Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Eovist/Primovist (Gadoxetic acid)

SE/W/0021/pdWS/001

Marketing Authorisation Holder: Bayer Pharma AG

Rapporteur:	SE
Finalisation procedure (day 120):	2015-03-04

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Eovist/Primovist
INN (or common name) of the active substance(s):	Gadoxetic acid
MAH:	Bayer Pharma AG
Currently approved Indication(s)	Magnetic resonance contrast imaging
Pharmaco-therapeutic group (ATC Code):	V08CA10
Pharmaceutical form(s) and strength(s):	Solution for injection

I. EXECUTIVE SUMMARY

Changes to sections 4.2 and 5.1 of the SmPC with corresponding changes in the package leaflet are recommended.

II. RECOMMENDATION[1]

Currently Primovist is not approved for the use in the paediatric population in the European Union. The MAH has submitted data from a company sponsored paediatric clinical study and the results from a literature review focusing on children below 18 years of age.

Based on the submitted data it can be concluded that beneficial effects of Primovist enhanced liver MRI in paediatric patients have been seen. Due to the relatively small number of patients the data cannot be considered to be confirmatory regarding the efficacy and safety of Primovist in the paediatric population.

The proposed rephrasing of section 4.2 of the SmPC, with the deletion of "cannot be recommended" in the paediatric population and addition of a cross reference to section 5.1 is acceptable. Shown with tracked changes below.

Addition of paediatric data in section 5.1 is acceptable, however with some revisions of the suggested text. The final recommendations for the SmPC and PL are found below. This is a new paragraph and therefore shown without tracked changes.

The corresponding texts in the package leaflet are shown below.

Final SmPC recommendations:

Section 4.2 (changes to current text in strikethrough/bold)
Paediatric population
The safety and efficacy of Primovist have not been established in patients under 18 years old. ~~Therefore, use of Primovist in this patient group cannot be recommended.~~ **Currently available data are described in section 5.1.**

Section 5.1 (new paragraph)
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

Package leaflet recommendations:

Package leaflet section 2 (changes to current text in strikethrough/bold)
Children and adolescents
~~The safety of Primovist in persons under 18 years has not yet been tested. Therefore, use of Primovist in this patient group cannot be recommended.~~ **The safety and efficacy of Primovist have not been established in patients under 18 years old as there is limited experience on its use. Further information regarding the use of Primovist in children is given at the end of the leaflet.**

Package leaflet section "The following information is intended for healthcare professionals only" (new paragraph):
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

III. INTRODUCTION

On June 16, 2014, the MAH submitted the report from a completed paediatric study for Primovist, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A critical expert overview has also been provided. The MAH stated that the submitted paediatric study does not influence the benefit risk for Primovist.

The MAH proposed a regulatory action with the following changes to the SmPC and the PL:

SmPC section 4.2
Paediatric population
The safety and efficacy of Primovist has not been established in patients under 18 years old. ~~Therefore, use of Primovist in this patient group cannot be recommended.~~ **Currently available data are described in section 5.1.**

SmPC section 5.1, addition of new paragraph
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

Package leaflet section 2
Children and adolescents
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Package leaflet section "The following information is intended for healthcare professionals only:"
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

In the paediatric study, the standard commercial formulation of Primovist was used. Primovist is an aqueous formulation for IV administration of gadolinium ethoxybenzyl-DTPA (Gd-EOB-DTPA) at a concentration of 0.25 mmol/ml

IV.2 Clinical aspects

1. Introduction

The MAH submitted the full final clinical study report for:

- Study no. 13729. The title of this study is: An observational study of the administration of Eovist/Primovist in paediatric subjects (> 2 months and < 18 years) who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions.

The MAH also submitted the results of a literature review including Primovist-enhanced MR imaging focusing on children below 18 years including short summaries of the following publications:

Tamrazi A; Vasanawala SS, Functional hepatobiliary MR imaging in children. Pediatric Radiology 2011; 41(10):1250-1258.

Marrone G; Carollo V; Luca A; Maggiore G; Sonzogni A.,Biliary cystadenoma with bile duct communication depicted on liver-specific contrast agent-enhanced MRI in a child. Pediatric Radiology 2011; 41(1):121-124.

Lai J; Iyer KR; Arnon R; Kerkar N; Taouli B; Thung SN; Magid MS, Cholangiolocellular carcinoma in a pediatric patient with small duct sclerosing cholangitis: A case report. Semin. Liver Disease 2012; 32(4):360-365.

Grazioli L; Bondioni MP; Tinti R; Frittoli B; Gambarini S; Donato F; Haradome H; Motosugi U; Colagrande S, Hepatocellular adenoma and focal nodular hyperplasia: Value of gadoxetic acid-enhanced MR imaging in differential diagnosis. Radiology 2012; 262(2):520-529.

Meyers AB; Towbin AJ, Serai S; Geller JI; Podberesky DI, Characterization of pediatric liver lesions with gadoxetate disodium. Pediatric Radiology 2011; 41:1183–1197.

Meyers AB;. Towbin AJ; Geller JI;. Podberesky DJ, Hepatoblastoma imaging with gadoxetate disodium-enhanced MRI-typical, atypical, pre- and post-treatment evaluation. Pediatric Radiology 2012; 42:859–866.

2. Clinical study

Study no. 13729
An observational study of the administration of Eovist/Primovist in paediatric subjects (> 2 months and < 18 years) who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions

➢ Description

In clinical development in adults, Primovist was shown to be efficacious in improving the detection, localization, and characterization of focal liver lesions using combined unenhanced and enhanced vs. unenhanced MR images alone. Primovist was well tolerated by the general study population, as well as in subjects with liver dysfunction, cirrhosis, and renal dysfunction.

In pediatric subjects, diseases associated with the liver are generally diffuse rather than focal. These liver diseases/disorders include metabolic disorders, intrahepatic cholestatic disorders, α1-antitryspsin deficiency liver disease, nonalcoholic steatohepatitis, autoimmune hepatitis, and various forms of viral hepatitis to name a few [Arya 2002]. Also, biliary atresia occurs frequently in this population. This disease is not generally perceived as a focal liver disease, but rather as a result of a structural abnormality of the biliary system.

Tumors (either benign or malignant) and metastases can occur in the liver in pediatric subjects; however, they are very infrequent [Arya 2002, Ries 2008, Reynolds 1999]. In the US there are approximately 100 to 150 new pediatric cases of liver tumors per year. Malignant tumors account for approximately two-thirds of the liver tumors.[Litten 2008] The majority of malignant tumors in children are hepatoblastomas, and according to Willert et al,[Willert 2013] there are approximately 100 new cases of hepatoblastomas per year in the US.

Because of the expected infrequent use of Primovist in the pediatric population, this study was an observational/retrospective study conducted at multiple sites to capture safety and efficacy data in pediatric subjects who had undergone a Primovist-enhanced liver MRI because of suspected or known focal liver lesions. This trial was conducted at the request of the US Food and Drug Administration (FDA) as a post-marketing requirement.

