# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-489**

# ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

## tem 13: Patent Information

| | | |
|---|---|---|
| 1) | Active Ingredient | gadoteridol |
| 2) | Strength | 279.3 mg/mL |
| 3) | Trade Name | ProHance® Multipack™<br>ProHance® |
| 4) | Dosage Form,<br>Route of Administration | Solution<br>Intravenous injection |
| 5) | Applicant Firm Name | Bracco Diagnostics Inc. |
| 6) | NDA Number(s) | 21-489 for ProHance Multipack<br>20-131 for previously approved ProHance |
| 7) | NDA Approval Date | 21-489 Pending<br>20-131 November 16, 1992 |
| 8) | Exclusivity | Not applicable |
| 9) | Applicable US Patent Numbers | 4,885,363<br>5,474,756<br>5,846,519<br>6,143,274 |

*See chart that follows*

## Item 13: Patent Information (continued)

Pursuant to 21 CFR 314.50 and 314.53 the following patent information is provided:

| Patent Number | Expiration Date | Type of Patent | Approved Method of Use | Name of Patent Owner |
|---|---|---|---|---|
| 4,885,363 | December 5, 2006 | Drug<br>Drug Product | | Bracco Diagnostics Inc. |
| 5,474,756 | December 12, 2012 | Method of Use | Contrast agent for MRI | Bracco Diagnostics Inc. |
| 5,846,519 | December 8, 2015 | Drug<br>Drug Product | | Bracco Diagnostics Inc. |
| 6,143,274 | December 12, 2012 | Method of Use | Contrast agent for brain MRI | Bracco Diagnostics Inc. |

**Item 13: Patent Information (continued)**

The undersigned declares that US Patent Numbers 4,885,363, 5,474,756, 5,846,519, and 6,143,274 cover the formulation, composition, and/or method of use of ProHance. This product is currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

M Benson

Bracco Diagnostics Inc
Melanie Benson
Director, US Regulatory Affairs

12/4/02
Date

# Exclusivity Summary Form

(Modified: October 14, 1998)

EXCLUSIVITY SUMMARY FOR NDA # 21-489
Trade Name: Prohance® Multipack™ Generic Name: Gadoteridol
Applicant Name: Bracco Diagnostics HFD # 160
Approval Date If Known: October 9, 2003

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PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

*1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.*

a) Is it an original NDA?

YES /x/ NO /___/

b) Is it an effectiveness supplement?

YES // NO /x/

If yes, what type? (SE1, SE2, etc.)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO /x/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

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If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 8/27/97
cc: Original NDA 20-937

Division File NDA 20-937

HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES // NO /x/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /x/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

*2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?* (Rx to OTC switches should be answered NO - please indicate as such)

YES /x/ NO //

If yes, NDA #20-131. Drug Name ProHance®.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

*3. Is this drug product or indication a DESI upgrade?*

YES /___/ NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO //

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials,

such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

*Signature: James Moore* *Date: October 10, 2003*
*Title:Project Manager*

*Signature of Office/Division Director*
*Signature:Sally Loewke* *Date:October 10, 2003*

*cc:* *DFS*
*HFD-93 Mary Ann Holovac*

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/s/

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Sally Loewke
10/10/03 04:20:33 PM

## Item 16: Debarment Certification

Bracco Diagnostics Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Food, Drug, and Cosmetic Act in connection with this submission.

MBenson

Bracco Diagnostics Inc.
Melanie Benson
Director, US Regulatory Affairs

12/04/02

Date

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | | |
|---|---|---|---|
| NDA 21-489 | Efficacy Supplement Type SE- | Supplement Number | |
| Drug: Prohance (gadoteridol) Multipack™ Injection | | Applicant: Bracco Diagnostics | |
| RPM: James Moore | | HFD-160 | Phone # (301) 827-7510 |
| Application Type: ( ) 505(b)(1) ( ) 505(b)(2) | | Reference Listed Drug (NDA #, Drug name): 20-131 Prohance | |

