(1) Does the application adequately address the issue of the public health need for the medicine?

Yes ☒ No ☐

The Applicant argues that it is important to include a contrast agent that can be used for MRI in the EML, as it is already the case for iodinated contrast agents. MRI contrast agents are currently used in about 40% diagnostic tests to increase contrast between normal tissues and pathological structures, to speed up image acquisitions and also to provide additional functional information on the tissues and organs under evaluation.

MRI is used for the diagnosis and treatment of diseases responsible for more than 25 million deaths per year. MRI procedures are mainly performed for central nervous system (CNS) diseases (50%), cancers and cardiovascular diseases (17%). About 40% of MRI examinations are performed with injection of contrast agents such as gadoterate meglumine.

The most popular agents are paramagnetic molecules including a gadolinium ion. However, gadolinium is a heavy metal, which in its free form is very toxic and may cause liver necrosis, hematological changes etc. It is therefore essential - the Applicant maintains - to choose an appropriate gadolinium chelate, which is as stable as possible to simultaneously ensure sufficient efficacy and short-term and long-term safety.

Three classes of GCs can be distinguished (see Table below):

1. macrocyclic chelates characterized by high kinetic stability (gadobutrol, gadoteridol and gadoterate), with the highest stability being reached with the ionic and macrocyclic GC gadoterate [Port 2008]);

2. ionic linear chelates (gadobenate, gadopentetate, gadofosveset) for which a moderate kinetic inertia leads to significant dissociation; and

3. nonionic linear chelates (gadodiamide and gadoversetamide), which exhibit poor kinetic stability and the highest extent of dissociation.
Characteristics of currently marketed gadolinium-based products for MRI

<table>
<thead>
<tr>
<th>Genic Name</th>
<th>Gadopentate dimeglumine</th>
<th>Gadopentate dimeglumine</th>
<th>Gadoveritam dolphin</th>
<th>Gadoteridol</th>
<th>Gadoteridol</th>
<th>Gadoterideqitam</th>
<th>Gadoteridol</th>
<th>Gadoterol</th>
<th>Gadoterate meglumine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name</td>
<td>Magnoxide®</td>
<td>Fort」®</td>
<td>Multihance®</td>
<td>Optimark®</td>
<td>Optima®</td>
<td>Promene®</td>
<td>Optimark®</td>
<td>Goteva®</td>
<td>Goteva®</td>
</tr>
<tr>
<td>Company</td>
<td>Bayer Healthcare</td>
<td>Bayer Healthcare</td>
<td>Bracco Imaging</td>
<td>GE Healthcare</td>
<td>Bracco Imaging</td>
<td>Siemens</td>
<td>Siemens</td>
<td>Bracco Imaging</td>
<td>Siemens</td>
</tr>
<tr>
<td>Chemical Structure</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Open-Chain</td>
<td>Macroyclic</td>
</tr>
<tr>
<td>Concentration of the marketed solution</td>
<td>0.1</td>
<td>0.25</td>
<td>0.3</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Formulation of the marketed solution</td>
<td>Free DTPA (1 mmol/l)</td>
<td>Ca-DTPA-BMA (sodium salt) 1.5 mmol/l</td>
<td>No added ligand</td>
<td>Free DTPA (0.5 mg/ml)</td>
<td>Ca-DTPA-(Na2-salt) (25 mmol/l)</td>
<td>Ca-DTPA-BMA (Na2-salt) (25 mmol/l)</td>
<td>Ca-DTPA-BMA (Na2-salt) (25 mmol/l)</td>
<td>Ca-DTPA-BMA (Na2-salt) (25 mmol/l)</td>
<td>No added ligand</td>
</tr>
<tr>
<td>pH Value</td>
<td>7.3</td>
<td>7.5</td>
<td>7.6</td>
<td>7.6</td>
<td>6.9</td>
<td>6.6</td>
<td>6.6</td>
<td>11.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Kinetic Stability</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>Medium</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Gadoterate meglumine can be efficiently used in three types of examinations:
1. MR imaging for intracranial and spinal cord diseases,
2. Whole body MR imaging,
3. Magnetic resonance angiography (though with caveat and limitations).

Listing of gadoterate meglumine is requested as an individual medicine. Although several agents are present on the market, the Applicant considers gadoterate meglumine (Dotarem®) to be a unique product for two reasons:
1. It is the only ionic macrocyclic gadolinium chelate and is consequently considered as the most stable of all gadolinium-based contrast agents.
2. No case of NSF (Nephrogenic Systemic Fibrosis, see below) has ever been reported with the use of gadoterate meglumine alone.

