LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Primovist
(disodium gadoxetate, gadoxetic acid)

SE/H/429/01-02/E/02
2002-0677, 2002-0678

This module reflects the scientific discussion for the approval of Primovist. The procedure was finalised on 2020-05-18. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Bayer AB has applied for a marketing authorisation for Primovist, 0.25 mmol/ml, solution for injection, prefilled syringe and solution for injection. The active substance is gadoxetic acid, disodium (a paramagnetic contrast agent for magnetic resonance imaging).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology and pharmacokinetics

Gd-EOB-DTPA is highly hydrophilic and cellular uptake is limited to hepatocytes. Gd-EOB-DTPA enters hepatocytes through a transporter protein belonging to the OATP1-group. Gd-EOB-DTPA is excreted unchanged in the bile via cMOAT and via glomerular filtration. The liver specific uptake of Gd-EOB-DTPA is the basis for the use in liver MR, allowing high contrast between normal liver parenchyma and a focal liver lesion.

Safety Pharmacology
Safety pharmacology studies showed no adverse effects on neural functions, respiratory function or cardiac function (blood pressure, heart rate and cardiac output). An inhibition of HERG potassium channel and prolonged repolarisation in guinea pig papillary muscle at high concentrations was found (in vitro). In vivo, QTcF and QtcQ intervals were slightly prolonged at the highest dose (0.5 mmol/kg, i.e. 20 times the human dose). This indicates a possibility to induce QT prolongation if Primovist is overdosed.

Pharmacodynamic drug interactions can be anticipated for drugs which interact with hepatic transporters involved in uptake and excretion of Gd-EOB-DTPA and Inhibitors of organic anion transporters located in the sinusoidal plasma membrane of the hepatocyte.

III.2 Toxicology
In the initial application 2004 preceding the authorisation, non-clinical GLP toxicity studies were performed. Gd-EOB-DTPA showed low acute toxicity. Lethal effects were observed in rats at a dose approximately 300 times the diagnostic dose. No lethality was observed in dogs at a dose 120 times the diagnostic dose.

The vacuolation of renal tubular cells, identified in both the rat and dog 4 week repeated dose toxicity studies was almost completely reversible. No impairment of kidney function was observed. The effect was attributed to the result of repeated treatment, whereas the intended diagnostic use in humans is a single administration. Minor effects on blood parameters were all fully reversible.

Standard genotoxicity studies showed no evidence for a genotoxic or mutagenic potential of Gd-EOB-DTPA.

Two impurities were identified, ZK131897 and ZK208983, and was considered not genotoxic.

Reproduction toxicity studies were performed in rats and rabbits. Embryotoxic effects was found in rabbit with an increase in post-implantation losses and abortions at the highest dose of 2.0 mmol/kg.

Severe local intolerance was observed after intramuscular injection. No other routes resulted in local intolerance reactions and no sensitising potential with respect to antibody production or cellular hypersensitivity was found.

Studies were considered appropriate according to RMS in 2004.

III.3 Ecotoxicity/environmental risk assessment
Since Primovist is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics
After rapid bolus injection (dose, 10 – 100 μmol /kg BW) the removal of Gd-EOB-DTPA from the circulation was characterised by a bi-exponential decline. The elimination is attributed to renal elimination and uptake by the liver (approximately 50 : 50 proportion). The mean terminal half-life and the total clearance were approximately 1 h and 250 ml/min, respectively. The steady-state volume was less than 20 L in a subject with body weight of 70 kg. The variability in CL and Vss was very low Dose independent fecal and urinary excretion over the dose range 10 – 100 μmol /kg BW indicated

that for up to 4-fold higher dose than the suggested clinical dose, the disposition processes are not saturated.

No drug-drug interaction studies were conducted due to the good tolerability, non-chronic clinical application, lack of biotransformation, insignificant protein binding, and short half-life of Gd-EOB-DTPA. The justification for not conducting drug interaction studies is accepted. The pharmacokinetics was investigated after single bolus injection of Gd-EOB-DTPA in groups of volunteer patients with various levels of organ dysfunction. In subjects with moderate renal impairment AUC was increased by about 48% compared with normal subjects. The pharmacokinetic was clearly affected by end-stage renal disease. In the patients with ESRF, significantly longer terminal t-half (i.e., 20.4 hours vs. <3 hours in all other groups) and significantly smaller CLt, (i.e., 36.0 mL/minute Vs 122 – 209 mL/minute in the rest of the groups), led to significantly increased systemic exposure to Gd-EOB-DTPA (6-fold higher). Hemodialysis increased the clearance of Gd-EOB-DTPA. In an average dialysis session of about 3 hour duration, about 30% of the Gd-EOB-DTPA dose was removed by hemodialysis. The influence of hepatic impairment was evaluated in subjects with mild, moderate and severe hepatic impairment. Mean AUC was higher in the hepatic impairment group, but there was no clear trend within the different degrees of impairment (CL was about 60-80% lower in HI). Pharmacokinetic differences attributed to gender and age were not considered clinically relevant.

IV.2 Clinical efficacy

MR imaging using extracellular gadolinium-containing agents provides useful information for whole body scan including the liver. Compared to Magnevist, Primovist has the additional property for uptake by hepatocytes as well as the properties of an extracellular gadolinium contrast agent. Therefore, a potential added advantage with Primovist is parenchymal enhancement. Lesions with no or minimal hepatocyte function (cysts, metastases, majority of hepatocellular carcinoma) will not accumulate Primovist.

