously with excellent quality.

Statistical analysis:
The population analysed for the primary endpoint consisted of all patients who had received the product and undergone all imaging sequences before and after injection. Diagnostic performance was assessed in all patients who received the product and for whom there were technically satisfactory digital angiography images.

Primary endpoint: quality of global and segmental visualisation of the arteries of the foot of each patient.

Results:

Efficacy:
Diagnostic performance was assessed in 163 patients *(secondary endpoints)*.
The on-site assessments and the blinded off-site assessments showed that global diagnostic accuracy improved because of the significant increase in both sensitivity and specificity [see Table 3].

- the sensitivity of MRA with MULTIHANCE in detecting stenosis or occlusive disease was significantly better than that of MRA without contrast for off-site reviewers ($p<0.001$);
- the difference in specificity between MRA with MULTIHANCE and MRA without contrast was statistically significant ($p<0.001$) for all reviewers;
- the difference in global precision between MRA with MULTIHANCE and MRA without contrast was statistically significant ($p<0.001$) for all reviewers.

Table 3: Diagnostic performance of MULTIHANCE compared with digital angiography - arteries of the foot

	Reviewer 1		Reviewer 2		Reviewer 3		On-site	
	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE	MRA without contrast	MRA with MULTIHANCE
Sensitivity	7.9%	60.9%*	41.2%	56.7%*	3.5%	42.9%*	24%	51%*
Specificity	17.8%	62.5%*	30.2%	66.4%*	16.4%	45.5%*	22.6%	64.4%*
Reliability	13.4%	61.7%*	35.3%	62.1%*	10.5%	44.3%*	23.4%	57.4%*

* difference statistically significant compared with MRA without contrast (McNemar's test)

** Adverse effects:*
A total of 8 of the 164 patients (4.9%) experienced adverse effects (AE). All were mild to moderate in severity. Six patients had AE considered to be related to the product administered. No patients reported local AE, died, experienced a serious AE or left the trial because of an AE. The most commonly reported adverse event was nausea (1.2%).

3.1.2 Clinical trials versus active comparator

3.1.2.1 Trial BBG605

This phase I trial compared MULTIHANCE and MAGNEVIST, administered at the same dose of 0.1 mmol/kg, for examination of the aortic bifurcation and iliac arteries, and the arteries of the lower limb, in 21 healthy volunteers.

The aim was an intra-patient comparison of both gadolinium chelates during a stage by stage examination of the arterial territories of the lower limbs.
Efficacy was assessed in terms of technical quality: the primary endpoint was the signal-to-noise ratio measured in nine vascular segments, from the abdominal aorta as far as the tibial-fibular trunks.
As this was not a clinical endpoint, the results of the trial will not be described.

3.1.2.2 Trial B19036/052

A phase II trial (B19036/052) compared MULTIHANCE with MAGNEVIST in examination of the renal arteries.

Aims:
The aim was to compare the quantitative and qualitative contributions of MULTIHANCE (0.1 mmol/kg) and MAGNEVIST (0.2 mmol/kg) to the technical performance of MRA with contrast.

Method:
Randomised, double-blind, crossover trial in patients requiring MRA of the renal arteries.

Patients:
Adult patients with known or suspected stenosis or occlusive disease of the renal arteries requiring MRA.

Evaluation:
Efficacy:
The territory examined corresponded to the abdominal aorta and renal arteries. This territory was divided into nine vascular segments: ostium of the right and left renal arteries (2 segments), right and left proximal renal arteries (2 segments), right and left distal renal arteries (2 segments), right and left segmental renal arteries (2 segments) and abdominal aorta (1 segment).
Diagnostic quality was assessed for each of the segments[2].

[2] Diagnostic quality was assessed using the following scale for each of the segments:
0: diagnostic information quality very poor, making it impossible to detect or exclude vascular lesions;
1a: diagnostic information quality moderate, vascular lesions might be absent;
1b: diagnostic information quality moderate, vascular lesions might be present;
2a: diagnostic information quality satisfactory, vascular lesions definitely absent;
2b: diagnostic information quality satisfactory, vascular lesions definitely present;

A quantitative assessment of the images obtained (signal-to-noise ratio for blood vessels and contrast-to-noise ratio for blood vessels and muscles) was carried out for the regions of interest in the supra-, juxta- and infra-renal segments of the aorta and on the psoas muscle. As the assessment criteria were not clinical, the efficacy results will not be described.

