European Medicines Agency

13 April 2007
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
OPINION FOLLOWING AN ARTICLE 36(1) REFERRAL

Gadograf/Gadovist
International Non-Proprietary Name (INN): Gadobutrol

BACKGROUND INFORMATION*

Gadovist/Gadograf 1.0 mmol/ml contains gadobutrol, a neutral macrocyclic gadolinium (Gd) complex with contrast-enhancing properties, which is used for magnetic resonance imaging (MRI). MRI is a widely used technique for the evaluation and detection of diffuse liver disease as well as for further characterisation of focal liver disease. Gd-based contrast agents are frequently administered prior to contrast-enhanced dynamic liver MRI and may improve both detection and classification of focal liver lesions.

Gadovist/Gadograf was approved for "***Contrast enhancement in cranial and spinal magnetic resonance imaging***" in Germany in January 2000 and subsequently in June 2000 in the EU and Norway via the mutual recognition procedure (MRP). A label extension to the indication "***Contrast-enhanced Magnetic resonance angiography***" (CE-MRA) followed in November 2003.

In June 2005, a MR procedure started for a type II variation to add the indication of "***Contrast enhanced MRI of other body regions: liver, kidneys***" and the following posology and method of administration/dosage: "***CE-MRI of other body regions: The recommended dose for adults is 0.1 mmol per kilogram body weight (mmol/kg BW). This is equivalent to 0.1 ml/kg BW of the 1.0 M solution***". After finalisation of the procedure the Spanish Agency for Medicines and Health Products initiated a referral for arbitration to the CHMP under article 36.1 of Directive 2001/83/EC.

Having considered the grounds for the referral triggered by Spain, the CHMP, during its May 2006 plenary meeting, adopted a List of Questions and a TT for a referral procedure under Article 36. The CHMP appointed Dr. Broich (DE) as Rapporteur and Dr. Prieto (ES) as Co-Rapporteur.

The questions identified pertained to insufficient data on the evaluation of disseminated liver disease that could justify an extrapolation to the general population undergoing examinations of liver and kidney. Concerns were further raised with regards to the Paediatric Indication and the use of the comparator Magnevist. Magnevist is not approved "to classify focal lesions [of liver or kidney] as benign or malignant" throughout the EU and it was questioned whether it would support the granting of an indication for which Magnevist has not been approved. The Applicant was asked to justify the choice of this comparator and the clinical utility of Gadovist/Gadograf with respect to diagnostic thinking, therapeutic management and clinical outcome. A Request for Supplementary Information was adopted on 16 November 2006. The company responded to these points on 30 November 2006. In its response the Applicant addressed the issue of clinical utility by comparing Gadovist-enhanced with Magnevist-enhanced MRI and underlined the diagnostic efficacy of Gadovist/Gadograf. The Applicant further agreed to the proposed wording by the CHMP as follows:

Section 4.1 (Indication):

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"Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant".

Section 4.2 (Posology):

"Paediatric patients
Gadograf is not recommended for use in population below age 18 due to a lack of data on efficacy and safety.
The CHMP opinion was converted into a Decision by the European Commission on 13 April 2007.

The list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II and the amended Summary of Product Characteristics in Annex III.

Notes:
The information given in this document and Annexes reflect only the CHMP Opinion dated 14 December 2006. The Member States competent authorities will continue to keep the product under regular review.