According to the Applicant gadoterate meglumine should be preferred due to its reduced potential to induce adverse reactions compared to other gadolinium-based contrast agents.

(2) Have all important studies that you are aware of been included in the application?

Yes ☐ No ☒


Other studies that are not referred to by the Applicant are mentioned at the end of section (3).

No Cochrane review is available so far. There should be a need for a careful search in the literature and for a critical analysis and summary of the efficacy and safety data reported. This is not feasible in the timeframe allowed for this review.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes ☐ No ☒

According to the Applicant gadoterate meglumine use was associated with an improved diagnostic efficacy when compared to unenhanced images, and with a non-inferior diagnostic ability when compared to competitors.

In support of this general conclusion the Applicant refers to several studies in various clinical indications (CNS, whole body including several districts, and angiography). Most studies are on file, unpublished, and their data are not (fully) provided. Most studies are not randomized, open, crossover, and the control, if any, is a different diagnostic approach, e.g. CT or unenhanced MRI. Very rarely the control is an alternative contrast agent.

CNS imaging
One possible exception in this respect in the CNS area is the SENTIO trial, which was a “multicenter, randomized, double-blind, fixed sequence (unenhanced MRI followed by either Dotarem- or Magnevist-enhanced MRI). Patients were randomly assigned to receive gadoterate meglumine or Magnevist in a 2 to 1 ratio. Pediatric patients were assigned to the gadoterate meglumine group only. This study demonstrated the superiority of gadoterate meglumine-enhanced MRI as compared to unenhanced MRI in terms of CNS lesion visualization. The validity of gadoterate meglumine efficacy as a contrast agent was validated against the approved contrast agent Magnevist and had a better safety profile, notably with fewer injection site conditions. The use of gadoterate meglumine in paediatric population appears effective and safe”.

However, this study has no reference and data are not provided. In addition, the better safety of gadoterate meglumine seems to be questioned by other findings. In the double-blind randomized trial by Brugières et al. (1994) comparing gadoterate meglumine and Magnevist® events occurred with a similar frequency in the two groups (17.3% and 19.3%, respectively). Minor neurological symptoms were the most frequent (48.6%), headache being the most common (29.2% of adverse events). No difference in efficacy was found.

The overall conclusion of the Applicant regarding the CNS setting is that “gadoterate meglumine is particularly useful for the assessment of extracerebral tumors (meningiomas, neuromas, pituitary tumors) and for a more precise topographic assessment of intracerebral tumors (gliomas, ependymomas, metastases) and their staging. Gadoterate meglumine also increases the sensitivity of MRI for the detection of metastases”.

However, no clear advantage with respect to other contrast agents is proved and the claimed superiority with respect to unenhanced MRI is not supported by quantitative data.

Whole body imaging
In the whole body imaging area the manufacturer Guerbet sponsored trials including 855 patients suffering from different diseases. No randomized blind trial was conducted in the hepatic, pancreatic, musculoskeletal, pelvic, cardiac, breast, chest area. No study compared gadoterate meglumine with other contrast agents. Descriptive reporting of results are most often not supported by data or references to published papers.
The only randomized trial in the whole body imaging area is an open, prospective trial conducted by Guerbet in 20 patients with various underlying renal diseases (Bellin et al., 1992). Subjects presenting a glomerular filtration rate <60 mL/min were randomly allocated to renal MRI imaging with gadoterate meglumine or without contrast agent. The diagnostic quality of MRI was considered as good or excellent in 7 patients out of 10 in the gadoterate meglumine group and in 3 out of 10 in the control group. In 3 patients the use of gadoterate meglumine modified diagnosis and therapeutic strategy based on baseline MRI examination without contrast agent.

The overall conclusion of the Applicant regarding the whole body imaging is that gadoterate meglumine-enhanced MRI contributes to detect tumors unseen on mammography, appears to be comparable or even slightly superior to that of CT in liver imaging, allowed distinguishing active parts of lesion from intra-tumor necrosis in musculo-skeletal diseases, provides useful information for assisting surgical planning and definition of therapeutic strategy in case of female pelvic masses. In renal imaging gadoterate meglumine allowed better detection and identification of the nature of localized lesions, the diagnosis of renal hypertension, the evaluation of glomerular filtration, the detection of smaller defects of perfusion. In addition, dynamic MR studies provided information about transplant perfusion and parenchymal function. In chest imaging gadoterate meglumine provided information in the preoperative assessment of lung carcinoma. In myocardial ischemia, serial MRI tomography with gadoterate meglumine enabled precise evaluation of infarct size, which is of great prognostic and therapeutic value. However, no clear advantage with respect to other contrast agents has been proved and the claimed superiority with respect to unenhanced MRI is only suggested by subjective evaluation from one open study in a few patients.