➢ Methods

Objectives
The objectives of this study were to obtain safety and additional diagnostic information on Primovist from the combined precontrast and postcontrast images as compared with the precontrast images in pediatric subjects > 2 months and < 18 years of age who had a liver MRI enhanced by Primovist.

Study design
This was an observational/retrospective, multicenter study evaluating safety and efficacy. The principal investigator reviewed the medical records to identify subjects who had received Primovist and qualified for the study. Consent was obtained for release of medical records, including electronic copies of the pre- and post-Primovist MRI scans.

In order to minimize bias in assessment of the images, a blinded read of the magnetic resonance (MR) images was performed. An independent radiologist, not affiliated with any of the clinical sites, reviewed the MR images and completed the blinded-read electronic case report forms (eCRFs) for the efficacy variables.

The study was conducted at 7 study centres in 4 countries: 3 sites in the United States (US), 2 sites in Italy, and 1 site each in Japan and Taiwan. Dr James Geller (Cincinnati Children's Hospital) was appointed as the co-ordinating investigator for the review of MAH´s study report.

Study population /Sample size

The sample size was specified by the FDA when the product was approved in the US. Because of the expected infrequent use of gadoxetate in this pediatric population, this study was conducted at multiple investigative sites in order to enroll at least 50 subjects (> 2 months and < 18 years of age), who underwent a contrast-enhanced (CE) liver MRI with gadoxetate because of suspected or known focal liver lesions, and who had evaluable safety and efficacy data.

The company attempted to include an equal distribution of subjects using the following age categories: infants (> 2 months to ≤ 2 years), children (> 2 to ≤ 12 years), and adolescents (> 12 years to < 18 years).

The study was planned for 50 patients and 52 were recruited.

Treatments

The dose (and/or volume) of intravenously administered Primovist was recorded. The administration of the product was made as a single injection. The sponsor did not supply study drug; instead commercial product was used by the study sites.

The subjects may have received medications prior to and after injection of Primovist.

All medications taken by the subject and all procedures (eg, surgical, diagnostic or therapeutic) performed from 24 hours prior to injection until 24 hours after injection were to be recorded in the eCRF, as available. Also, medications taken in association with serious and unexpected AEs reported up to 1 year after the Primovist MRI were to be recorded in the eCRF.

There was no control group in the study.

Schedules of procedures

Individual subject records were reviewed for data up to 1 year after injection. The following observational/retrospective variables were to be recorded for each subject:

- Demographics (age, gender, and race)
- Indication (referral diagnosis)/reason for scan
- Dose/volume of Primovist administered
- Date of MRI with Primovist
- AEs up to 24 hours after injection
- 1-year follow-up post-Primovist MRI for all serious and unexpected AEs. (If a subject had a diagnosis of nephrogenic systemic fibrosis [NSF], it was recorded).
- If during the 1-year follow-up, the subject was known to be pregnant, the outcome of the pregnancy was to be followed.
- Final diagnosis based on the principal investigator's/designee's review of the subject's medical records up to 1 year post-Primovist MRI

Outcomes/endpoints, Efficacy

The primary efficacy variable was additional diagnostic information obtained from the combined precontrast and postcontrast images as compared with the precontrast images and was recorded with regard to the following (all that applied were indicated):

- Change in number of lesions: less/fewer, equal, or more/greater
- Improved border delineation of the primary lesion: yes / no
- Increased contrast of primary lesion vs background: yes / no
- Change in size of the primary lesion: larger, no change, smaller
- Change in information about lesion characterization (lesion type): improved, unchanged, worsened

Secondary efficacy variables, based on the comparison of combined precontrast/postcontrast with precontrast images, were:

- Change in diagnosis
- Change in confidence of diagnosis
- Change in the number of nonmalignant lesions
- Change in the number of malignant lesions
- Change in recommended next course of subject management / therapy

For the precontrast as well as the combined precontrast / postcontrast images, the number of subjects with true positive diagnoses and true negative diagnoses (ie, the sensitivity and the specificity), and the accuracy of diagnoses were calculated using the final diagnosis based on the review of the subject's medical records by the investigator and/or designee for up to 1 year post-Primovist MRI as standard of truth. The assessments of the final diagnoses were divided into a group of benign diagnoses and a group of malignant diagnoses.

Safety endpoints

Safety was determined based on adverse events, laboratory test results (hematology and serum chemistry parameters, as well as glomerular filtration rate), physical examinations, and vital signs.

All documented AEs up to 24 hours after Primovist injection, and all AEs that were serious and unexpected up to 1 year after injection were recorded and analyzed.

By definition, all reported AEs were to be regarded as treatment emergent AEs (TEAEs), ie, not observed before treatment, or if already present before treatment, worsened after start of treatment.

The analyses of Adverse Events (AEs), Serious Adverse events (SAEs), and unexpected AEs were also analyzed for 3 different age groups (> 2 months to ≤ 2 years, > 2 years to ≤ 12 years, > 12 years to < 18 years) and by time of onset after Primovist injection (up to 24 hours; > 24 hours and up to 120 days; > 120 days and up to 240 days; and > 240 days and up to 365 days.

Statistical Methods

The efficacy and safety analyses were performed on the full analysis set (FAS). The FAS for safety and efficacy includes all subjects who received any amount of Primovist. To be included in the efficacy analysis, subjects in the FAS were to have both enhanced and unenhanced images.

The statistical evaluation was to be performed using the software package SAS release 9.1 or higher. Continuous variables were to be analyzed using descriptive statistical methods. The

number of data available, mean, standard deviation, minimum, quartiles, median, and maximum were to be calculated for metric data. Frequency tables were to be generated for categorical data.

95% confidence intervals (CIs) were to be provided for the primary efficacy variables, the percentage of subjects with AEs, and the percentage of subjects with the most frequent (≥ 5% of subjects) AEs as defined by MedDRA preferred term (PT).

- **Results**

Recruitment/ Number analysed

The investigators identified 52 subjects for participation in this observational/retrospective study. During the preparation for the blinded read study, it was discovered that 1 subject (22001-0005) did not have unenhanced images. Therefore, 51 subjects were included in the efficacy analysis. All 52 subjects were included in the safety analysis.

Baseline characteristics

The subjects ranged in age from > 2 months to < 18 years. There were slightly more females (54%) than males. The majority of the subjects (35; 68.6%) were white, 13 (25.5%) were Asian, and 3 (5.9%) were Black or African American. Race was not recorded for 1 subject, but ethnicity for this subject was Hispanic/Latino. Weight ranged from 6.6 to 85.6 kg.

