Medicinal product for diagnostic use
Sectors: Retail and hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

16 DECEMBER 2020

The legally binding text is the original French opinion version

gadoxetic acid

PRIMOVIST 0.25 mmol/mL, solution for injection, prefilled syringe

First assessment

Key points

Favourable opinion for reimbursement in the detection of focal liver lesions and the provision of information on the character of lesions in T1-weighted magnetic resonance imaging (MRI), when delayed phase imaging is required and not available with unenhanced magnetic resonance imaging.

What therapeutic improvement?

No clinical added value compared to MULTIHANCE (gadobenic acid).

Role in the care pathway?

Contrast agents are used to improve the display of parenchymal or vascular structures, giving better magnetic resonance image quality. Explorations using these products are conducted according to the *"Guide du bon usage des examens d'imagerie médicale"* (Guide to medical imaging examination best practices), which defines the role of the various examinations according to the disease.

The 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) guidelines in MRI of the liver are as follows:

- Liver-specific contrast agents are recommended in MRI of the liver.

In France, the liver-specific contrast agents with an MA are PRIMOVIST (gadoxetic acid) and MULTIHANCE (gadobenic acid). These two contrast agents provide identical vascular and interstitial enhancement images to other extracellular gadolinium contrast agents, but have the additional property of being taken up by hepatocytes before being partially excreted in the bile. This enables positive enhancement of biliary structures.

- The hepatobiliary phase (or late phase), characteristic of liver-specific contrast agents, improves detection and characterisation of hepatocellular lesions.

- Liver-specific contrast agents can improve the detection of liver cancers.

In 2019, the French National Gastroenterology Society (SNFGE) published guidelines on hepatocellular carcinoma (HCC/primary liver cancer). According to the SNFGE, the two reference investigations for the diagnosis of HCC are CT scan and MRI. MRI appears to be slightly better than CT in terms of sensitivity for the detection and characterisation of nodules.

The EASL (European Association for the Study of the Liver) issued similar guidelines in 2018. The EASL highlights that all studies tend to show that liver-specific contrast agents have a better sensitivity than extracellular contrast agents in the detection of HCC.

Role of the medicinal product in the care pathway

PRIMOVIST (gadoxetic acid) is used in the first-line diagnostic investigation of the liver when MRI diagnosis and delayed phase contrast enhancement are necessary, in the same way as MULTIHANCE (gadobenic acid).

Insofar as all GBCAs can cause gadolinium retention, healthcare professionals are advised to use these contrast agents only when the essential diagnostic information cannot be obtained by imaging without contrast enhancement. In addition, the lowest possible dose should be used.

It should be noted that the PRIMOVIST concentration (0.25 mol/L) is half that of MULTIHANCE (0.5 mol/L), enabling lower exposure to GBCA.

Special recommendations

Insofar as all gadolinium-based contrast agents (GBCAs) can cause gadolinium retention, and as indicated in the SPC, healthcare professionals are advised to use these contrast agents only when the essential diagnostic information cannot be obtained by imaging without contrast enhancement. In addition, the lowest possible dose should be used.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ The seriousness of the hepatic condition is only known following MRI investigation of the liver.

◗ PRIMOVIST (gadoxetic acid) is a medicinal product for diagnostic use. It can be used to improve contrast during MRI to increase detection of structural or functional abnormalities.

◗ Its efficacy/adverse effects ratio is high in the MA indication and PRIMOVIST is classed as intermediate-risk for nephrogenic systemic fibrosis and high-risk for gadolinium accumulation in the brain.

◗ The only diagnostic alternative in liver MRI with delayed phase contrast enhancement with an MA is MULTIHANCE (gadobenic acid).

◗ PRIMOVIST is used in the first-line diagnostic investigation of the liver when MRI diagnosis and delayed phase contrast enhancement are necessary.

Public health impact

Considering:

- the seriousness of the liver condition, which is defined on the basis of liver MRI results,
- the prevalence and incidence, which depend on the liver condition being investigated by MRI,
- the contribution of PRIMOVIST (gadoxetic acid) to meet the identified need for delayed phase enhancement with hepatocyte uptake, in the same way as MULTIHANCE (gadobenic acid),
- the absence of demonstrated impact on the management of patients following the diagnosis made on the basis of MRI conducted with PRIMOVIST (gadoxetic acid),
- the absence of impact on morbidity and mortality or quality of life,

PRIMOVIST (gadoxetic acid) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of PRIMOVIST (gadoxetic acid) is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **demonstration in a phase 3 study of the non-inferiority of gadoxetic acid (PRIMOVIST) compared to gadobenic acid (MULTIHANCE), a relevant comparator, in terms of relative enhancement of normal hepatic parenchyma, on T1-weighted images before and after contrast agent injection, in delayed phase imaging (primary endpoint) in patients with a known or presumed focal lesion (ratio of 1.75; CI95% = [1.46; 2.13]),**
- **exploratory results with respect to diagnostic performance on a liver segment scale suggest a sensitivity of 75.8% (CI95% = [70.7; 80.8]) for gadoxetic acid and 79.5% (CI95% = [75.0; 83.9]) for gadobenic acid and a specificity of 83.9% (CI95% = [80.8; 87.0]) for gadoxetic acid and 81.5% (CI95% = [78.0; 85.1]) for gadobenic acid,**
- **safety data with an identical classification for these two contrast agents as being intermediate-risk for nephrogenic systemic fibrosis and having a higher risk of gadolinium accumulation and retention in the brain and other organs and tissues than with macrocyclic gadolinium-based contrast agents,**

the Transparency Committee considers that PRIMOVIST (gadoxetic acid) provides no clinical added value (CAV V) compared to MULTIHANCE (gadobenic acid).