| | |
|---|---|
| ❖ Application Classifications: | |
| • Review priority | (x) Standard ( ) Priority |
| • Chem class (NDAs only) 3C | |
| • Other (e.g., orphan, OTC) | |
| ❖ User Fee Goal Dates October 17, 2003 | |
| ❖ Special programs (indicate all that apply) | (x ) None<br>Subpart H<br>( ) 21 CFR 314.510 (accelerated approval)<br>( ) 21 CFR 314.520 (restricted distribution)<br>( ) Fast Track<br>( ) Rolling Review |
| ❖ User Fee Information | |
| • User Fee | (x ) Paid |
| • User Fee waiver | ( ) Small business<br>( ) Public health<br>( ) Barrier-to-Innovation<br>( ) Other |
| • User Fee exception | ( ) Orphan designation<br>( ) No-fee 505(b)(2)<br>( ) Other |
| ❖ Application Integrity Policy (AIP) | |
| • Applicant is on the AIP | ( ) Yes (x ) No |
| • This application is on the AIP | ( ) Yes (x ) No |
| • Exception for review (Center Director's memo) | N/A |
| • OC clearance for approval | N/A |
| ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent. | ( x) Verified |
| ❖ Patent | |
| • Information: Verify that patent information was submitted | (x ) Verified |
| • Patent certification [505(b)(2) applications]: Verify type of certifications submitted | 21 CFR 314.50(i)(1)(*i*)(A)<br>( ) I ( ) II ( ) III ( ) IV<br><br>21 CFR 314.50(i)(1)<br>( ) (ii) ( ) (iii) |
| • For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice). | ( ) Verified |
| ❖ Exclusivity Summary (approvals only) | x |
| ❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)* | August 11, 2003 |

| General Information | |
|---|---|
| ❖ Actions | |
| • Proposed action | (x) AP ( ) TA ( ) AE ( ) NA |
| • Previous actions (specify type and date for each action taken) | |
| • Status of advertising (approvals only) | ( x) Materials requested in AP letter<br>( ) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | ( ) Yes (x ) Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | (x ) None<br>( ) Press Release<br>( ) Talk Paper<br>( ) Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | |
| • Most recent applicant-proposed labeling | x |
| • Original applicant-proposed labeling | x |
| • Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)* | N/A |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | N/A |
| Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | x |
| • Applicant proposed | x |
| • Reviews | x |
| ❖ Post-marketing commitments | |
| • Agency request for post-marketing commitments | N/A |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | N/A |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | x |
| ❖ Memoranda and Telecons | x |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | N/A |
| • Pre-NDA meeting (indicate date) | N/A |
| • Pre-Approval Safety Conference (indicate date; approvals only) | N/A |
| • Other | N/A |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | N/A |
| • 48-hour alert | N/A |
| Federal Register Notices, DESI documents, NAS, NRC (if any are applicable) | N/A |

| Clinical and Summary Information | |
|---|---|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)* | |
| ❖ Clinical review(s) *(indicate date for each review)* | N/A |
| ❖ Microbiology (efficacy) review(s) *(indicate date for each review)* | June 3, 2003 |
| ❖ Safety Update review(s) *(indicate date or location if incorporated in another review)* | August 11, 2003***** |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | N/A |
| ❖ Statistical review(s) *(indicate date for each review)* | N/A |
| ❖ Biopharmaceutical review(s) *(indicate date for each review)* | N/A |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)* | N/A |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | N/A |
| • Bioequivalence studies | N/A |
| **CMC Information** | |
| ❖ CMC review(s) *(indicate date for each review)* | August 11, 2003 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion *(indicate review date)* | See Review |
| • Review & FONSI *(indicate date of review)* | See Review |
| • Review & Environmental Impact Statement *(indicate date of each review)* | See Review |
| ❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)* | See Review |
| ❖ Facilities inspection (provide EER report) | Date completed: N/A<br>( ) Acceptable<br>( ) Withhold recommendation |
| ❖ Methods validation | ( ) Completed<br>(X) Requested N/A<br>( ) Not yet requested |
| **Nonclinical Pharm/Tox Information** | |
| ❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | N/A |
| ❖ Nonclinical inspection review summary | N/A |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | N/A |
| ❖ CAC/ECAC report | N/A |

NO MEETINGS HELD

Administrative Summary for ProHance® Multipack Injection NDA 21-489

September 6, 2003

This New Drug Application for Prohance® Multipack Injection was submitted by Bracco Diagnostics on December 16, 2002, and received by FDA on December 19, 2003. The PDUFA date is October 17, 2003.

This New Drug Application proposes new packaging for this marketed product. The application provides for use of this product with a suitable transfer device.

No pharmacology, statistical or clinical pharmacology review was required because there was no change in the product and no clinical trial data was submitted for analysis or evaluation. Clinical data was incorporated by reference only. However, the Sponsor provided a safety update dated April 10, 2003, that was reviewed by the medical officer assigned to this application. The clinical reviewer recommended no labeling changes. The chemistry reviewer and the microbiology reviewer have recommended that the application be approved.

The chemist recommended labeling changes and those changes were incorporated in revised labeling submitted by Bracco Diagnostics on July 14, 2003.