Table 1 Demographic data

	Number of subjects (%)
Age (yr)	N=52
Mean (SD)	8.0 (5.8)
Median	9.5
Min, Max	0-17
Age group	N=52
>2 months to ≤2 years	14 (26.9)
>2 years to ≤12 years	25 (48.1)
>12 years to <18 years	13 (25.0)
Height (cm)	N=24[a]
Mean (SD)	126.10 (32.79)
Median	138.75
Min, Max	62.4,168.9
Weight (kg)	N=33[a]
Mean (SD)	37.55 (22.77)
Median	35.90
Min, Max	6.6, 85.6
Sex	N=52
Male	24 (46.2)
Female	28 (53.8)
Race	N=51[a]
White	35 (68.6)
Asian	13 (25.5)
Black or African American	3 (5.9)
Ethnicity	N=52
Hispanic or Latino	8 (15.4)
Not Hispanic or Latino	44 (84.6)

Prior and concomitant medications

Forty-four subjects (84.6%) received at least 1 prior or concomitant medication. The most frequently administered prior or concomitant medications included sodium chloride (normal saline) (28.8%), vancomycin (17.3%), piperacillin/tazobactam (17.3%), ursodeoxycholic acid (15.4%), ondansetron (15.4%), triclofos (13.5%), paracetamol (13.5%), oxycodone (11.5%), heparin (11.5%), and co-trimoxazole (11.5%)

Efficacy results

Primary efficacy variables – blinded read

The primary efficacy analysis showed that additional diagnostic information was obtained for 86.3% of the 51 subjects (95% CI: 73.7% to 94.3%) based on the combined precontrast/postcontrast images as compared with the precontrast images.

The additional diagnostic information mainly concerned improved border delineation of the primary lesion in 70.6% of the subjects (95% CI: 56.2% to 82.5%), increased contrast of the primary lesion vs background in 78.4% of the subjects (95% CI: 64.7% to 88.7%), and better characterization of the primary lesion in 76.5% of the subjects (95% CI: 62.5% to 87.2%). Also, additional information regarding the change in number of lesions was found for 33.3% of subjects (95% CI: 20.8% to 47.9%) and the change in size of the primary lesion was found for 25.5% of subjects (95% CI: 14.3% to 39.6%).

The 95% CIs were generated for the proportion of subjects for whom additional diagnostic information was obtained (ie, for a subject if a change in at least 1 of the 5 variables above was documented). The primary efficacy analysis showed that additional diagnostic information was obtained for 86.3% of subjects (95% CI: 73.7% to 94.3%) when comparing the combined precontrast/postcontrast images with the precontrast images.

Table 2; Additional diagnostic information (combined precontrast / postcontrast images as compared with precontrast images)

Additional diagnostic information regarding:	N (%)[a] (N=51)
Change in number of lesions	
Less	3 (5.9%)
Equal	34 (66.7%)
More	14 (27.5%)
Improved border delineation of the primary lesion	
Yes	36 (70.6%)
No	15 (29.4%)
Increased contrast of primary lesion vs background	
Yes	40 (78.4%)
No	11 (21.6%)
Change in size of the primary lesion	
Larger	12 (23.5%)
No change	38 (74.5%)
Smaller	1 (2.0%)
Change in information about lesion characterization	
Improved	39 (76.5%)
Unchanged	12 (23.5%)
Worsened	0

Table 3; Additional diagnostic information – Proportion of subjects (combined precontrast / postcontrast images as compared with precontrast images)

Additional diagnostic information regarding	Proportion of subjects N (%)[a] (N=51)	95% CI (lower, upper limit)
Overall (Change in at least 1 of the 5 variables below)	44 (86.3)	73.7% to 94.3%
Change in number of lesions (less and more vs equal)	17 (33.3)	20.8% to 47.9%
Improved border delineation of the primary lesion (yes vs no)	36 (70.6)	56.2% to 82.5%
Increased contrast of the primary lesion (yes vs no)	40 (78.4)	64.7% to 88.7%
Change in size of the primary lesion (larger and smaller vs no change)	13 (25.5)	14.3% to 39.6%
Change in information about lesion characterization (Improved and worsened vs unchanged)	39 (76.5)	62.5% to 87.2%

Secondary efficacy variables – blinded read

Table 4 summarizes the number of subjects with a diagnosis of non-malignant/benign, malignant, and no lesion on precontrast and combined precontrast/postcontrast images. On the precontrast images, nonmalignant lesions were detected in 18 subjects (35.3%) and on the combined precontrast/postcontrast images, nonmalignant lesions were detected in 19 subjects (37.3%). Malignant lesions were detected on the precontrast images in 18 subjects (35.3%) and on the combined precontrast/postcontrast images in 22 subjects (43.1%). Both malignant and nonmalignant lesions were detected on the precontrast images in 1 subject (2.0%) and on the combined precontrast/postcontrast images in 4 subjects (7.8%). Two lesions (both wither malignant or benign) were detected in 1 subject (2.0%) on the precontrast images and 1 subject (2.0%) on the combined precontrast/postcontrast images. No lesions were detected for 13 subjects (25.5%) on the precontrast images and for 5 subjects (9.8%) on the combined precontrast/postcontrast images.

Table 4; Number and percent of subjects with nonmalignant, malignant, and no lesions detected on precontrast and combined precontrast / postcontrast images

Lesion detected	Precontrast N (%)[a] (N=51)	Combined N (%)[a] (N=51)
Nonmalignant/Benign	18 (35.3)	19 (37.3)
Malignant	18 (35.3)	22 (43.1)
Two lesions (1 malignant and 1 nonmalignant/benign)	1 (2.0)	4 (7.8)
Two lesions (both nonmalignant/benign)	1 (2.0)	1 (2.0)
No lesion	13 (25.5)	5 (9.8)

a Percentage is calculated as number of subjects in the category divided by 51 subjects with available precontrast and combined precontrast/postcontrast images

For secondary efficacy assessment, the most frequent changes in the comparison of the combined precontrast/postcontrast images with the precontrast images were observed for change in recommended next course of subject management/therapy (ie, change from additional imaging with contrast enhanced MRI to definitive therapy, such as biopsy, in 88.2% of subjects), increase in diagnostic confidence in 72.5% of subjects, and change in diagnosis in 49.0% of subjects. In the latter case, there were relevant changes, enabling detection of a lesion vs finding no abnormality/no lesion and specification of the type of lesion, ie, HCC or hepatoblastoma vs malignant tumor. See table 5.

Table 5; Changes in secondary efficacy parameters (combined precontrast / postcontrast images as compared with precontrast images)

Secondary efficacy parameter	N (%)[a] (N=51)
Change in diagnosis	
Yes	25 (49.0%)
No	26 (51.0%)
Change in confidence of diagnosis	
Yes[b]	37 (72.5%)
No	14 (27.5%)
Change in number of nonmalignant lesions	
Yes	18 (35.3%)
No	33 (64.7%)
Change in number of malignant lesions	
Yes	11 (21.6%)
No	40 (78.4%)
Change in recommended next course of subject management/therapy	
Yes	45 (88.2%)
No	6 (11.8%)

Change in diagnosis

Overall, there were relevant changes in diagnoses for 25 subjects (49.0%), enabling detection of a lesion vs finding no abnormality/no lesion, and better specification of the type of lesion, ie, HCC or hepatoblastoma vs malignant tumor. Table 6 lists the subjects whose diagnosis changed based on the combined precontrast/postcontrast images compared to precontrast images. As noted in Table 6, 8 subjects had no lesion on precontrast images and had at least 1 lesion (benign or malignant) on the combined precontrast/postcontrast images.

