HAUTE AUTORITÉ DE SANTÉ

PAEDIATRIC DIAGNOSTICS
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

MULTIHANCE (gadobenic acid), paramagnetic contrast agent

High clinical benefit in liver magnetic resonance imaging in children over the age of 2 years and minor clinical added value relative to other contrast agents.

Main points

- MULTIHANCE has now been granted an MA in paediatrics for children ≥ 2 years for liver magnetic resonance imaging (MRI). It should only be used when diagnosis is necessary and when this diagnosis cannot be reached by magnetic resonance imaging (MRI) without contrast enhancement.
- In July 2017, a PRAC report confirmed that gadolinium accumulated in larger amounts and for longer periods of time when linear rather than macrocyclic contrast agents were used. The MA for MULTIHANCE, a linear product, was restricted to use in liver imaging.
- The only available data are pharmacokinetic studies, that concluded that systemic exposure and maximum concentrations were similar in children over the age of 2 years and adults, requiring no change in the existing dosage according to body weight to achieve the same efficacy.

Therapeutic strategy

- MRI is more readily recommended in child follow-up to avoid repeat exposure to ionising radiation and the associated risk of cancer.
- 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 place of the various examinations according to diseases screened for or monitored.
- Insofar as all gadolinium-based contrast agents 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. Moreover, the lowest dose providing sufficient contrast enhancement for diagnostic purposes must systematically be used.
- Contrast agents provide vascular information with dynamic imaging, along with morphological and for MULTIHANCE, functional data with hepatospecific late phase enhancement.
- **Role of the medicinal product in the therapeutic strategy**
  During the dynamic early phase in liver imaging, MULTIHANCE is a first-line medicinal product, as well as the other gadolinium-based contrast agents. MULTIHANCE represents a higher risk than other gadolinium-based contrast agents (macrocyclic products) in terms of systemic nephrogenic fibrosis and gadolinium accumulation in tissues, in particular the brain.
  During MRI late phase, MULTIHANCE is the only first-line medicinal product, due to its hepatocyte uptake specificity.

Clinical data

- The assessment of the clinical benefit of MULTIHANCE for liver MRI in children between the ages of 2 and 18 years relies primarily on pharmacokinetic data, that concluded that systemic exposure and maximum concentrations were similar in children over the age of 2 years and adults, requiring no change in the existing dosage according to body weight to achieve the same efficacy.
- Recently, the indications of MULTIHANCE were restricted to use in liver imaging, following a tolerance signal concerning the accumulation of gadolinium in tissues. To date, no evidence of harmful effects for patients has been identified, but the long-term risks associated with gadolinium retention in the brain are unknown (potential

risk for neurological, motor and cognitive functions). To limit this accumulation and its associated risks, restrictions for use of the lowest possible dose, and only when the essential diagnostic information cannot be obtained by imaging without contrast enhancement, were implemented in adults and children, for all products in this class.

Benefit of the medicinal product

- The actual clinical benefit* of MULTIHANCE is high
- MULTIHANCE provides a minor improvement in actual clinical benefit (minor, IACB IV) in the current liver imaging therapeutic strategy for children between the ages of 2 and 18 years.
- Approved for continuing non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 25 July 2018 (CT-16959) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"