Results:

Patients

A total of 41 patients (20 men) received one (n=6) or both (n=35) contrast agents. Mean age was 59.1 (23-92) years, and mean weight was 74 kg. There was no difference between the two groups after randomisation. Only 35 patients received both agents; 3 patients received only MULTIHANCE and 3 patients received only MAGNEVIST.

There was no significant difference between MULTIHANCE 0.1 mmol/kg and MAGNEVIST 0.2 mmol/kg in terms of mean image quality.

Adverse effects

Two of the 38 patients (5.3%) experienced adverse events (AE) after injection of MULTIHANCE: one patient had nausea (causal relationship with AE probable) and the other had cholesterol embolism during a revascularisation procedure (considered to have no causal relationship with AE). One of the 38 patients (2.6%) had an AE after injection of MAGNEVIST.

3.2. Conclusion

In the phase III clinical trials of MRA of the arteries ranging from the upper aortic territory to the circulation of the foot, off-site reviewers observed with MULTIHANCE 0.1 mmol/kg a 10-33% improvement in diagnostic precision in detecting clinically significant stenosis or occlusive disease (i.e. stenosis > 51%, or > 60% depending on the vascular territory) compared with MRA without contrast, using conventional angiography as a reference examination

Analysis of adverse events over all the studies showed a similar profile to that of other gadolinium chelate contrast agents indicated in MRA. The most commonly reported adverse events were nausea, headache, and a sensation of heat at the injection site.

The Committee regrets the absence of phase III studies comparing the diagnostic performance of MULTIHANCE used in MRA with that of MAGNEVIST In the same indication.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Angiography (MRA)

The severity of the disorders concerned depends on the results of the diagnostic investigation.

The product is a paramagnetic contrast agent for diagnostic use.

The efficacy/adverse effects ratio in MRA contrast enhancement is high.

There are alternative diagnostic options.

> Public health benefit: in the absence of criteria making it possible to assess the impact of MULTIHANCE in terms of morbidity, and in view of the availability of other contrast agents for magnetic resonance angiography to which MULTIHANCE has not

The primary endpoint was total score for diagnostic quality obtained by adding scores for each segment for each patient (maximum possible score = 18).

been compared in a Phase III trial, it is not anticipated that MULTIHANCE will provide any public health benefit.

The actual benefit of the medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

The available data are inconclusive with regard to the superiority of MULTIHANCE over other gadolinium salts in terms of diagnostic performance in MRA.
Consequently, MULTIHANCE does not provide any improvement in actual benefit (IAB level V) compared with other gadolinium salts used in MRA.

4.3. Therapeutic use

MULTIHANCE is a gadolinium contrast agent indicated in MRA. The clinical situations in which MRA is recommended are described in the ANAES Guide to proper use of medical imaging examinations (2005)[3]. The most important are:
- completed or transient stroke,
- sudden acute headache (detection of vascular malformation),
- visualisation of the internal carotid arteries when an aneurysm or arteriovenous fistula is suspected,
- lower limb ischaemia,
- high arterial blood pressure (in a young adult or a patient not responding to drug therapy) to look for renal artery stenosis,
- visualisation of arteries in a kidney transplant.

It would appear that MRA with MULTIHANCE is an imaging modality which does not subject the patient to radiation. It is performed as a first-line investigation if CT angiography is contraindicated (severe renal failure, allergy to iodine, gammopathy). MRA is mainly contraindicated in patients with metal implants.
Paramagnetic contrast agents, including MULTIHANCE, are used to enhance contrast in images of certain tissues during MRA.

