LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

ProHance
(gadoteridol)

Asp no: 2018-0560

This module reflects the scientific discussion for the approval of ProHance. The procedure was finalised on 2019-08-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Bracco International B.V has applied for a marketing authorisation for ProHance, 279.3 mg/ml, solution for injection in pre-filled syringe. The active substance gadoteridol is the same as in ProHance, 279.3 mg/ml, solution for injection., marketed by Bracco International B.V since 1993. There is no Public Assessment Report for ProHance, 279.3 mg/ml, solution for injection.

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

This is an extension application for a new pharmaceutical form (pre-filled syringes) of ProHance, an approved gadolinium-based contrast agent, i.e., the same solution for injection is now being packaged in glass pre-filled syringes in addition to the currently available glass vials.
No new non-clinical documentation has been submitted. The non-clinical documentation pertaining to the formulation in glass vials supports this extension application.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is an extension application for a new pharmaceutical form (pre-filled syringes) of ProHance an approved gadolinium-based contrast agent, i.e., the same solution for injection is now being packaged in glass pre-filled syringes in addition to the currently available glass vials.
No new clinical documentation has been submitted. The clinical documentation pertaining to the formulation in glass vials supports this extension application.

IV.2 Risk Management Plans

The MAH has submitted a risk management plan (RMP, version 5, dated Feb 7, 2018), 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 ProHance.

Safety specification in RMP ver 5
The safety concerns have been updated, based on the Final Assessment Report issued by PRAC on 06 July 2017 following the re-examination procedure relevant to Referral under Article 31 of Directive 2001/83/EC (procedure EMEA/H/A-31/1437).

Important identified risks	• Nephrogenic systemic fibrosis (NSF) • Anaphylactic/anaphylactoid reactions
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in the brain • Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues
Missing information	• Safety in children • Safety in pregnancy and lactation

Pharmacovigilance Plan

The table below summarises the additional pharmacovigilance activities for the product.

Study Status	Summary of objectives	Safety concern(s) addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
GMRA-102 **Title:** A prospective multicentre cohort study evaluating the long term retention of gadolinium in human bone and skin after the retrospective administration of MultiHance or ProHance in comparison with a control group receiving no exposure to gadolinium **On-going**	• To evaluate the long term retention of gadolinium in human bone and skin after the retrospective administration of MultiHance or ProHance in comparison with a control group receiving no exposure to gadolinium	NSF, gadolinium retention in tissues No IP administered for this study	Protocol finalised	April 2012 (Amended Feb 2016
			Enrollment begun	Oct 2014
			Enrollment to conclude	Dec 2018
			Interim Reports	Yearly progress reports on enrollment
			Final report	6 mos after last patient enrolled

Study GMRA-102 may provide safety information on the ProHance safety concerns and was agreed upon with EMA in response to the Article 31 procedure (EMEA/H/A-31/1097) concluded with an EC decision on 5 July 2010.

Risk minimisation measures

A DHCP communication to inform healthcare professionals about the new information regarding gadolinium retention as concluded in the Article 31 safety referral procedure (EMEA/H/A-31/1437) has been circulated.
Except for this DHPC, 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 5 signed Feb 7, 2018 is considered acceptable.

It is noted that the company has voluntarily planned/initiated a study that may provide safety information on the product. This relates to study gadolinium retention in human autopsy samples. Study short name and title: GMRA-104; a retrospective, multicentre study evaluation autopsy tissue specimen for levels of gadolinium and other metals after the single agent administration of one of four gadolinium-based contrast agents in comparison with a control group having no exposure to gadolinium.

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 MPA;
- 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 for ProHance was accepted in the national procedure 5.4.3-2012-122809.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product, ProHance in pre-filled syringes is found adequate. There are no objections to approval of ProHance in pre-filled syringes from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore 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

ProHance, 279.3 mg/ml, solution for injection in pre-filled syringe, was approved in the national procedure on 2019-08-09.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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