Taiwan Food and Drug Administration

Assessment Report

Trade Name：普優顯注射液 / ProHance 279.3 mg/ml solution for infusion

Active Ingredient：Gadoteridol

License Number：MOHW-PI 028914

Applicant：富富企業股份有限公司

Approval Date：114/04/09

Indication：

適用於：

- **6 個月以上病人，改善大腦、脊髓和周圍組織的顯影劑增強磁振造影(contrast-enhanced MRI)成像的可視度。**
- **成人病人全身磁振造影，包括頭部、頸部、肝臟、乳房、肌肉骨骼系統和軟組織疾病。**

應只在當診斷資訊獲得是必要的且非顯影劑增強磁振造影無法獲得診斷資訊時使用。

Background Information

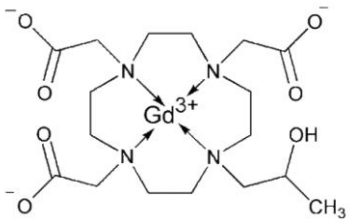
Trade Name	普優顯注射液 / ProHance 279.3 mg/ml solution for infusion
Active Ingredient(s)	Gadoteridol
Applicant	富富企業股份有限公司
Dosage Form & Strengths	注射劑 279.3 mg/ml solution for infusion
Indication	適用於： 1. 6 個月以上病人，改善大腦、脊髓和周圍組織的顯影劑增強磁振造影(contrast-enhanced MRI)成像的可視度。 2. 成人病人全身磁振造影，包括頭部、頸部、肝臟、乳房、肌肉骨骼系統和軟組織疾病。 應只在當診斷資訊獲得是必要的且非顯影劑增強磁振造影無法獲得診斷資訊時使用。
Posology	詳見仿單 / Please refer to the approved package insert
Pharmacological Category ATC Code	V08CA04

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, gadoteridol, is chemically designated as 10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, gadolinium complex and has the following structure:



It is a white to yellowish tan powder. The molecular formula and the molecular weight are $C_{17}H_{29}GdN_4O_7$ and 558.75, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of gadoteridol has been confirmed by elemental analysis, IR spectrum and mass spectrometry. Adequate specification has been presented for the drug substance and the test items include appearance, identification, water content, heavy metals, assay, regioisomer, free gadolinium, Gd-containing impurities, non Gd-containing impurities, free ligand and residual solvents. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for intravenous injection use as 0.5 M sterile clear colorless to slightly yellow aqueous solution containing 279.3 mg/mL of gadoteridol. The specifications for excipients used in the drug product formulation are adequate.
Adequate specification has been presented for the drug product and the test items includes appearance, colour, pH, identification, assay, free gadolinium, free ligand, tromethamine, net content, visible particles, particulate matter, sterility and bacterial endotoxins. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long-term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. No significant chemical or physical changes are observed for the drug product, the shelf life and storage condition of drug product can be granted for 36 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Gadoteridol is a macrocyclic gadolinium agent that is more stable and has a lower propensity to release gadolinium than linear agents. EMA has evaluated the benefits and risks of the GdCAs including gadoteridol. This report excerpted the EMA's report and agreed with the conclusion.

2.2.2 Toxicological Studies

Both *in vitro* and *in vivo* genotoxicity studies of gadoteridol presented negative results. The carcinogenicity study is not warranted. The reproductive and developmental toxicity studies of gadoteridol did not reveal any treatment-related adverse effect on fertility or reproduction at daily doses of 1.5 mmol/kg (15 times the clinical dose), and no teratogenic effect at doses up to 10 mmol/kg (100 times the clinical dose) in rats and 6 mmol/kg (60 times the clinical dose) in rabbits. GdCAs are not recommended for use during pregnancy. Nonclinical safety information has been mentioned in the package insert.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

In healthy volunteers, the pharmacokinetics of ProHance was described by a two-compartment open model with excretion from the central compartment. The pharmacokinetic parameters were independent of dose. ProHance appears to be confined to the vascular and interstitial space with whole body clearance >94% ±5% in 24 hours, distribution half-life 0.20 ± 0.04 hours, elimination half-life 1.57 ± 0.08 hours, total volume of distribution 204 ± 58 mL/kg, serum clearance 1.50 ± 0.35 mL/min/kg, and urinary clearance 1.41 ± 0.33 mL/min/kg. The renal and blood clearance are essentially identical, indicating no alteration in elimination kinetics on passage through the kidneys, and that the drug is essentially cleared through the kidney. The volume of distribution is equal to that of extracellular water, and the clearance is similar to that of substances that are subject to glomerular filtration.