James Moore, R.Ph., M.A.
Project Manager, HFD-160

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/s/

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James Moore
10/21/03 12:41:51 PM
CSO

| RECORD OF TELEPHONE CONVERSATION/MEETING | Date: 9/22/03 |
|---|---|
| I called Melanie Benson to discuss two labeling issues, recently raised in the OPADRA labeling consult. I told Melanie that the labels and the insert should carry the labeled strength of 279.3 mg/mL labeled either in front of the drug name or underneath the established name. After some discussion why is this needed now (since the existing ProHance does not contain the labeled strength), she agreed to label the strength. The second issue discussed was ——— lk d ——— I told Melanie that I will pass on her concerns regarding ——— co the division management. Meanwhile, she said that she will submit draft labeling containing the labeled strength, both via Fax and hard copy to the division ASAP.<br><br>Since ProHance (NDA 20-131) labeling does not contain the labeled strength, she indicated that they will update that labeling at the next printing cycle (to include the labeled strength in identical fashion) and report that in the annual report. This is satisfactory.<br><br>Ravindra K. Kasliwal, Ph.D.<br>---<br>**Name:** **HFD-160** | **IND 21-489**<br><br>**Telecon/Meeting initiated by:**<br><br>O Applicant/Sponsor<br>**X** FDA<br><br>**By:**<br>Ravindra K. Kasliwal<br><br>**Product Name:**<br><br>**ProHance Multipack**<br><br>**Firm Name:**<br><br>Bracco Diagnostics<br><br>**Name and Title of Person with whom conversation was held:**<br><br>Melanie Benson<br>Director, Regulatory<br><br>**Phone:**<br><br>(609)514-2254 |

cc : Orig.21-489
HFD-160/Division File/Moore
R/D Init. by: Leutzinger

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/s/

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Ravi Kasliwal
9/22/03 10:45:18 AM
CHEMIST

Eldon Leutzinger
9/23/03 03:23:55 PM
CHEMIST

**CONSULTATION RESPONSE**
**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**(DMETS; HFD-420)**

| **DATE RECEIVED:** MAY-27-2003 | **DESIRED COMPLETION DATE:** JUL-27-2003<br>**PDUFA DATE:** OCT-17-2003 | **ODS CONSULT #:** 03-0171 |
|---|---|---|

**TO:** Sally Loewke, MD
Acting Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

**THROUGH:** James Moore
Project Manager, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

| **PRODUCT NAME:**<br>ProHance Multipack<br>(Gadoteridol Injection)<br>279.3 mg/mL<br><br>**NDA #** 21-489 | **NDA SPONSOR:**<br>Bracco Diagnostics Inc. |
|---|---|

**SAFETY EVALUATOR:** Marci Lee, PharmD

**SUMMARY:** In response to a consult from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, "ProHance Multipack", to determine the potential for confusion with approved proprietary and established names as well as pending names.

**RECOMMENDATIONS:**

1. DMETS does not recommend use of the modifier "Multipack" in conjunction with the proprietary name, ProHance.

2. If the sponsor has any information or reports about errors or misuse of the currently marketed 50 mL ProHance product, DMETS recommends that this is incorporated into a strategy for prevention of similar problems with the proposed 50 mL ProHance Multipack product.

3. DMETS recommends the labeling revisions outlined in Section III to promote the safest possible use of this product.

4. DDMAC finds the proprietary name, ProHance Multipack, acceptable from a promotional perspective.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support**
**Office of Drug Safety**
**HFD-420; Parklawn Building Room 6-34**
**Center for Drug Evaluation and Research**

## PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** August 7, 2003

**NDA NUMBER:** 21-489

**NAME OF DRUG:** ProHance Multipack (Gadoteridol Injection) Pharmacy Bulk Package 279.3 mg/mL

**NDA SPONSOR:** Bracco Diagnostics Inc.

## I. INTRODUCTION

This consult was written in response to a request from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160) for an assessment of the proposed proprietary name for the pharmacy bulk package of Gadoteridol Injection, ProHance Multipack. The draft container labels, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor is currently marketing Gadoteridol Injection as "ProHance". ProHance was approved November 16, 1992. See Figure 1 for the "HOW SUPPLIED" portion of the ProHance insert labeling (Revised January 2001).

DMETS notes that the sponsor is already marketing ProHance as a 50 mL single dose vial (NDC 0270-1111-40). [redacted] There are very few differences between these two packaging configurations. While one is a single dose vial, the other is used to prepare multiple single doses.