**Angiography**

The Applicant reports that among the 50 clinical trials that it found in Medline, a total of 16 trials “bring significant and valuable results for a diagnostic performance analysis”. Criteria for this selection are not provided. The results of these 16 trials are summarized in a table (Table 17) which actually includes 28 studies reporting “satisfactory diagnostic performance”, with sensitivity ranging from 70% to 100% and specificity ranging from 82% to 100%.

However, there are discrepancies among the results of the studies addressing the same arterial territories and indications, there is no complete information regarding the design, the possible comparator, the results and their variability, the independency of the study conception, conduction and analysis.

Two randomized single-blind trials were conducted by Gruber in the MR angiography area. One trial aimed at evaluating the diagnostic efficacy of two doses of gadoterate meglumine-enhanced MRA compared to X-ray angiography in the assessment of vascular lesions of the lower limbs in 40 patients. The specificity by segment was 89% with the higher gadoterate meglumine dose and 84% with the lower dose. Regarding the evaluation of collateral arteries, MRA with gadolinium reportedly provided good or excellent results in 73.9% of the cases. No data are shown about the comparison with X-ray angiography.

The other randomized clinical trial was aimed at assessing the efficacy of two doses of gadoterate meglumine-MRA for the diagnosis of pulmonary embolism. The sensitivity and
the specificity of the MRA with gadoterate meglumine were respectively 71.4% and 100% with no difference between the two tested gadoterate meglumine doses. No comparison was made between MRA and CT angiography.

As in the other clinical indications, also in the angiography area there is no evidence that the gadoterate meglumine is non-inferior to other contrast agents or provides any advantage with respect to other diagnostic approaches.

**Gadoterate meglumine Vs. other contrast media**

Contrary to the Applicant’s statement that “gadoterate meglumine use was associated ... with a non-inferior diagnostic ability when compared to competitors”, there appears to be a better efficiency/efficacy of other low-risk gadolinium-based contrast media as compared with gadoterate meglumine. Looking for “gadoterate meglumine AND (gadoteridol OR gadobutrol)” in PubMed and the Cochrane Library this reviewer found the following information.

a. On the basis of the results of a multicenter, randomized, single-blind, intra-individually controlled, comparison study in 136 patients with CNS neoplastic lesions Anzalone et al (Eur J Radiol, 2011) concluded that gadobutrol was statistically superior compared to gadoterate meglumine in terms of overall diagnostic preference. This conclusion was challenged by Pierre Desché, an employee of the manufacturer of gadoterate meglumine, who argued that “a higher signal does not seem to bring any clinical benefit in terms of diagnostic confidence or performance” (Eur J Radiol, 2012:e967). However, later on Anzalone et al (Eur J Radiol, 2013) confirmed a significantly higher qualitative and quantitative preference for gadobutrol compared to gadoterate meglumine.

b. Kramer et al. (Investig Radiol, 2013) compared equimolar doses of gadolinium-based contrast agents in dynamic and static MRA of the supra-aortic vessels in 20 healthy volunteers and showed that gadobutrol had higher signal-to-noise ratio and contrast-to-noise ratio than did gadobenate dimeglumine and gadoterate meglumine, with superior image quality as compared with gadoterate meglumine for dynamic and static carotid MRA.

c. Voth et al. (Eur Radiol, 2011) had previously shown that in 40 patients undergoing MRA of the peripheral vessels the image quality provided by gadobutrol ranked significantly higher compared to gadoterade meglumine with a diagnostic IQ in 97% vs. 78%.

Of course conflicts of interests may play a role in this debate: Voth had been an employee of Bayer, the manufacturer of gadobutrol (Gadovist). This also applies to Simona Gatti who co-authored the paper of Anzalone. In any case, gadoterate meglumine does not appear to be the best option among the low-risk gadolinium-based contrast agents.

In conclusion, no evidence is provided that gadoterate meglumine improves diagnostic approaches based on unenhanced technologies or does as well as (and even less so, better than) other contrast media.
(4) Is there evidence of efficacy in diverse settings and/or populations?

Yes ☒ No ☐

Gadoterate meglumine has been used in a variety of clinical indications including CNS and whole body imaging and angiography.