Table 6; Change in diagnosis – comparison of precontrast versus combined precontrast/postcontrast images (only subjects for whom a change was documented)

Subject no.	Diagnosis Precontrast	Diagnosis Combined precontrast / postcontrast	Final diagnosis category (benign or malignant)
14001-0002	No lesion[a]	Adenoma	Benign
14001-0005	No lesion	Benign tumors	Benign
14001-0008	No lesion	FNH	Benign
14001-0010	No lesion	Metastasis	Benign
14004-0013	No lesion	Benign tumors	Malignant
14004-0017	No lesion	Benign tumors	Malignant
20001-0011	No lesion	Benign tumors	Malignant
22001-0003	No lesion	Malignant tumor	Benign
14001-0007	Benign tumors[b]	FNH	Benign
14004-0002	Benign tumors	Malignant tumor	Malignant
14004-0018	Benign tumors	Malignant tumor	Benign
20001-0005	Benign tumors	Hemangioendothelioma	Benign
22001-0002	Benign tumors	Malignant tumor	Benign
22001-0006	Benign tumors	FNH	Benign
61001-0001	Benign tumors	FNH	Malignant
14004-0007	Malignant tumor	Hepatoblastoma	Malignant
14004-0010	Malignant tumor	Metastasis Cyst	Malignant
14004-0011	Malignant tumor	Hepatoblastoma	Malignant
14004-0014	Malignant tumor	Hepatoblastoma	Malignant
20001-0003	Malignant tumor	Hepatoblastoma	Malignant
14001-0004	HCC	HCC Dysplastic nodule	Benign
14002-0001	HCC	HCC Other (regenerative nodule)	Benign
14004-0004	Metastasis	Malignant tumor	Malignant
22001-0001	Focal steatosis	Metastasis	Benign
20001-0008	Other (small, probably fat-containing lesion)	Metastasis	Benign

Key: FNH = focal nodular hyperplasia; HCC = hepatocellular carcinoma

For the 26 subjects for whom no change in diagnosis was documented, the diagnoses were: no lesion or a malignant tumor (5 subjects each); a cyst or a hepatoblastoma (3 subjects each); benign tumors, a focal steatosis, or a hepatocellular carcinoma (2 subjects each); and another diagnosis (4 subjects). The other diagnoses included: postoperative irregularity at resection margin (subject 14001-0001); recurrent malignant tumor (subject 20010-010); mesenchymal hamartoma, assuming this is a neonate (subject 20001-0009); and regenerative nodule in Caroli-cirrhotic liver (subject 22002-0001).

Change in number of non-malignant lesions

18 subjects reported a change in the number of nonmalignant lesions. Twelve subjects had more lesions and 6 subjects had fewer lesions on the combined precontrast / postcontrast images compared to the precontrast image. Of the 12 subjects who had more lesions on the combined precontrast / postcontrast images:

- 9 subjects had no lesions precontrast (normal precontrast)
- 3 subjects had 1 lesion precontrast

Of the 6 subjects who had fewer lesions on the combined precontrast / postcontrast images:

- 5 subjects had 1 or 2 lesions precontrast and no lesions on the combined precontrast / postcontrast images (normal combined precontrast/postcontrast)
- 1 subject had 10 lesions precontrast and 1 lesion on the combined precontrast / postcontrast images

Change in number of malignant lesions
For 11 subjects a change in the number of malignant lesions was reported. Eight subjects had more lesions and 3 subjects had fewer lesions on the combined precontrast / postcontrast image compared to the precontrast images.
Of the 8 subjects who had more lesions on the combined precontrast / postcontrast images:
- 7 had no lesions (normal) precontrast
- 1 subject had 1 lesion precontrast

All 3 subjects with fewer lesions on the combined precontrast / postcontrast images compared to the precontrast images had at least 1 lesion on the combined precontrast / postcontrast images.

Change in recommended next course of subject management/therapy
A comparison of the recommended next course of subject management/therapy based on precontrast images vs combined precontrast/postcontrast images is shown in Table 7. Overall, 45 subjects had a change from additional imaging with contrast-enhanced MRI based on the precontrast images to definitive therapy. For 37 of the 45 subjects (82.2%), the recommended next course of subject management/therapy was 'other' based on the precontrast images; 'other' included contrast enhanced MRI, with or without additional sequences, such as short tau-inversion recovery (STIR) and diffusion weighted MRI (DWI). For the 37 subjects, the most frequent recommended subject management/therapy based on the combined images was biopsy in 24 subjects and follow-up in 13 subjects.

For the 7 subjects whose recommended next course of subject management/therapy based on precontrast images was 'Other/ultrasound', the recommended next course of subject management/therapy based on the combined precontrast/postcontrast was biopsy for 3 subjects and follow-up for 4 subjects.

Table 7; Change in recommended next course of subject management/therapy – comparison of precontrast versus combined precontrast/postcontrast images

Recommended next course of management/therapy	Precontrast N (%)[a] N=45	Combined precontrast / postcontrast N (%)[a] N=45
Ultrasound	0	1 (2.2)
Biopsy	0	24 (53.3)
Follow-up examination	1 (2.2)	13 (28.9)
Other	37 (82.2)[b]	2 (4.4)
No action	0	3 (6.7)
Other/ultrasound	7 (15.6)	0
Other/biopsy	0	2 (4.4)

Final diagnosis – Clinical investigator
The final diagnosis was based on the principal investigator's/designee's review of the subject's medical records up to 1 year post Primovist MRI, see table 8. The investigators were confident (17 subjects, 32.7%) or very confident (35 subjects, 67.3%) in their final diagnoses.

Table 8; Final diagnosis – Clinical investigator

Final diagnosis	N (%) (N=52)
Benign Lesions	28 (53.8)
Atypical hepatocellular lesion consistent with at least high grade dysplastic nodule	1 (1.9%)
Benign tumors	5 (9.6%)
Biliary atresia	1 (1.9%)
FNH	11 (21.2%)
No abnormal finding	1 (1.9%)
Focal steatosis	1 (1.9%)
Hemangioma	1 (1.9%)
History of HCC status post liver transplantation	1 (1.9%)
Liver focal lesions in Caroli disease	1 (1.9%)
No liver lesions of neuroblastoma[a]	1 (1.9%)
Oxysterol 7A Hydroxylase deficiency	1 (1.9%)
Suspected hepatic angioma	1 (1.9%)
Telangiectasis lesions	1 (1.9%)
Wolman disease	1 (1.9%)
Malignant Lesions	24 (47.1%)
Enhanced lesion	16 (30.8%)
Hepatic tumor	1 (1.9%)
Hepatoblastoma	2 (3.8%)
Hepatocellular carcinoma	3 (5.8%)
Liver formation unknown origin	1 (1.9%)
Liver tumor	1 (1.9%)

a Subject 22001-0005 whose final diagnosis was "no liver lesions of neuroblastoma" was not included in the blinded read

Key: FNH = focal nodular hyperplasia, HCC = hepatocellular cancer

Sensitivity/Specificity/Accuracy

Whereas the sensitivity of blinded read was better based on the combined precontrast/postcontrast images, the specificity and accuracy were better for the precontrast images.