**FIGURE 1. ProHance Insert Labeling**

**HOW SUPPLIED**
ProHance (Gadoteridol Injection) is a clear, colorless to slightly yellow solution containing 279.3 mg/mL of gadoteridol in rubber stoppered vials. ProHance is available in boxes of:

| | |
|---|---|
| Five 5 mL fills in single dose 15 mL vials | (NDC 0270-1111-04) |
| Five 10 mL fills in single dose 30 mL vials | (NDC 0270-1111-01) |
| Five 15 mL fills in single dose 30 mL vials | (NDC 0270-1111-02) |
| Five 20 mL fills in single dose 30 mL vials | (NDC 0270-1111-03) |
| Five 50 mL fills in single dose 50 mL vials | (NDC 0270-1111-40) |
| Five 10 mL fills in single dose 20 mL prefilled syringes | (NDC 0270-1111-16) |
| Five 17 mL fills in single dose 20 mL prefilled syringes | (NDC 0270-1111-45) |

PRODUCT INFORMATION

ProHance Multipack is the proposed name for the pharmacy bulk package of Gadoteridol Injection. Gadoteridol is indicated for use in magnetic resonance imaging (MRI) in adults and children over two years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues. Gadoteridol is also indicated for use in MRI in adults to visualize lesions in the head and neck. The recommended dose for adults and children over two years is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min to 60 mL/min) or bolus (>60 mL/min). In adult patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose. ProHance Multipack will be available in boxes of five 50 mL pharmacy bulk packages. Each milliliter contains 279.3 mg of gadoteridol.

## II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1, 2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "ProHance Multipack" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, ProHance Multipack. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

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[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

[3] The DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

1. The Expert Panel identified potential for confusion between ProHance and ProHance Multipack. The product information is listed in Table 1 (See below on page 4), including the dosage forms available and usual dosage.

2. DDMAC did not have concerns about the name with regard to promotional claims.

Table 1. Potential Sound-Alike and/or Look-Alike Names Identified by DMETS Expert Panel

| **Product Name** | **Established name, Dosage form(s)** | **Usual adult dose*** | **Look-alike or Sound-alike** |
|---|---|---|---|
| **ProHance Multipack** | **Gadoteridol Injection 279.3 mg/mL Boxes of five 50 mL Pharmacy Bulk Packages** | **0.1 mmol/kg (0.2 mL/kg) as a rapid infusion or bolus** | |
| ProHance | Gadoteridol Injection 279.3 mg/mL<br>Five 5 mL fill in single dose 15 mL vial<br>Five 10 mL fill in single dose 30 mL vial<br>Five 15 mL fill in single dose 30 mL vial<br>Five 20 mL fill in single dose 30 mL vial<br>Five 50 mL fill in single dose 50 mL vial<br>Prefilled syringes<br>Five 10 mL fill in single dose 20 mL<br>Five 17 mL fill in single dose 20 mL | 0.1 mmol/kg (0.2 mL/kg) as a rapid infusion or bolus | Look-alike and Sound-alike |
| *Frequently used, not all-inclusive. | | | |

B. ADVERSE EVENT REPORTING SYSTEM (AERS)

A search of the FDA Adverse Event Reporting System (AERS) did not yield any medication error reports with the names, ProHance or gadoteridol. However, DMETS acknowledges that medication errors may be occurring with ProHance, which are not reported to the agency.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. ProHance Multipack Proprietary Name Confusion

In reviewing the proprietary name, ProHance Multipack, the primary concern was related to the potential for misinterpretation of the "Multipack" portion of the name. The modifier "Multipack" may suggest a packaging configuration that contains *multiple individual items*. Therefore, "Multipack" can lead to confusion, especially for practitioners responsible for ordering the product. It is difficult to determine if "Mulitpack" is the name for the container (50 mL bottle) or the carton of five bottles. However, based on the container labels submitted for review, our interpretation is that the ProHance modifier "Multipack" refers to a pharmacy bulk package (50 mL bottle).

A pharmacy bulk package is a bulk container used to facilitate compounding of multiple individual units. Pharmacy bulk packages have specific recommendations for use to minimize the risk of contamination. Contents of a pharmacy bulk package should be used in one continuous operation immediately after initial container entry. If this is not possible, the contents must be used within four hours of entry. A pharmacy bulk package is NOT a multiple dose container.

There is also potential for the "Multipack" portion of the proprietary name to suggest that the product is a multiple dose container. This type of confusion could lead to misuse of the pharmacy bulk package.