Among the 2813 patients who were given gadoterate meglumine in 50 clinical studies sponsored by Guerbet and whose ethnicity was recorded, most were Caucasian (1181 patients [74.4%]), followed by Asian (11.9%), Black (4.0%) and others (9.6%). No information is provided with regard to the possible different efficacy and/or safety in different settings.

Based on the number of MRI examinations made in children below 2 years of age in France in the year 2011 and the market share of gadoterate meglumine in that country and on data collected from main countries in Europe, from South Korea, Turkey, Taiwan, Mexico, and Brazil, the Applicant has estimated that the number of children below 2 years of age injected with gadoterate meglumine between 2005 and 2012 was around 51,000. However, no efficacy and safety data have been provided for patients from this fragile subset included in studies that were not randomized, not controlled, and open.

Data on children below 2 years of age are available from 3 pre-marketing studies and 6 post-marketing studies. Three non-randomized trials were conducted by Guerbet in CNS imaging indication and involved 99 children, 7 of whom were below 2 years. One adverse event was reported in a female child (1.8 year old) who experienced a brief episode of mild vomiting 20 minutes after gadoterate meglumine injection. The event was considered as not related to gadoterate meglumine by the reporter.

In six post-marketing studies (Maurer et al., 2012; Emond et al., 2011; Ishiguchi e al., 2010; Briand et al., 1992; Neiss et al., 1991; and SECURE DGD-55-001) no AE was reported in a population of 234 children below 2 years.

Before awareness of the risk of Nephrogenic Systemic Fibrosis had arisen, the potential nephrotoxicity of gadoterate meglumine was studied in patients with chronic renal failure and patients who had undergone renal transplantation.

Gadoterate meglumine has been used in one trial of 20 patients with chronic renal failure with no excess of nephrotoxicity as compared with parallel controls not given contrast media (Bellin et al., 1992). Gadoterate meglumine was also used to assess renal transplants without inducing nephrotoxicity ((Hanna et al., 1991, Helenon et al.,1992). One case of nephrotoxicity was reportedly observed in 75 patients injected with gadoterate meglumine in the DGD-44-044 study. This study showed that gadoterate meglumine enhanced MRI is not inferior to unenhanced-MRI in terms of nephrotoxicity.

Gadoterate meglumine has also been tested in patients with high risk for cardiovascular events in whom it is intended to be used in doses up to 0.3 mmol/kg in angiographic indications.
(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐  No ☒ apparently (refers to the 2nd Q)

According to the Applicant, besides 2813 patients receiving gadoterate meglumine in clinical studies, over 147,000 patients received gadoterate meglumine in post marketing studies (PMS), and based on global sales and marketing data (as of December 2013), it is estimated that over 41 million administrations of gadoterate meglumine have been given since it was first launched in France in 1989.

Of 2813 patients given gadoterate meglumine in the 50 clinical studies conducted by the manufacturer Guerbet 263 (9.3%) experienced mild severity (71.1%) or moderate severity (16.3%) AEs. The Applicant reports that 363 AEs in 111 patients (4.6%) were considered to be related to treatment, 44 AEs were not recovered or ongoing (12.1%), and for 11 AEs from 8 patients, the outcome was death (3.0%). None of the deaths was considered to be related to gadoterate meglumine. A total of 23 patients treated with gadoterate meglumine (0.8%) experienced 29 SAEs, 2 of which were considered to be possibly related to treatment (one was moderate hypersensitivity and the other was mild renal failure).

Six post-marketing observational studies including more than 147,000 patients reportedly provided reassuring additional safety data for both adult and pediatric populations.

In the pharmacovigilance database including safety data of approximately 41 million doses, most AEs were reported in the system organ classes of Skin and subcutaneous tissue disorders (28.0%), Gastrointestinal disorders (18.9%) and Respiratory, thoracic and mediastinal disorders (12.3%). According to the Applicant 859 serious cases were reported; the incidence of serious cases is estimated to be about 2.1 serious cases for 100,000 patients exposed.

As for the worrying issue of the Nephrogenic Systemic Fibrosis (NSF) (see section (7)), the Applicant states that “No cases of NSF or NSF-like symptoms have been observed in clinical studies. No single-agent/un-confounded cases of NSF were reported for gadoterate meglumine the post-marketing experience, according to an assessment based on available clinical and histological information (Girardi et al., 2011)”. It is not clear whether gadoterate meglumine caused NSF when combined with other medicines and which were considered as confounding factors. As the only ionic macrocyclic gadolinium chelate - the Applicant maintains - gadoterate meglumine is considered the most stable of all gadolinium contrast agents.