In the initial application in 2004, there were four pivotal phase III studies, in addition to three supportive phase II dose-finding studies. The phase III studies were multi-centre, open-label, single dose clinical studies with two identical studies (twin studies) designed for lesion detection and lesion characterization, respectively as primary efficacy variable. For all studies, data from the open-label *clinical studies* and from the respective masked evaluation of images in separate *blinded readings* were analyzed. The results of blinded reads were presented for individual readers to show variability between readers.

The basic structure of all four studies was comparable. This was achieved by using the same standardized imaging sequences and by evaluating the contrast-enhanced images, either post-contrast or combined pre-and post-contrast images, in comparison to the pre-contrast images within individuals. In addition, enhanced spiral CT was performed as a comparative imaging procedure in all four studies.

Improvement in correctly detected liver lesions in combined pre-and post-contrast MRI compared to pre-contrast MRI was shown. The size of the increase was of the order of about 10%. Statistically significant increase in sensitivity in lesion detection was observed in some but not all of the blinded reads. Concomitant loss in specificity was also noted. The Applicant has clarified the clinical relevance of the improvement in lesion detection and the trade-off between gain in sensitivity versus loss in specificity. As the “truth” could be established using another radiological procedure for some lesions, separate analyses were provided and they showed that there was consistently an increase in the proportion of correctly characterised lesions, irrespective whether a histological or radiological standard of reference was used.

The studies were considered as appropriate by the RMS.

In procedure SE/H/429/01-02/II/47, in 2019, the MAH provided data which had become available after the submission of the original MAA. This comprised three clinical studies.

The first study showed that pre/post-contrast MRI is more sensitive than CT. Contrast-MRI is more sensitive than pre-contrast-MRI. This confirms what is already known about imaging of the liver.

The second study compared Primovist to MultiHance and it is acknowledged that Primovist is more time efficient than MultiHance, without the need of a second MRI.

The third study showed that pre- and post-contrast imaging improves the diagnostic confidence in lesion characterization.

The provided studies were acknowledged with no further questions.

Additional supportive literature regarded use of Primovist in distinguishing pseudolesions (perfusional anomalies) from true lesions, differentiating hemangiomas from metastases, characterization of incidentally discovered focal liver lesions, delineating HCC from benign dysplastic/high risk nodules, detection of HCC, detection of liver metastases, hepato-biliary imaging and patient management and cost effectiveness.

In a pediatric population, focal liver lesions are rare, and larger controlled prospective studies to evaluate efficacy and safety in such a population are not feasible. Provided studies from the Mah gave some evidence that the efficacy and safety of Primovist did not significantly differ between pediatric and adult patients.

The provided data in the type II-variation SE/H/429/01-02/II/47 was acknowledged by the RMS. No SmPC changes were proposed by neither part.

IV.3 Clinical safety

In the initial application in 2004, apart from QT prolongation, non-serious adverse events were reported in less than 10% of patients. The commonest adverse events in descending order of occurrences, were headache, nausea, abdominal pain, back pain, vasodilatation, anxiety, dizziness, taste perversion, rash, and others, each affecting 1.2% or less of patients. QTcB increase between 30 and 60 msec was observed in about 16% of patients while less than 2% had increase greater than 60 msec. QT increase associated with the use of gadolinium-containing MR contrast agents is recognised. None of the QTc prolongation in this clinical development program was associated with any adverse events. The majority of QT prolongation was recorded at one single time point without any clustering. No relationship to the single dose administration of Primovist at the recommended dose could be identified, neither was renal or hepatic impairment identified as a predisposing factor. There were several coexisting factors in the patients with QTc changes that could have caused the change by itself but no risk factor seemed to dominate. It is recognised that the agent is likely to be used “once-only” and no clinical events associated with QTc prolongation were reported in the clinical development program.

At present, Primovist has been administered to over 2500 patients in clinical studies and 5 million doses have been administered post-marketing. The side effects are similar to other GBCAs. No new information was included in the product information in procedure SE/H/429/01-02/II/47.

IV.4 Risk Management Plans

The MAH did submit a risk management plan, version 3.0, in procedure SE/H/429/01-02/II/47. The RMP is in accordance with the requirements of Directive 2001/83/EC as amended, describing the

pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Primovist.

Safety specification

Table 1: Summary of safety concerns

Important identified risks	•	Anaphylactoid reactions
Important potential risks	•	Nephrogenic systemic fibrosis (NSF)
	•	Convulsions (Seizures)
	•	Accumulation and retention of gadolinium in the brain
	•	Gadolinium accumulation in organs and tissues other than brain tissues
Missing information	•	Safety of use in pregnancy and lactation
	•	Clinical significance of gadolinium retention in the brain
	•	Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 3.0 signed the 19 September 2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The user test was assessed and accepted in SE/H/429/II/47/G.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Primovist, 0.25 mmol/ml, solution for injection, prefilled syringe and solution for injection is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The mutual recognition procedure for Primovist, 0.25 mmol/ml, solution for injection, prefilled syringe and solution for injection was positively finalised on 202005.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se