As shown in Table 9-8, there were 6 more false positive (6 fewer true negatives) diagnoses for the combined precontrast/postcontrast diagnoses compared to the precontrast diagnoses. The review of these 6 cases showed the following:

1. For 3 subjects, the final diagnosis was focal nodular hyperplasia; the blinded reader noted that these subjects had metastases.
2. For 1 subject each, the final diagnosis was benign tumor, telangiectasis, and suspected hepatic angioma; the blinded reader noted that these 3 subjects had metastases or malignant tumor.

For 3 subjects, both the precontrast and combined precontrast/postcontrast diagnoses were false positive, ie, the precontrast and combined diagnoses agreed. The final diagnoses for these 3 subjects were: biliary atresia, atypical hepatocellular lesion consistent with at least high grade dysplastic nodule, and focal nodular hyperplasia.

An overview of the precontrast, combined precontrast/postcontrast, and the final diagnoses of all subjects, as well as the respective classification of diagnoses as true positive, true negative, false positive or false negative, is provided in Section 14, Table 73.

Table 9; Sensitivity, specificity and accuracy of blinded read of precontrast and combined precontrast/postcontrast images (N=51)

	Precontrast	Combined precontrast / postcontrast
True positive subjects/diagnoses [N][a]	16	17
True negative subjects/diagnoses [N][a]	24	18
False positive subjects/diagnoses [N]	3	9
False negative subjects/diagnoses [N]	8	7
Sensitivity [%][b]	66.7%	70.8%
Specificity [%][c]	88.9%	66.7%
Accuracy [%][d]	78.4%	68.6%

Analysis is based on subjects with available precontrast and combined precontrast/postcontrast images (n=51)

a A malignant diagnosis of the precontrast (or the combined precontrast and postcontrast) images is true positive if the final diagnosis is 'malignant'. Similarly, a benign diagnosis of the precontrast (or the combined precontrast and postcontrast) images is true negative if the final diagnosis is 'benign'.

b Sensitivity [%] = (True positive subjects / (True positive + False negative subjects))*100

c Specificity [%] = (True negative subjects / (True negative + False positive subjects))*100

d Accuracy [%] = ((True positive + true negative subjects) / all subjects)*100

MAH´s efficacy conclusions

The primary efficacy analysis showed that additional diagnostic information was obtained for 86.3% of the 51 subjects (95% CI: 73.7% to 94.3%) based on the combined precontrast/postcontrast images as compared with the precontrast images.

The additional diagnostic information mainly concerned improved border delineation of the primary lesion in 70.6% of the subjects (95% CI: 56.2% to 82.5%), increased contrast of the primary lesion vs background in 78.4% of the subjects (95% CI: 64.7% to 88.7%), and better characterization of the primary lesion in 76.5% of the subjects (95% CI: 62.5% to 87.2%). Also, additional information regarding the change in number of lesions was found for 33.3% of subjects (95% CI: 20.8% to 47.9%) and the change in size of the primary lesion was found for 25.5% of subjects (95% CI: 14.3% to 39.6%).

For secondary efficacy assessment, the most frequent changes in the comparison of the combined precontrast/postcontrast images with the precontrast images were observed for change in recommended next course of subject management/therapy (ie, change from additional imaging with contrast enhanced MRI to definitive therapy, such as biopsy, in 88.2% of subjects), increase in diagnostic confidence in 72.5% of subjects, and change in diagnosis in 49.0% of subjects. In the latter case, there were relevant changes, enabling detection of a lesion vs. finding no abnormality/no lesion and better specification of the type of lesion, i.e. hepatocellular carcinoma or hepatoblastoma vs. malignant tumor.

Change in the number of malignant and non-malignant lesions comparing precontrast images and combined precontrast/postcontrast images was also evaluated. For the 18 subjects with a change in the number of non-malignant lesions, 12 subjects had more lesions and 6 subjects had fewer lesions on the combined precontrast/postcontrast images compared to the precontrast image. Nine of the 12 subjects with more lesions on the combined precontrast/postcontrast images had no lesions precontrast (normal precontrast) and 3 subjects had 1 lesion precontrast.

For the 11 subjects with a change in the number of malignant lesions, 8 subjects had more lesions and 3 subjects had fewer lesions on the combined precontrast/postcontrast image compared to the precontrast images. Of the 8 subjects who had more lesions, 7 had no lesions (normal) precontrast and 1 subject had 1 lesion precontrast.

Sensitivity was 70.8% for the combined precontrast/postcontrast images compared with 66.7% for the precontrast images; specificity was 66.7% vs. 88.9%, respectively; and accuracy was 68.6% vs 78.4%, respectively.

Safety results

Twenty-two of the 52 subjects (42.3%) experienced at least 1 (S)AE. One subject experienced an AE within 24 hours post-injection and 21 subjects (40.4%) experienced at least 1 SAE up to 1 year post-Primovist MRI. Nine subjects (17.3%) experienced at least 1 severe (S)AE.

None of the (S)AEs was assessed by the investigators as related to Primovist or to the MRI procedure. There were no adverse drug reactions and no unexpected adverse events. There were no deaths in this study, and no signs or symptoms of nephrogenic systemic fibrosis (NSF).

All AEs were TEAEs. The most frequent SOCs with AEs were Infections and infestations (11 subjects [21.2%]) and Blood and lymphatic system disorders (7 subjects [13.5%]).

At least 1 (S)AE was experienced by 22 subjects (42.3%, 95% CI: 27.8% to 56.8%). The most frequent (S)AE by SOC was in the Infections and infestations (21.2%) followed by Blood and lymphatic system disorders (13.5%), General disorders and administrative site conditions (9.6%), and Gastrointestinal disorders (7.7%).

By PT, the most frequent (S)AEs were febrile neutropenia 7 (13.5%) subjects and pyrexia in 3 (5.8%) subjects.

The only AE reported within 24 hours after the Primovist injection was benign tumor excision. This event was assessed by the investigator as severe in intensity and not related to Primovist or the MRI procedure. All other AEs were classified as SAEs.

All of the AEs with the exception of hepatocellular carcinoma in patient (14001-0001) were resolved/recovered. Patient 14001-0001 was included in the study after having been referred for imaging for the indication hepatocellular carcinoma (HCC). The ADR is described as recurrence of HCC which was not resolved.