2.3.2 Interaction Studies

In vitro, no measurable biotransformation or in vivo degradation of this substance was detected. Therefore, no further clinical DDI studies were conducted.

2.3.3 Special Populations

Based on population PK analysis, the pharmacokinetics of gadoteridol was not affected by age (≧65), BMI, body weight and sex.

In renal impairment study, the distribution half-life is 0.55 ± 0.08 hours in moderate renal impairment and 0.25 ± 0.06 hours in severe renal impairment, and the elimination half-life is 10.65 ± 0.60 hours in moderate renal impairment and 9.10 ± 0.26 hours in severe renal impairment. No relationship between the dose of ProHance injection administered and either the distribution or elimination half-life were noted. No dose adjustment is needed in patients with mild and moderate renal impairment. In patients with severe renal impairment (GFR < 30 mL/min/1.73m^2) or in patients in the perioperative liver transplantation period, ProHance should only be used after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. If it is necessary to use ProHance, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, ProHance injections should not be repeated unless the interval between injections is at least 7 days.

In hepatic impairment study, mean whole blood gadolinium profiles were virtually superimposable at most timepoints in adult subjects with moderate to severe impaired hepatic function (Class B or C of the modified Child-Pugh Classification) compared with the healthy subjects. No dose adjustment is needed in patients with mild, moderate

and severe hepatic impairment.

In pediatric population PK analysis, the AUC exposure was 63.9% (male) and 64.8% (female) of adult values for 6 to 12-month old subjects. The C_{max} was 62.7% (male) and 62.8% (female) of adult values for 6 to 12-month-old subjects. The percent of AUC or C_{max} for subjects aged 1 to 18-year-old was within the range of 6 to 12-month-old and adult subjects. Combined with the proposed population PK model and analogous drug utilization experience, 0.1 mmol/kg (0.2 mL/kg) was recommended in pediatric subjects aged between 6 months and 18 years.

Pharmacokinetic simulations indicate similar half-life, AUC, and C_{max} values for ProHance in pediatric subjects less than 2 years of age when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided more than 20 trials conducted 2 decades ago to demonstrate the enhancement ability of ProHance (Gadoteridol) for MRI diagnosis in adults with different body pathology and pediatric patients with Intra-cranial/Spinal lesions. Most of these trials were intra-subject comparison of pre- and post-dose ProHance images by independent blinded readers. Several trials were comparative designs (ProHance vs other gadolinium containing contrast agent).

The comparison of pre- and post-dose ProHance demonstrated that ProHance is an effective agent for MR contrast enhancement of whole body pathology with T1 weighted imaging sequences. Additional diagnostic information was provided variably by scanned area and reader ability. ProHance showed similar enhancement ability to other gadolinium containing contrast agent.

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2.4.2 Safety Results

The reported overall adverse event incidence rate was low according to the clinical trial data and literature. The most common ARs were GI (nausea, vomiting) and anaphylactoid-type skin reactions (urticaria, retching, pruritus/itching, flush), pain, taste perversion, vasodilation/hypotension, cough, vomiting, headache, injection site reaction and watery eyes. It was concluded ProHance with less deposition in brains, bone and less risk of NSF compared among GdCAs.

Insufficient PK studies were provided from the sponsor and hence, the differences between East Asians and non-East Asians were remained unknown from PK's perspective. A phase III study (Study Hirohashi et al) conducted in Japan to compare the imaging results of Prohance and Magnevist (already approved in Taiwan) for 251 patients with liver disease was provided for BSE. The results showed similar efficacy in Prohance and Magnevist with regard to contrast enhancement, diagnostic capability and efficacy. As for safety, the submitted phase III clinical trials conducted in Asian population (Japan, China) showed that ProHance was well-tolerated, with no serious adverse events reported. This finding is consistent to a literature report of an observational study conducted in Korea.

The ethnicity sensitivity was clarified via sufficient East Asian efficacy and safety data. Therefore, the BSE of ProHance was waived.

2.6 Conclusion

This multidisciplinary review recommends approval for ProHance solution for infusion (Gadoteridol) indicated for

-MRI in adults and pediatric patients ages 6 months and older:-Improved visualization of contrast-enhanced magnetic resonance imaging (MRI) of the brain, spinal cord and surrounding tissues.

-In MRI ProHance can be used in adults for the whole body including head, neck, liver, mammary glands, the musculoskeletal system and soft tissue diseases.

-ProHance should be used only if the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI).

3. Post-Marketing Requirements

NA