HAUTE AUTORITÉ DE SANTÉ

PAEDIATRIC DIAGNOSTICS
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TRANSPARENCY COMMITTEE OPINION SUMMARY

GADOVIST (gadobutrol), paramagnetic contrast agent

High clinical benefit in angiography and magnetic resonance imaging in its diagnostic indications in children aged 0 to 2 years, and minor clinical added value in the current therapeutic strategy.

Main points

- GADOVIST has now been granted an MA in children under the age of 2 years, in the same indications as those already defined for children over the age of 2 years and in adults. It should only be used when diagnosis is necessary and when this diagnosis cannot be reached by magnetic resonance imaging (MRI) without contrast enhancement.
- The assessment rests primarily on a study of pharmacokinetic parameters in children under the age of 2 years, relative to children over the age of 2 years and adults.
- Long-term risks associated with gadolinium retention in the brain have been identified by the PRAC, more so for linear products than for macrocyclic products (GADOVIST is a member of this group). Children are thus likely to be more exposed to this risk than adults; this risk should therefore be taken into account considering the possibility of multiple examinations.

Pre-existing indications*

GADOVIST had already been granted an MA in children over the age of 2 years, for contrast enhancement in MRI of cranial and spinal regions, the liver, kidneys, whole-body diseases and for magnetic resonance angiography. It facilitates the viewing of abnormal structures or lesions and helps distinguish between healthy and diseased tissues.

Therapeutic strategy

- Compared to irradiating imaging techniques, 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 disease.
- 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 functional data with hepatospecific enhancement (late phase specific to MULTIHANCE).
- **Role of the medicinal product in the therapeutic strategy**

  GADOVIST is a first-line medicine, like DOTAREM and PROHANCE in their common indications.

* This summary does not concern these indications.

Clinical data

- The assessment of the indication extension to children aged 0 to 2 years is based on a pharmacokinetic study conducted on 44 children relative to those in the 2-17 year age group, diagnostic performances being secondary exploratory endpoints. Pharmacokinetic differences were observed in the AUC, with slower gadobutrol elimination in children aged 0 to 2 months and higher systemic exposure than in older children (2 months to 17 years). Between the AUC in children aged 0 to 2 months and adults however, the concentrations are considered to be bioequivalent (CI 95% = [0.89; 1.12]).
- Another observational study on 60 patients under the age of 2 years suggested that a diagnosis established by MRI with gadobutrol administration matched the final diagnosis and that image contrast enhancement was achieved in indications for which MRI with contrast agent is recommended.
- The accumulation of gadolinium in tissues was assessed for all gadolinium-based contrast agents. To date, no evidence of harmful effects for patients has been identified, though the long-term risks associated with gadolinium retention in the brain are unknown (potential risk for neurological, motor and cognitive functions). Children are likely to be more exposed to gadolinium-based contrast agents than adults, considering the cumulative risk with repeat examinations involving contrast agent and the child's life expectancy. Tolerance data for children under the age of 2 years are limited. Insofar as renal function in children aged 0 to 2 months is immature, gadobutrol elimination in this age group is thus slower and systemic exposure higher than in older children. Moreover, the blood-brain barrier is also immature and the risk of gadolinium accumulation in the tissues, particularly the brain, is all the more probable in this population.

Benefit of the medicinal product

- The actual clinical benefit* of GADOVIST is high.
- GADOVIST provides an improvement of actual clinical benefit** (IACB IV, minor) in the current therapeutic strategy.
- Approved for 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-16222) 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"