Table 10; Overall summary of adverse events

	Number of subjects (%) (N=52)
Subjects with any (S)AE	22 (42.3)
Subjects with maximum intensity of all (S)AEs[a]	
Mild	2 (3.8)
Moderate	11 (21.2)
Severe	9 (17.3)
Subjects with Eovist/Primovist-related (S)AE	0
Subjects with procedure (MRI)-related (S)AE	0
Subjects with (S)AE resulting in death	0
Subjects with SAE	21 (40.4)

a For subjects with (S)AEs that occurred more than once, only the maximum intensity is presented.

Table 11; Adverse events by system organ class and preferred term

System organ class Preferred term	Number of events	Number of subjects (%) (N=52)
Any adverse event[a]	52	22 (42.3)
Blood and lymphatic system disorders	13	7 (13.5)
Anaemia	1	1 (1.9)
Febrile neutropenia	11	7 (13.5)
Thrombocytopenia	1	1 (1.9)
Gastrointestinal disorders	6	4 (7.7)
Abdominal pain	2	2 (3.8)
Caecitis	1	1 (1.9)
Pneumatosis intestinalis	1	1 (1.9)
Small intestinal obstruction	1	1 (1.9)
Vomiting	1	1 (1.9)
General disorders and administration site condition	6	5 (9.6)
Device occlusion	1	1 (1.9)
Gait disturbance	1	1 (1.9)
Pyrexia	4	3 (5.8)
Hepatobiliary disorders	1	1 (1.9)
Cholangitis acute	1	1 (1.9)
Infections and infestations	17	11 (21.2)
Rhinovirus infection	2	2 (3.9)
Appendicitis	1	1 (1.9)
Bacteraemia	1	1 (1.9)
Bronchitis	1	1 (1.9)
Clostridium difficile colitis	1	1 (1.9)
Enterococcal bacteraemia	1	1 (1.9)
Gastroenteritis rotavirus	1	1 (1.9)
Herpes zoster	1	1 (1.9)
Lobar pneumonia	1	1 (1.9)
Parainfluenzae virus infection	1	1 (1.9)
Pneumonia	1	1 (1.9)
Sepsis	1	1 (1.9)
Septic shock	1	1 (1.9)
Staphylococcal infection	1	1 (1.9)
Tracheitis	1	1 (1.9)
Upper respiratory tract infection	1	1 (1.9)
Metabolism and nutrition disorder	1	1 (1.9)
Feeding disorder	1	1 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (1.9)
Hepatocellular carcinoma	1	1 (1.9)
Nervous system disorders	3	2 (3.8)
Headache	1	1 (1.9)
Intracranial aneurysm	1	1 (1.9)
Neuropathy peripheral	1	1 (1.9)
Renal and urinary disorders	1	1 (1.9)
Renal tubular acidosis	1	1 (1.9)
Surgical and medical procedures	2	2 (3.8)
Benign tumour excision[a]	1	1 (1.9)
Portal shunt	1	1 (1.9)
Vascular disorders	1	1 (1.9)
Hypertension	1	1 (1.9)

a All of the AEs fulfilled the criteria for SAEs with the exception of benign tumor excision.
Note: Subjects could have experienced more than 1 SAE

Most subjects with AEs underwent hospitalization (or prolonged hospitalization) and were therefore classified under the category of SAE. A total of 21 (40.4%) subjects experienced 51 SAEs. Subject 14004-0003 had 11 SAEs; Subject 14004-0004 had 6 SAEs; Subjects 14004-0002 and 14004-0007 had 5 SAE each; Subjects 14004-0001, 14004-0005 and 14004-0012 had 3 SAEs each; and Subject 14004- 0010 had 2 SAEs.

The SAEs were assessed by the investigators as mild in 4 subjects (7.7%), moderate in 14 subjects (26.9%), and severe in 8 subjects (15.4%).
The severe SAEs included the following; febrile neutropenia (2 subjects); caecitis; pneumatosis intestinalis; small intestinal obstruction; appendicitis; Clostridium difficile colitis; enterococcal bacteremia; sepsis; septic shock; hepatocellular carcinoma; hypertension.

SAEs by age subgroup.
Eleven of the 14 subjects (78.6%) in the > 2 months to ≤ 2 years old age group experienced an SAE compared with 8 of the 25 subjects (32%) in the > 2 years to ≤ 12 years old age group and 2 of the 13 subjects (15.4%) in the > 12 years to < 18 years old age group. The subjects in the youngest age group are more vulnerable, therefore, it is not unexpected that this age group compared to the older age groups had a higher percent of subjects with SAEs. None of the SAEs reported in any of the age groups was related to Primovist or the MRI procedure

Clinically relevant laboratory abnormalities.
Three of the 40 subjects (7.5%) with available laboratory data at the preinjection time point had clinically relevant laboratory abnormalities (AST and BUN in subject 14001-0001; alkaline phosphatase and AST in subject 14002-0001; and liver values out of range due to presence of gastrointestinal problems in subject 22001-0006).

None of the 30 subjects with available laboratory data at the postinjection time point had clinically relevant laboratory abnormalities.

Vital signs
The mean changes from baseline/preinjection to 24 hours postinjection were small for heart rate (-4.17 beats/min; n=30), systolic blood pressure (-1.76 mmHg; n=25), and diastolic blood pressure (-0.46 mmHg; n=24) for subjects who had data available at both time points. 5.3.5.4.1
Of 30 subjects with available heart rate data:

- 2 (6.7%) had transitions from normal preinjection to low postinjection
- 1 (3.3%) had a transition from normal to high

Of 25 subjects with available systolic blood pressure data:

- 2 (8.0%) had transitions from normal preinjection to low postinjection
- 2 (8.0%) had a transition from normal to high

Of 24 subjects with available diastolic blood pressure data:

- 3 (12.5%) had transitions from normal preinjection to low postinjection
- 1 (4.2%) had a transition from normal to high

One subject experienced an SAE that involved a change in vital signs. Subject 14004-0005, a 2-year-old African American female with hypertension at study entry, experienced hypertension that required hospitalization 3 days after injection. Blood pressure measurements for this subject were 130/73 mm Hg at baseline and 174/112 mm Hg at 24 hours postinjection. The subject underwent an MRI scan to evaluate her disease post tumor resection. The event, assessed as severe and was considered resolved after 10 days, was attributed to the subject's medical history.

MAH´s safety conclusions

Safety data were available for 52 pediatric subjects in this observational/retrospective study, including 14 subjects > 2 months to ≤ 2 years, 25 subjects > 2 years to ≤ 12 years, and 13 subjects > 12 years to < 18 years of age. No safety issues with Primovist injection up to a dose of 0.2 mL/kg BW (0.05 mmol/kg BW) were identified with regard to the age groups and overall in this pediatric population > 2 months and < 18 years of age.

