CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-489

MEDICAL REVIEW(S)

Division Director Memo to the File

NDA:	21-489 (Pharmacy Bulk Pack)
DRUG	ProHance® Multipack™ (gadoteridol injection)
DOSAGE:	0.1mmol/kg (0.2mL/kg) in solution administered as a rapid intravenous infusion or bolus, a second dose of 0.2 mmol/kg (0.4mL/kg) may be given up to 30 minutes after the first dose
ROUTE:	Intravenous
MODALITY:	Magnetic Resonance Imaging (MRI)
INDICATION:	Contrast enhancement in CNS (adults and pediatrics)
SPONSOR:	Bracco Diagnostics, Inc.
CATEGORY:	1S
SUMBITTED:	December 16, 2002
COMPLETED:	October 8, 2003

ProHance® is a gadolinium based contrast agent that was approved in 1994 (NDA 20-131) for use in MRI imaging in adults and children to visualize lesions with abnormal vascularity in the brain, spine and associated tissues as well as to visualize lesions in the head and neck in adults.

The Sponsor has submitted this application to obtain marketing approval of a pharmacy bulk pack (50 mL vial). The submission has been reviewed by the chemist who finds it acceptable for approval. The reviewing microbiologist has determined that there is sufficient data to justify the 8 hour use period and has recommended approval as well. A safety update was submitted and reviewed by the medical officer. He has concluded that no labeling changes are needed based on the data submitted. Overall, I concur with all the reviewers' assessments.

The Division of Medication Errors and Technical Support has some concerns about the use of the modifier "Multipack" as part of the proprietary name. Their concern is that the modifier suggests that the product is a multiple dose container and may lead to confusion and misuse of the pharmacy bulk pack. The modifier, "Multipack", has been used as part of the proprietary name for a previously approved pharmacy bulk pack, Isovue® Multipack™ (NDA 20327), for which Bracco is the Sponsor. To date, there is no evidence of any safety problems to suggest that this product has been misused. Therefore, the proposed name is acceptable.

Recommendation: Approval.

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/s/

Sally Loewke
10/9/03 04:28:34 PM
MEDICAL OFFICER

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

Medical Officer Review

NDA# 21-489
Supplement # SU

M.O. Review # 1

Date of letter: 4/10/2003
Date FDA received: 4/11/03
Date reviewer received: 5/21/03
Date review completed: 8/21/03

Drug name:	ProHance
Generic name:	Gadoteridol Injection
Proposed trade name:	
Chemical name:	Gadolinium-tetraazacyclododecanetriacetic acid (gadoteridol)

Sponsor: Bracco Diagnostics , Inc.
Princeton, NJ 08540

Pharmacologic Category:	MRI Contrast Agent
Proposed Indication(s): visualize	CNS: " … in adults and children over 2 years of age to lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues."
Dosage Form(s) and Route(s) of Administration, Directions for Use:	0.2 mL/kg (0.1 mmol/kg) in solution administered as a rapid intravenous infusion 10 mL/min-60 mL/min or by an IV bolus and at a rate of 60 mL/min; and a second dose of 0.2 mmol/kg may be given up to 30 min after the first dose
NDA Drug Classification:	
Related Drugs:	Omniscan-gadodiamide, Optimark-gadoversetamide, Magnevist-gadodimeglumine
Related Reviews:	Chemistry Review dated: 8-1-03

Scope: This submission contains a "FOUR-MONTH SAFETY UPDATE" for pending supplemental NDA – The ProHance Multipak - which was originally submitted on December 16, 2002. As per introductory letter, the period covered for this update is November 1997 through January 2003.

The current labeling for ProHance states in the Adverse Reactions section that "The most commonly noted adverse experiences were nausea and taste perversion with an incidence of 1.4%. These events were mild to moderate in severity. (The following) additional adverse events occurred in fewer than 1% of the patients: ....." and the package insert lists individual adverse events as grouped by body systems. The latter adverse events are not classified by severity.

The sponsor reports tha — patients were treated with ProHance between November 1997 and January 2003, and 1522 cases with adverse events (— , were reported during this postmarketing period. Of these, 197 were serious adverse events. Compilation of adverse events data in the current labeling differs from the reporting system in this submission in that the relative frequencies of adverse events are not listed in the current labeling. Thus, the available data does not lend itself to a direct comparison in frequencies with the adverse event list in the current labeling. From a broader perspective, the adverse events in both are about similar in types, their frequencies, body systems involved, etc., although more adverse event categories are provided in this submission than listed in the current labeling.

In this submission 3 deaths are mentioned, all of them ascribed to sequaellae of anaphylactoid/anaphylactic reactions. Among serious adverse events, one case of Torsades de Pointes is attributed to a concomitant use of Cisapride. These explanations are plausible, but may be incomplete since, it can not be determined from the available data whether the higher frequencies of dyspnea and hypotension are mainly anaphylactic and/or anaphylactoid in origin, or not. These could be potentially cardiac in origin. The most frequent serious adverse events reported in this submission in descending order are as follows:

Most frequent serious adverse events (N=3 752,081 patients exposed)			
Adverse event	**Frequency**	**Adverse event**	**Frequency**
Dyspnea	44	Angioneurotic edema	8
Hypotension	42	Anaphylactoid reaction	7
Shock	16	Exanthem	7
Convulsions	15	Cough	7
Loss of consciousness	14	Dry throat	7
Laryngeal edema	13	Respiratory arrest	6
Hypersensitivity	12	Chest tenderness	6
Throat tightness	10	Bronchospams	6
Urticaria	9	Cardiac arrest	5
Anaphylactic shock	9	Cardiac flutter	5
Blood pressure decreased	9	Gingival swelling	5
Arterial pressure decreased NOS	8		

Among total of 2971 adverse events reported (serious and non-serious), the most frequent were nausea (630) and vomiting (345).

Other examined sources: The case of Torsades de Pointes was recently reported in the internal FDA report (ODS PID # [redacted], regarding QT prolongation and Torsade de Pointes prepared by DDRE (ODS). Med Watch reports on some of these adverse events were submitted under the original NDA # 20171.

Conclusion: In conclusion, the compilation of the adverse events submitted as a part of this "FOUR-MONTH SAFETY UPDATE" is comparable to the list of adverse events in current labeling. However, a detailed comparison can not be made, as the current labeling does not state respective frequencies. It should be noted that the safety update data were obtained from patients receiving the drug provided under existing packaging configuration. However, if the review of chemistry and manufacturing controls finds the drug delivered in the new packaging is substantially similar to the existing one, there is no reason to believe that the safety profiles would be different for the new packaging configuration. This safety update is similar in the safety profile to comparable drugs under the class of gadolinium-chelates.

Recommendation: No labeling change is needed in order to implement the change from the previously approved product, Prohance-gadoteridol injection, to the new, ProHance Multipack - a Pharmacy Bulk Package.

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/s/

Joseph Zolman
9/21/03 02:07:56 PM
MEDICAL OFFICER

Ramesh Raman
10/3/03 06:52:08 PM
MEDICAL OFFICER
Concur in essence with Dr. Zolman's recommendations.

Sally Loewke
10/8/03 11:59:25 AM
MEDICAL OFFICER