CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-489

CHEMISTRY REVIEW(S)

NDA 21-489

ProHance Multipack™
(gadoteridol injection)

Bracco Diagnostics Inc.
P.O.Box 5225, Princeton, NJ 08543-5225

Ravindra K. Kasliwal, Ph.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products

Table of Contents

Chemistry Review Data Sheet

1. **NDA 21-489**

2. REVIEW #: 1

3. REVIEW DATE: 17-Jul-03

4. REVIEWER: Ravindra K. Kasliwal, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	16-Dec-03
Amendment (BC)	14-Jul-03

7. NAME & ADDRESS OF APPLICANT:

Name: Bracco Diagnostics Inc.

Address: PO Box 5225

Representative: Princeton, NJ 08543

Telephone: (609) 514-2254 (Melanie Benson)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ProHance Multipack
b) Non-Proprietary Name (USAN): Gadoteridol
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2); LD – NDA 20-131, ProHance Injection, Strength – 279.3 mg/mL, NDA Holder – Brocco Diagnostics.

10. PHARMACOL. CATEGORY: MRI Contrast Agent.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 279.3 mg/mL

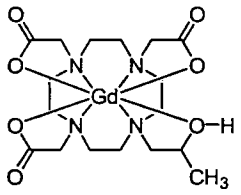
13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{17}H_{29}GdN_4O_7$
Exact Mass: 559.13
Mol. Wt.: 558.68
C, 36.55; H, 5.23; Gd, 28.15; N, 10.03; O, 20.05

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-131	Approved application

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	NA		
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	NA		
Microbiology	Approval	20-Jun-03	David Hussong, Ph.D.

The Chemistry Review for NDA 21-489

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An approval action is recommended. The application is for a pharmacy bulk package of an approved drug product application. The issues concerning the packaging, labeling and use of the pharmacy bulk pack have been satisfactorily addressed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product contains gadoteridol drug substance (279.3 mg/mL), Calteridol calcium (0.23 mg/mL), Tromethamine, USP (1.21 mg/mL), HCl and NaOH (for pH adjustment) in water for injection. The formulation has been marketed in the united states since November 1992. This application concerns the marketing of the same formulation in a pharmacy bulk pack (50 mL vial).

B. Description of How the Drug Product is Intended to be Used

The drug product is an injectable drug product which is used for contrast enhancement during MRI imaging. Adults may be given two doses (first dose of 0.2 mL/kg, and then if necessary a second dose of 0.4 mL/kg after 30 minutes), and the children (2-18 years) may be given a single of 0.2 mL/kg. Since multiple doses and multiple subjects may be evaluated in a short span of time, using a pharmacy bulk package may offer economic advantage to the end user. The pharmacy bulk pack is handled under aseptic conditions and the product is dispensed utilizing a transfer device which assures the integrity of the remaining vial contents.

C. Basis for Approvability or Not-Approval Recommendation

The company wants to manufacture pharmacy bulk package for a drug product that has been marketed for several years in the US. The issues related to the labeling and use of the pharmacy bulk package have been satisfactorily been addressed. The drug is typically handled / used in the hospitals or imaging centers. The conditions of use for the currently

available 50 ml multi-dose vial allow for multiple insertion of the needle into the vial, that would create a risk of contamination of the product leftover in the vial for subsequent use. The availability of the pharmacy bulk pack should reduce this risk as the user is required to use a suitable transfer device (commercially available in the hospitals) to obtain the dose and the product vial is only inserted once during the entire use period. Because of this additional safety assurance an approval recommendation has been made.

III. Administrative

A. Reviewer's Signature

Signed by Ravindra K. Kasliwal, Ph.D. on 17-Jul-03

B. Endorsement Block

Chemist Name/Date: Kasliwal/ 17-Jul-03
Chemistry Team Leader Name/Date: Leutzinger /
Project Manager Name/Date: Moore /

C. CC Block

7 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

__ § 552(b)(5) Deliberative Process

__ § 552(b)(4) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ravi Kasliwal
8/7/03 05:24:02 PM
CHEMIST

Eldon Leutzinger
8/11/03 07:33:13 AM
CHEMIST
I concur with the conclusions and recommendation based on chemistry, manufacturing and controls.

NDA CHECKLIST FOR FILABILITY
CHEMISTRY, MANUFACTURING, AND CONTROLS(DNDC-II, HFD-160)

NDA # : **21-489** DRUG PRODUCT NAME: ProHance® Multipack™
(gadoteridol injection)

SPONSOR: Bracco Dignostic Inc., P.O. Box 5225, Princeton, NJ 08543-5225
REVIEWER: Ravindra K. Kasliwal, Ph.D. ASSIGNED DATE: 16-Dec-2002
CHECKLIST DATE: 30-Jan-2003

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes
(If "no," state on a separate page why it is not.)

[The following parameters are necessary to initiate a full review, i.e., complete enough to review but may have deficiencies]

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section organized in a manner to allow substantive review to begin?	✔		
2.	Is the CMC section indexed and paginated in a manner to allow substantive review to begin?	✔		
3.	Is the CMC section legible so that substantive review can begin?	✔		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	✔		
5.	Is a statement provided that all the facilities ate ready for cGMP / PAI inspection?	NA	NA	It is an approved drug product to be manufactured at existing approved manufacturing facilities.
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	✔		
7.	Does the section contain controls for drug substance?	NA	NA	It is referenced to the existing ProHance NDA 20-131.
8.	Does the section contain controls for drug product?	NA	NA	The necessary microbiological information is provided in the submission. The other information is referenced to the ProHance NDA 20-131.
9.	Has the stability data and analysis been provided to support the proposed expiry?	✔	NA	The NDA concerns relabeling of currently approved 50 mL multidose vial to a pharmacy bulk pack. There is no new packaging and long term stability issues do not exist. Microbiological data to support use for 8 hour, subsequent to vial penetration is provided.
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	NA	NA	
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	✔		

12.	Has an investigational formulations section been provided?	NA	NA	
13.	Has the applicant provided a method validation package?	NA	NA	
14.	Is a separate microbiological section included?		✔	Since the package is relatively small a copy was made by PM and given to the microbiology reviewer.

Signature: RK Kasliwal 1/30/03

Ravindra K. Kasliwal, Ph.D., Review Chemist

Signature: E. Leutzinger 1/30/2003 Concur

Eldon E. Leutzinger, Ph.D. , Chemistry Team Leader

CC: Orig. NDA 21-489
HFD-160/Division File
HFD-160/Chemist/Kasliwal
HFD-160/PM/Kang