The Primovist injection up to a dose of 0.2 mL/kg BW was well tolerated in the subjects evaluated in this study. One subject (1.9%) experienced an AE up to 24 hours postinjection (benign tumor excision), and 21 subjects (40.4%) experienced at least 1 SAE up to 1 year (365 days) after the MRI procedure. The most frequent SAEs were febrile neutropenia (7 subjects [13.5%]) and pyrexia (3 subjects [5.8%]). Nine subjects (17.3%) experienced at least 1 severe (S)AE.

None of the (S)AEs was assessed by the investigators as related to Primovist or to the MRI procedure. There were no unexpected AEs, adverse drug reactions, or deaths in this study. There were no signs or symptoms of NSF.

There were no clinically notable effects on blood laboratory parameters in these pediatric subjects (> 2 months to < 18 years old) following Primovist injection in the 8 subjects who had both preinjection and postinjection assessments for at least 1 laboratory parameter. In addition, there were no clinically notable effects on vital signs in the 30 subjects who had both preinjection and postinjection assessments for at least 1 vital sign measurement.

IV.3 Literature review

A comprehensive literature review including Primovist-enhanced MR imaging focusing on children below 18 years was performed. Publications up to 1 November 2013 were included. The search was conducted in the databases Medline, Embase, Biosis, Current Contents, Derwent Drug File and the company's Product Literature Database to identify any articles mentioning the use of Primovist in paediatric population, regardless of the indication.

Overall, a total of 56 abstracts were identified. All abstracts identified through the literature search described above were reviewed. Those articles that presented clinical trials or case reports on the use of Primovist in children younger than 18 years of age, and relevant reviews or papers in which Primovist was mentioned were included into the evaluation. To allow for a comprehensive presentation in particular of the safety experience in children, no restriction was made with regard to the study indication or population.

- **Published data on clinical efficacy**

The literature search yielded six relevant publications on the use of Primovist in the pediatric population, including 2 review articles.

Only paediatric patients with only Primovist administration:

Tamrazi et al (2011) evaluated congenital and acquired hepatobiliary pathologies in the paediatric population. Twenty-one (21) consecutive children who had Gd-EOBDTPA (dose not specified) enhanced MRI for functional hepatobiliary evaluation were retrospectively identified. Definite added value of Gd-EOB-DTPA was found in 12 patients, with potential value in 4 patients, and no value in 5 patients. Benefit was seen in cases of iatrogenic and non-iatrogenic biliary strictures, perihepatic fluid collections for biliary leak, hepatobiliary dysfunction in the

absence of hyperbilirubinemia, and in the functional exclusion of cystic duct occlusion that can be seen in acute cholecystitis.

Marrone et al (2011) described a case of a 9-year-old boy with biliary cystadenoma, diagnosed by Primovist enhanced MRI. Dose of Gd-EOB-DTPA was 3 ml (0.025 mmol/kg. BW). The images clearly demonstrated the communication between the multiloculated cystic mass and the biliary tree, suggesting the possibility of biliary cystadenoma.

Lai et al (2012) described a case of cholangiolocellular carcinoma in a 13-year-old male patient with small duct sclerosing cholangitis. Follow up MRIs with Gd-EOBDTPA administered at the approved adult dose of 0.025 mmol/kg raised suspicion for malignancy such as HCC developing within a preexisting dysplastic nodule. This was confirmed by histopathology of the resected specimen. Pathologic examination confirmed the presence of cholangiolocarcinoma, a tumor found primarily in adults with a history of viral hepatitis. To the authors' knowledge, this is the first such report in a paediatric patient.

Both adult and paediatric patients

Grazioli et al (2012) retrospectively evaluated the utility of Gd-EOB-DTPA enhanced MRI in the differential diagnosis of hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH). Eighty-two patients (58 patients with FNH and 24 patients with HCAs) with 111 lesions were included in the study. There were 74 female patients and eight male patients (mean age, 41.9 years ± 13.2 [standard deviation]; age range, 11-78 years). The number of patients < 18 years was not specified. They concluded that Gd-EOB-DTPA enhanced MRI facilitated the differentiation of FNH from HCA by comparison of the differences in contrast enhancement ratio. This was significantly higher in FNH in the arterial phase (mean, 94.3% ± 33.2) than that of HCAs (mean, 59.3% ± 28.1) (P <.0001).

The above four publications included at least 24 paediatric patients.

Review papers in the paediatric population

Meyers et al (2011) reported their findings in the evaluation of malignant, as well as nonmalignant liver lesions in children who had Gd-EOB-DTPA enhanced liver MRI. They noted that "the usefulness of Gd-EOB-DTPA is in the sharp distinction between most primary and metastatic tumors and the adjacent normal liver parenchyma during the hepatocyte phase". They also noted that they "believe that this allows for more confident definition of the tumor margins and detection of satellite lesions."

In another publication by Meyers et al (2012) their experiences and the benefit of Gd-EOB-DTPA enhanced liver MRI both before and after initiating therapy in children with hepatoblastoma were described. They found that Gd-EOB-DTPA enhanced liver MRI was useful in the evaluation of the biliary anatomy in patients who are post partial hepatotectomy or status post liver transplantation. Gd-EOB-DTPA was administered at a dose of 0.05 mml/kg, which is twice the dose approved in adults. The authors reported that they have not seen any adverse events in more than 120 administrations of Gd-EOBDTPA in their paediatric population. They concluded that MRI enhanced with Gd-EOBDTPA is useful in the pretreatment evaluation of hepatoblastoma, particularly in defining the relationship of the tumor to hepatic and portal veins. In conclusion, the data from the literature provided evidence of the utility and benefit of Gd-EOB-DTPA enhanced liver MRI and that relevant diagnostic information can be obtained from Gd-EOB-DTPA enhanced liver MRI in the pediatric population.

Conclusion by the MAH – literature data.
The data from the literature provided evidence of the utility and benefit of gadoxetate enhanced liver MRI and that relevant diagnostic information can be obtained from gadoxetate enhanced liver MRI in the pediatric population.

IV.4 Post marketing experience, safety reports

The safety database at the company two spontaneous post-marketing reports of adverse events occurring in patients < 18 years of age who received gadoxetate disodium. Additionally, the database contains one report derived from literature.

Brief summaries of safety reports (n=3)

A healthcare professional reported that a 16 year old female in Great Britain who received Primovist (dose unspecified) for a liver MRI to check for hemangioma vomited while in the scanner. The previous day, she had undergone an intravenous pyelogram with Ultravist (iopromide, dose unspecified) and also vomited.
Company comment: Vomiting has been recognized to occur in association with both Primovist and Ultravist and is listed in the reference safety information for both products.