4.4. Target population

The patients likely to benefit from MRA with injection of MULTIHANCE are those with clinically significant stenosis or occlusive vascular disease when vascular disease of the abdominal or peripheral arteries is suspected or known (SPC). The aetiologies studied in clinical trials are:

<u>Renal artery stenosis</u>
Approximately 40-50% of patients with peripheral vascular disease have a narrowing of a renal artery[4]. Renal artery stenosis is present in 15-30% of coronary disease patients[5] and in 10-22% of patients presenting with terminal renal failure[6]. The estimated prevalence of renal artery stenosis is between 0.5 and 3% for a population of individuals with hypertension (prevalence of hypertension in France in 2006 = 13 million[7]). The estimated number of patients with renal artery stenosis is between 65 000 and 390 000.

[3] ANAES, *Guide de bon usage des examens d'imagerie médicale* (Guide to proper use of medical imaging examinations), 2005
[4] Choudhri AH, Cleland JGF, et al. Unsuspected renal artery stenosis in peripheral vascular disease. BMJ 1990; 301: 1197-8.
[5] Uzu T, Inoue T, Fujii T, et al. Prevalence and predictors of renal artery stenosis in patients with myocardial infarction. Am J Kidney Dis 2000; 29 : 733-8
[6] Mailloux LU, Napolitano B, Bellucci AG, et al. Renal vascular disease causing end-stage renal disease, incidence, clinical correlates, and outcomes. A 20-year clinical experience. Am J Kidney Dis 1994; 24 : 622-9
[7] MONICA Project

Aneurysm of the abdominal aorta and aortic dissection

Approximately 3% of the general population in North America[8,9]are thought to have an aneurysm of the abdominal aorta. Extrapolating this to the French population aged over 18 years (MULTIHANCE has no indication in children) gives a figure of 1 800 000 patients.

Abdominal aortic dissection is rare, with a global frequency thought to be about 5-10 per year per million inhabitants.

Chronic peripheral arterial occlusive disease (PAOD) of the lower limbs

This disease affects approximately 2 million patients in France.[10].

As the product is a contrast agent, i.e. a product for purely diagnostic purposes, it does not seem possible to estimate the relevant target population for the indication with any accuracy, as there is a very wide range of aetiologies that require this type of examination, and a single patient may have two indications for it.
It is only possible to extrapolate, from the frequency of the vascular diseases that may be investigated using MRA with injection of a gadolinium chelate.
A search of the *Echantillon Généraliste des Bénéficiaires (EGB)* database (a representative sample of individuals covered by French National Insurance[11]) made it possible to estimate the number of patients who had undergone MRA in 2008 as 0.04% (95% CI [0.035-0.045%]), i.e. 185 patients out of the 492 727 patients in the general sample who had not died.
This estimate can only give an idea of the population as the sample population consisted only of individuals covered by the *régime général* (the basic French health insurance scheme) which represents 75% of the French population and the request concerns patients who have undergone MRI in the independent sector. The sample does not take account of MRA examinations carried out in the public sector (i.e. hospitals formerly receiving a global subsidy).

If these figures are extrapolated to the data for the population covered under the *régime général* (i.e. about 48 million), this gives a figure of 17 945 patients (95% CI [15 360 - 20 530]).

4.5. Transparency Committee recommendations

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

4.5.1. Packaging: appropriate for the prescription conditions

4.5.2. Reimbursement level: 65%

[8] Anévrysmes de l'aorte abdominale. A. Branchereau. Revue du Praticien. 1992; 42 (6): 761-766
[9] Anévrysme de l'aorte abdominale. Fabiani JN, Saliou C. Revue du Praticien 1995; (45): 1309-1316
[10] *Prise en charge de l'artériopathie chronique oblitérante athéroscléreuse des membres inférieurs (indications médicamenteuses, de revascularisation and de rééducation)* [Management of chronic arterial or atherosclerotic occlusive disease of the lower limbs (indications for drug therapy, revascularisation and rehabilitation) - in French] Haute Autorité de Santé Clinical Practice Guidelines April 2006
[11] The creation and use of the EGB are regulated by the Ministerial Order of 20 June 2005 relating to the implementation of a shared national information system for all health insurance providers