Please, refer to section (4) for the safety of gadoterate meglumine in patients with chronic renal insufficiency and in patients at high cardiovascular risk.

**ADDITIONAL CONSIDERATIONS:**
Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☒ No ☐

There is a need for radiologists in the assessment of patients that would benefit from a gadolinium-enhanced MRI and the equipment and facilities to do MRI. This would suggest the inclusion of gadoterate in the complementary list at the most. Laboratory tests are also needed as they are more effective to assess the renal function of all at-risk patients, since changes in renal function are often not reflected symptomatically or clinically.

Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☒ No ☐

In 2006 Nephrogenic Systemic Fibrosis (NSF) was associated with the administration of gadolinium contrast agents to patients with renal failure. NSF is a rare, serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs. In 2007, the EMA suggested that the risk of developing NSF depends on the type of gadolinium chelates used, and advised that these agents should be categorized into three groups:

1. High risk: gadoversetamid (OptiMARK®), gadodiamide (Omniscan®) and gadopentetic acid (Magnevist®, Magnegita®, and Gado-MRT-Ratiopharm®);
2. Medium risk: gadofosveset (Vasovist®), gadoxetic acid (Primovist®) and gadobenic acid (MultiHance®);
3. Low risk: gadoteric acid (Dotarem®), gadoteridol (ProHance®) and gadobutrol (Gadovist®).

According to this risk classification the EMA also issued recommendations, warnings and contraindications for the various agents, which are summarized as follows:
In 2010 in the assessment report on a Referral procedure (Procedure No. EMEA/H/A-31/1097) the EMA, having considered the evidence that toxic free gadolinium ions are retained in human tissues, concluded that studies evaluating the potential for long-term retention of gadolinium in bone are needed. Manufacturers of gadolinium-based contrast agents were requested to submit protocols and timelines for the studies of gadolinium accumulation in human bones, taking advantage from bone samples from patients undergoing hip and knee replacement surgery. Co-factors that may increase the risk of NSF such as serum calcium and phosphate levels at the time of administration of a gadolinium-based contrast agent should be studied and biomarkers evaluated.

No follow-up of these commitments could be traced by this reviewer in the EMA web site. A safety study of gadolinium analysis in bone and tissue samples from patients undergoing routine hip or knee replacement who had received gadolinium-containing contrast agents in the past is registered in the ClinicalTrial.gov web site as NCT01853163. The study started in May 2013, was supposed to end by October 2014 but it is currently recruiting the 350 planned patients.

In the meantime, an EMA report of November 2014 noted that “no new cases of NSF have been identified in EU that have occurred since the introduction of the EU risk minimizations measures”.

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☑

No WHO guidelines currently address gadolinium-based contrast media.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

These issues are not addressed by the Applicant. Costs apparently are homogeneous across the class of gadolinium-based contrast agents. Gadoterate meglumine is authorized in Western countries and in 15 Latin American, 13 Asian, and 8 African countries. No data are provided about their actual use in disadvantaged settings.

(10) Any additional comments?

The alleged advantage of gadoterate meglumine over other contrast media rests on its better stability and the consequent possible better safety which is due to the lower release of toxic free gadolinium. However, there is no proof of this from comparative RCTs including other gadolinium-based contrast media, even those classified as high-risk by the EMA as gadopentetic acid (Magnevist) (Brugieres P, et al. Neuroradiology 1994; 36: 27-30). There are instead findings of the potential better efficacy of other low-risk gadolinium-based contrast agents (see section (3)).
(11) Please summarise the action you propose the Expert Committee takes.

The unsettled safety issues, the questionable performances in terms of diagnostic accuracy, the need for specific expertise and facilitates, the lack of comparative trials driving the selection of particular products in specific clinical conditions have led this reviewer to argue against the inclusion of gadopentate dimeglumine and any gadolinium-based contrast media in the complementary EML. This recommendation may well apply to gadoterate meglumine too whose efficacy seems to be equivalent to or lower than other gadolinium-based contrast media. The argument for a better safety which is based on the property of gadoterate meglumine to release less toxic free gadolinium has not convincingly been proved. Instead, even the possible better tolerability as compared with high-risk gadolinium-based agents has been questioned.

The inclusion of any gadolinium-based contrast agent in the complementary list should be subject to the availability of

- confirmatory data on their safety in the current conditions of use after the implementation of risk minimization plans aimed at facing the risk of NSF;
- data of their comparative efficacy, safety and cost effectiveness from systematic reviews and/or RCTs.