Although pharmacy bulk packages may commonly be used for imaging agents (e.g., Magnevist®, Ultravist®, Optiray® and OptiMARK®), the term "Multipack" will likely be unfamiliar to those practitioners using this product. The ProHance Multipack product will be used primarily in a compounding area (e.g., pharmacy IV lab). Pharmacy bulk packages are not generally dispensed to nursing units, etc. Additionally prescribers of ProHance will usually provide a dose (e.g., mL/kg) and will not use the modifier "Multipack" when prescribing. The proper use information on the pharmacy bulk package labels and labeling may prevent misuse of ProHance Multipack.

2. Package Confusion

Currently, there is a 50 mL single dose vial (NDC 0270-1111-40) listed in the HOW SUPPLIED section of the existing ProHance insert labeling. DMETS is not able to determine how this product will differ from the proposed ProHance Multipack (NDC 0270-1111-70). DMETS also identified a listing for a second manufacturer of ProHance (BYK GULDEN LOMBERG CHEMISCHE FABRIK) in a 50 mL bottle (NDC 47234-111-40). The only differences DMETS could identify between the 50 mL single dose vial and the 50 mL pharmacy bulk package was the time frame for use of the pharmacy bulk package and that one was for multiple single-dose preparations and one is for a single dose.

DMETS notes that it is unusual for a sponsor to market a single dose vial and a pharmacy bulk package of the same volume. See Appendix A for a comparison of pharmacy bulk package volumes.

DMETS anticipates that although some pharmacies may order and store various imaging agents, these products are routinely handled by the staff in nuclear medicine and radiology departments. The sponsor should ensure that the container and carton of ProHance Multipack is adequately differentiated from other products in their product line, especially those that may be stored near ProHance Multipack.

## III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

DMETS has reviewed the draft container label, carton labeling and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. Upon review of the draft labels and labeling DMETS has identified the following areas of improvement, in the interest of minimizing user error and maximizing patient safety. Please forward copies of the final printed labels and labeling when they are available.

A. GENERAL COMMENTS (ProHance Multipack 50 mL )

1. ProHance Multipack contains pharmacy bulk packages. In accordance with the issues raised in the Interim MAPP 7217.1, Uniform Labeling for Pharmacy Bulk Package Dosage Forms, consider the recommendations below.

2. Copies of the labels and labeling were provided in black and white, and may not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used in the marketplace (i.e. color, placement of name, design, etc.).

3. The draft copies of the labels and labeling provided did not contain a scale for size. Therefore, DMETS cannot assess if the font sizes and placement of the information are likely to contribute to confusion or errors.

4. Ensure that ProHance Multipack labels and labeling are adequately differentiated from other products in the Bracco product line, especially those that may be stored near ProHance Multipack.

5. The product strength should be prominently displayed under the established name. Currently, [redacted]. Revise accordingly.

B. CONTAINER LABELS (ProHance Multipack 50 mL)

1. Add a prominent [redacted] reading "Pharmacy Bulk Package – Not for Direct Infusion" immediately following the proprietary and non-proprietary names. Use bold face type, large size type or contrasting color to make this more visible.

2. Currently, the label reads that the container should be discarded no later than 8 hours after initial entry. However, unless there is significant scientific data to support the eight-hour time frame, this is not consistent with a pharmacy bulk package. Revise the statement to read, "Discard the container no later than 4 hours after initial closure puncture."

3. Increase the prominence of the statement, "Discard the container no later than [redacted] after initial closure puncture."

4. Increase the prominence of the statement, "Once bottle has been penetrated, withdrawal of contents should be completed without delay."

5. Add a statement to refer to the package insert for further information on the use of the pharmacy bulk package.

C. CARTON LABELING (ProHance Multipack 50 mL)

See comments in B.1. through B.5. above.

D. INSERT LABELING (ProHance Multipack 50 mL)

1. PRODUCT TITLE

Add a prominent, [redacted] "Pharmacy Bulk Package – Not for Direct Infusion" immediately following the proprietary and non-proprietary names. Use bold face type, large size type or contrasting color to make this more visible.

2. DOSAGE AND ADMINISTRATION

Currently, the insert reads, "...a maximum time of 8 hours from initial closure entry is permitted to complete fluid transfer operation." Unless there is significant scientific data to support the eight-hour time frame, revise the statement to read, "a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operation."

3. HOW SUPPLIED

Add special handling and storage instructions for the pharmacy bulk package into this section.

do not freeze
do not
not

CFR 201.57 K

## IV. RECOMMENDATIONS

1. DMETS does not recommend use of the modifier "Multipack" in conjunction with the proprietary name, ProHance.

2. If the sponsor has any information or reports about errors or misuse of the currently marketed 50 mL ProHance product, DMETS recommends that this is incorporated into a strategy for prevention of similar problems with the proposed 50 mL ProHance Multipack product.