This report concerns a nine year old 54 kg male in the United States with Type I Tyrosinemia who experienced an anaphylactoid reaction after receiving 10 mL Eovist intravenously to evaluate tyrosinemia and a liver lesion. Immediately post-injection, the patient reported experiencing chest pain, throat pain, throat tightness, and a feeling of “throat closing” with an associated dry cough. Initial preliminary reports had indicated he experienced chest tightness, throat swelling and tongue swelling. The patient was treated with diphenhydramine, methylprednisolone, and normal saline. Blood pressure decreased to 70/30s and epinephrine was administered for treatment of anaphylaxis. The patient was hospitalized overnight for observation and discharged the following day.
Company comment: As with all other intravenous contrast agents, Eovist can be associated with anaphylactoid/hypersensitivity reactions characterized by cardiovascular, respiratory and cutaneous manifestations which can in rare cases be severe. Warnings about this type of event are contained in the reference safety information for Primovist.

This report was derived from the medical literature (Tomas M et al (2012), and refers to a four year old North African female who experienced a positive intradermal test for Primovist and Gadovist. The patient had a history of low-grade chiasmatichypothalamic glioma that had been treated with chemotherapy. Her condition was monitored with magnetic resonance imaging every six months. After previously tolerating MRI with Magnevist, in July 2010 she developed a generalized rash after an MRI with ProHance (gadoteridol). Skin prick and intradermal tests were performed with the agent implicated in the reaction and several alternatives. Skin prick tests were negative for all agents tested. Intradermal test results were negative for Magnevist and MultiHance, and positive for ProHance, Gadovist and Primovist. The patient was challenged with MultiHance, which had yielded negative skin prick and intradermal results, and tolerated it well. Authors felt that the positive intradermal skin test results might indicate an IgE-associated mechanism, and that the positive intradermal skin results for several GBCAs might suggest cross-reactivity.

Company comment: In this case, the patient did not experience a reaction to Primovist per se, but rather experienced a positive intradermal skin test to it and several other agents after experiencing a generalized rash with ProHance. The majority of contrast media reactions are not thought to be immunologically mediated and can occur randomly and on first exposure.

Conclusion by the MAH – post marketing reports
The reactions that have been reported to occur in association with the use of Primovist in the paediatric population are consistent with those occurring in adults and those occurring with other gadolinium-based contrast media in children and adults. The majority of reactions are mild to moderate in severity. As with other gadolinium containing contrast agents, severe hypersensitivity reactions may occur in any age group. No reports of NSF in paediatric or adult patients have been received. No safety concerns unique to the paediatric population were identified.

IV.5 Overall conclusions by the MAH

The findings from study no. 13729, as well as the studies mentioned in the literature review, indicate the beneficial effects of Primovist enhanced liver MRI in paediatric patients.

In study 13729, based on the comparison of the precontrast images with the combined precontrast/postcontrast images, Primovist was efficacious and additional diagnostic information was obtained for 86.3% of the pediatric subjects in this study. There were no safety issues identified in this pediatric population > 2 months to < 18 years old who had Primovist-enhanced liver MRI (up to a dose of 0.2 mL/kg BW) for known or suspected focal liver lesions.

However, due to the relatively small number of patients, the data from the clinical study and literature cannot be considered to be confirmatory regarding the efficacy of Primovist in the pediatric population.

Based on these results and taking into account the recommendations of the European Commission's "Guideline on summary of product characteristics (SmPC)", we propose to rephrase the "posology and method of administration" section of the SmPC and describe the currently available data in section 5.1 of the SmPC. 2.5

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Currently Primovist is not approved for the use in the paediatric population in the European Union and currently its use is not recommended. The MAH has provided paediatric data from an observational study in paediatric patients (study no. 13729) as well as results from a literature review and PMS data. Study 13729 was a blinded evaluator study with a comparison of the precontrast images with the combined assessment of precontrast and postcontrast images being the primary efficacy assessment. The combined assessment of precontrast and postcontrast images resulted in additional diagnostic data compared to unenhanced images alone. In this study, 51 serious adverse events (SAEs) were reported in 21 subjects but none of the SAEs were assessed to be related to Primovist or to the MRI procedure. No signs or symptoms of nephrogenic systemic fibrosis were observed.

The data presented by the MAH from a literature review indicates that relevant diagnostic information can be obtained from gadoxetate enhanced liver MRI in the pediatric population. As regards post marketing experience, the reactions that have been reported to occur in association with the use of Primovist in the paediatric population are consistent with those occurring in adults and no safety concerns unique to the paediatric population were identified.

Also, a recent article by Kolbe et al (The impact of hepatocyte phase imaging from infancy to young adulthood in patients with a known or suspected liver lesion, Pediatr Radiol. 2014 Sep 23; Epub ahead of print) is based on a study in 112 patients (mean age: 9.25 years) undergoing MRI between September 2010 and August 2012 using gadoxetate disodium as the contrast agent. The purpose was to assess the impact of contrast enhanced imaging on lesion detection, tumor staging and diagnostic confidence. A total of 33 patients had a malignant tumor and the remainder had either a benign lesion or no lesion. The addition of contrast agent significantly improved the diagnostic confidence for all patients ($p < 0.0001$) as well as specifically for patients diagnosed with focal nodular hyperplasia (FNH, $p = 0.003$). In nearly a quarter of patients, the contrast enhanced imaging allowed the reviewer to detect additional lesions ($P = 0.005$). The authors concluded that the addition of contrast enhanced imaging helps to improve lesion detection and increase the diagnostic confidence for all liver tumors, as well as for FNH in particular.

Based on the results presented by the MAH is can be concluded that there are data demonstrating a beneficial effect of gadoxetate enhanced liver MRI in paediatric patients. This view is also supported by the recent publication by Kolbe (Epub Sept 2014).

Recommendation

The proposed rephrasing of section 4.2 of the SmPC, with the deletion of “cannot be recommended” in the paediatric population and addition of a cross reference to section 5.1 is acceptable. Shown with tracked changes below.

Addition of paediatric data in section 5.1 is acceptable, however with some revisions of the suggested text. The final recommendations for the SmPC and PL is found below. This is a new paragraph and therefore shown without and tracked changes.

The corresponding texts in the package leaflet are shown below.

Final SmPC recommendations:

Section 4.2 (changes to current text in strikethrough/bold)
Paediatric population
The safety and efficacy of Primovist have not been established in patients under 18 years old. ~~Therefore, use of Primovist in this patient group cannot be recommended.~~ **Currently available data are described in section 5.1.**

Section 5.1 (new paragraph)
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

Package leaflet recommendations:

Package leaflet section 2 (changes to current text in strikethrough/bold)
Children and adolescents
~~The safety of Primovist in persons under 18 years has not yet been tested. Therefore, use of Primovist in this patient group cannot be recommended.~~ **The safety and efficacy of Primovist have not been established in patients under 18 years old as there is limited experience on its use. Further information regarding the use of Primovist in children is given at the end of the leaflet.**

Package leaflet section "The following information is intended for healthcare professionals only" (new paragraph):
Paediatric population
An observational study was performed in 52 paediatric patients (aged > 2 months and < 18 years). Patients were referred for Primovist enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population.

Type IB variation to be requested from the MAH by 2015-04-03.