3. DMETS recommends the labeling revisions outlined in Section III to promote the safest possible use of this product.

4. DDMAC finds the proprietary name, ProHance Multipack, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, PharmD
Safety Evaluator
Office of Drug Safety (DMETS)

Concur:

Denise Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

# Appendix A – Comparison of Volumes for Pharmacy Bulk Packages

| Product Name | How Supplied | Pharmacy Bulk Package |
|---|---|---|
| Magnevist | Single dose vials:<br>5 mL, 10 mL, 15 mL , 20 mL<br>Prefilled disposable syringes:<br>10 mL, 15 mL , 20 mL | 100 mL |
| Ultravist | Vials<br>50 mL, 100 mL, 150 mL<br>200 mL fill in 250 mL vial | 500 mL bottles |
| OptiMARK | Syringe<br>10 mL, 15 mL, 20 mL, 30 mL<br>Vial<br>5 mL, 10 mL, 15 mL , 20 mL | 50 mL in glass bottles |
| Optiray | Vial<br>20 mL, 30 mL, 50 mL<br>Bottle<br>50 mL, 75 mL, 100 mL, 150 mL, 200 mL<br>Pre-filled syringe<br>30 mL, 50 mL, 75 mL, 100 mL, 125 mL | 250 mL, 500 mL |
| ProHance | Gadoteridol Injection<br>279.3 mg/mL<br>Five 5 mL fill in single dose 15 mL vial<br>Five 10 mL fill in single dose 30 mL vial<br>Five 15 mL fill in single dose 30 mL vial<br>Five 20 mL fill in single dose 30 mL vial<br>Five 50 mL fill in single dose 50 mL vial<br>Prefilled syringes<br>Five 10 mL fill in single dose 20 mL<br>Five 17 mL fill in single dose 20 mL | *Proposed 50 mL bottle* |

single dose vial

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/s/
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Marci Ann Lee
8/25/03 10:07:28 AM
PHARMACIST

Denise Toyer
8/25/03 12:19:53 PM
PHARMACIST

Denise Toyer
8/25/03 12:27:40 PM
PHARMACIST

Denise Toyer
8/25/03 12:28:18 PM
PHARMACIST

Jerry Phillips
8/25/03 12:33:40 PM
DIRECTOR

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE: July 8, 2003**

| | |
|---|---|
| **To:** Melanie Benson | **From:** James Moore |
| **Company:** Bracco Diagnostics | Division of Medical Imaging and Radiopharmaceutical Drug Products |
| **Fax number:** (609) 514-2539 | **Fax number:** (301) 480-6036 |
| **Phone number:** (609) 514-2254 | **Phone number:** (301) 827-7510 |

**Subject:** Fax of Revised Labeling for Prohance

**Total no. of pages including cover:** 4

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

July 8, 2003

The reviewing chemist has requested that Bracco revise the labeling for the ProHance® Multipack™ Injection. Please revise you labeling as requested by the reviewing chemist.

NDA 21-489 [ProHance Multipack (gadoteridol) Injection]

The DOSAGE AND ADMINISTRATION section of the package insert should be modified as follows to include the DRUG HANDLING section as described below:

**DOSAGE AND ADMINISTRATION**
**Central Nervous System**
**ADULTS:** The recommended dose of ProHance (Gadoteridol Injection) is 0.1 mmol/kg (0.2mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus ( >60 mL/min). In patients suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans, a second dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose.
**CHILDREN (2-18 years):** The recommended dose of ProHance is 0.1 mmol/kg (0.2mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (> 60 mL/min). The safety and efficacy of doses > 0.1 mmol/kg, and sequential and/or repeat procedures has not been studied.
**Extracranial/Extraspinal Tissues**
**ADULTS:** The recommended dose of ProHance is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus ( > 60 mL/min).
**CHILDREN:** Safety and efficacy for extracranial/extra-spinal tissues has not been established. Dose adjustments in renal and liver impairment have not been studied.
To ensure complete injection of the contrast medium, the injection should be followed by a 5 mL normal saline flush. The imaging procedure should be completed within 1 hour of the first injection of ProHance.

DRUG HANDELING
Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the solution if it is discolored or particulate matter is present. Any unused portion must be discarded in accordance with regulations dealing with the disposal of such materials.

Concurrent medications or parenteral nutrition should not be physically mixed with contrast agents and should not be administered in the same intravenous line because of the potential for chemical incompatibility.

**Directions for Proper Use of ProHance (Gadoteridol Injection) Pharmacy Bulk Package**
The pharmacy bulk package is used as a multiple dose container with an appropriate transfer device to fill empty sterile syringes.

ProHance Multipack injection should be drawn into the syringe and administered using sterile technique. If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. Unused portions of the drug must be discarded.

When ProHance Multipack injection is to be injected using plastic disposable syringes, the agent should be drawn into the syringe and used immediately.

a. The transferring of ProHance (Gadoteridol Injection) from the Pharmacy Bulk Package should be performed in a suitable work area, such as a laminar flow hood, utilizing aseptic technique.
b. The container closure may be penetrated only one time, utilizing a suitable transfer device. Once the pharmacy bulk package is punctured, it should not be removed from the aseptic work area during the entire period of use.
c. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 8 hours from initial closure entry is permitted to complete fluid transfer operation. Any unused ProHance Multipack injection must be discarded 8 hours after initial puncture of the bulk package.
d. Storage temperature of container after the closure has been entered should not exceed 25° C (77° F).

If you have questions, contact CAPT James Moore at (301) 827-7510.

James Moore, R.Ph., M.A.
Project Manager, HFD-160

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/s/

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James Moore
7/8/03 10:02:31 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

**NO FILING REVIEW ISSUES IDENTIFIED**

NDA 21-489

Bracco Diagnostics, Inc.
Attention: Ms. Melanie Benson
Director, U.S. Regulatory Affairs
P.O. Box 5225
Princeton, New Jersey 08543-5225

Dear Ms. Benson:

Please refer to your December 16, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ProHance® Multipack™ (gadoteridol) Injection 279.3 mg/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on February 14, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call CAPT James Moore, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

*{See appended electronic signature page}*

Kyong Kang, PharmD.
Chief, Project Management Staff
Division of Medical Imaging and
Radiopharmaceutical Drug Products,
HFD-160
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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/s/

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Kyong Kang
3/10/03 01:40:13 PM

## Moore, James W

**om:** Moore, James W
**nt:** Wednesday, January 15, 2003 10:28 AM
**To:** 'Melanie.Benson@diag.bracco.com'
**Cc:** Moore, James W; Kang, Kyong A
**Subject:** RE: ProHance PBP Question

Melanie I don't need a copy of the approval letter. I found the letter and the referenced supplement. Since we have the info from the original application we may not need to refer to the supplement. If we need any additional info for the application I let you know. Thanks so much for your prompt response.
James.

-----Original Message-----
From: Melanie.Benson@diag.bracco.com
[mailto:Melanie.Benson@diag.bracco.com]
Sent: Wednesday, January 15, 2003 10:08 AM
To: Moore, James W
Cc: Kang, Kyong A; Moore, James W
Subject: RE: ProHance PBP Question

Hi James,

Supplement 018 was approved March 9, 2001. If needed, I could fax a copyof
e approval letter to you. The approvable letter for Supplement 019
ated March 26, 2001.

Supplement 018 contained information in support of transferring the ProHance finished product manufacturing process from

to Byk Gulden, Singen Germany for vials only. The supplement provided for manufacturing, testing, labeling and release of the
finished product. Included in this supplement was all the packaging information (vials, stoppers, etc) and stability data on the 50-mL presentation (as well as the manufacturing instructions, testing, labeling,
etc). If you would like, I can retrieve our copy and provide you with the
page numbers where this data can be found.

As soon as I hear back from you and we close this question, I will follow
up with hard copy correspondence to the PBP NDA.

As an FYI, SCM-019 provided the same transfer information (manufacturing through release) for ProHance glass syringes. SCM-019 was approved July 19, 2001.

Please let me know if you need any of the addtional information mentioned
above.

Best regards,
Melanie Benson
Director
U.S. Regulatory Affairs
Phone: (609) 514-2254

Fax: (609) 514-2539

"Moore, James W"

<MOOREJ@cder.fda.gov>

01/15/2003 09:31 AM

To: Melanie J Benson/BDI/US/BRACCO@BRACCO

cc: "Moore, James W" <MOOREJ@cder.fda.gov>, "Kang, Kyong A" <KANGK@cder.fda.gov>

Subject: RE: ProHance PBP Question

I didn't see a supplement that was approved in March, 2001. I did see an approveable letter for supplement 19 that was issued during March of 2001.
Do you have the supplement number for the 50ml fill size. Supplement 19 was approved in July, 2001 and listed the 10ml and 17ml fill sizes. Melanie should you follow-up your e-mail this morning with a hard-copy to the file for NDA 21-489. We found the information regarding the 50ml size for the original application.
Melanie thanks again.
James.

-----Original Message-----
From: Melanie.Benson@diag.bracco.com [mailto:Melanie.Benson@diag.bracco.com]
Sent: Wednesday, January 15, 2003 8:20 AM
To: moorej@cder.fda.gov
Subject: ProHance PBP Question

Good Morning James,

I was out of the office yesterday, so I apologize for not getting back to you sooner.

The 50-mL fill size for ProHance was initially approved as part of the original NDA (20-131), back in November 1992. This fill size was also part of the manufacturing transfer supplement approved in March 2001. If you need any additional particulars, please feel free to call.

Best regards,

Melanie Benson
Director
U.S. Regulatory Affairs
Phone: (609) 514-2254
Fax: (609) 514-2539

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-489

Bracco Diagnostics, Inc.
Attention: Melanie Benson
Director, US Regulatory Affairs
107 College Road East
Princeton, New Jersey 08540

Dear Ms. Benson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

| | |
|---|---|
| Name of Drug Product: | ProHance®, Multipack™ (gadoteridol) Injection |
| Review Priority Classification: | Standard (S) |
| Date of Application: | December 16, 2002 |
| Date of Receipt: | December 17, 2002 |
| Our Reference Number: | NDA 21-489 |

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 14, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 17, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call CAPT James Moore, Regulatory Project Manager, at (301) 827-7510.

Sincerely,

*{See appended electronic signature page}*

Kyong Kang, PharmD.
Chief, Project Management Staff
Division of Medical Imaging and
Radiopharmaceutical Drug Products,
HFD-160
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Kyong Kang
1/13/03 11:26:07 AM

# USER FEE VALIDATION SHEET

NDA # 21,489 Supp. Type & # N000 UFID # _____
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. YES (NO) APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

(REF) IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

| NDA # | Division | | |
|---|---|---|---|
| N_____ | HFD-_____ | Fee | No Fee |
| N_____ | HFD-_____ | Fee | No Fee |

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

| NDA # | Division | NDA # | Division | NDA # |
|---|---|---|---|---|
| N_____ | HFD-_____ | N_____ | HFD-_____ | N_____ |

7. P (S) PRIORITY or STANDARD APPLICATION?

James W. Green 1-7-2003
PM Signature / Date
2/14/00

Yvonne King 1/11/03
CPMS Concurrence Signature / Date
2/14/2003

BRACCO

THE IMAGE OF INNOVATION

December 2, 2002

Food and Drug Administration (360909)
Mellon Client Service Center – RM 670
500 Ross Street
Pittsburgh, PA 15262-0001

**Re: ProHance Pharmacy Bulk Package NDA 21-489 (IND 32,521) Application Fee**

Dear Sir/Madam:

Enclosed please find a check for $266,700.00 which is payment for the ProHance Pharmacy Bulk Package NDA 21-489 (IND 32,521) Application Fee. The user fee ID # is 4296.

Should you have any questions, please contact the undersigned at 609-514-2254.

Sincerely,

M Benson

Melanie Benson
Director US Regulatory Affairs

Bracco Diagnostics Inc.
od East - Princeton, New Jersey 08540 USA - Telephone: (609) 514-2200 / (800) 631-5245 Facsimile: (609) 514-2424 www.bdi.bracco.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

# USER FEE COVER SHEET

***See Instructions on Reverse Side Before Completing This Form***

A c[illegible] form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the [illegible]. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

| APPLICANT'S NAME AND ADDRESS | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER |
|---|---|
| Bracco Diagnostics Inc.<br>PO Box 5225<br>Princeton, NJ 08543-5225 | NDA 021-489 |
| | 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? ☒ YES ☐ NO<br>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.<br>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:<br>☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.<br>☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: NDA 020-131<br>(APPLICATION NO. CONTAINING THE DATA). |
| TELEPHONE NUMBER *(Include Area Code)*<br>( 609 ) 514-2254 | |
| PRODUCT NAME<br>ProHance® Multipack™ (gadoteridol injection) | 6. USER FEE I.D. NUMBER<br>4296 |

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
*(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
*(See item 7, reverse side before checking box.)*

☐ [illegible]E APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
*(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
*(Self Explanatory)*

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
*(See item 8, reverse side if answered YES)*

[illegible]ic reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing [illegible]uctions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. [illegible] comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

[illegible]rtment of Health and Human Services
[illegible] and Drug Administration
[illegible]R, HFM-99
[illegible] Rockville Pike
[illegible]ville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

| [illegible]TURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| [signature] | Melanie Benson<br>Director, US Regulatory Affairs | December 2, 2002 |

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Created by: PSC Media Arts (301) 443-2454 EF

Item 19: Financial Disclosure
Item 20: Other
Item 2: Labeling
[illegible]tional [illegible] Labels
Application [illegible]mary